Description

This invention relates to an oral bandage that can be adhered to the oral mucosa to prevent a drug administered to the oral mucosa from running out and to cover or protect the affected part of the oral mucosa, and to oral preparations comprising such a bandage having incorporated therein a topical drug.

In the field of dental and oral surgery, various topical preparations in the form of ointments or solutions have hitherto been administered to the oral mucosa for prophylaxis and therapy of oral diseases, such as periodontal disease, stomatitis, etc. The most serious problem in administering drugs to the oral mucosa is that the drug runs away in a short time by salivary secretion or through eating or drinking, thereby failing to fully exert its medical effects.

On the other hand, protection of the affected part in the oral cavity has scarcely been conducted because no effective oral bandage has been developed. As mentioned above, the continuous salivary secretion and taking of foods and drinks constitute an insuperable barrier to the protection of the oral mucosa.

In recent years, many proposals have been made in an attempt to effectively administer a drug to the mucosa of the oral cavity, so as to overcome the above-described problems. Among them, proposals relevant to the present invention relate to preparations adhesive to the oral mucosa, which contain water-soluble high-molecular substances as an adhesive. When water-soluble high-molecular substances absorb a small amount of water, they become a viscous aqueous solution or gel having adhesion, though varying in extent with their kind. Making use of this property, various preparations adhesive to the oral mucosa have been proposed, including pastes as disclosed in Japanese Patent Publication No. 27491/81, sponges as disclosed in Japanese Patent Publication No. 25211/81, tablets as disclosed in Japanese Patent Publication No. 7605/83, sheets as disclosed in Japanese Patent Publication No. 16676/69 and Japanese Patent Application (OPI) No. 186913/84 (the term "OPI" has herein used means "unexamined published application").

However, these conventional preparations only are intended to have enough adhesion to allow them to remain in position for a period of time enough to administer the drug to the mucosa. In other words, these preparations do not possess strong adhesion for an extended period of time as required for an oral bandage. On the contrary, an oral bandage is intended to prevent running-off of the administered drug or to provide protection by adhesion to the affected or injured part of the oral cavity. Therefore, it is required to have strong and long-lasting adhesion to the oral mucosa which may be less adherable due to the administered drug or stomatorrhagia. Since both adhesive strength and duration of adhesion of the aforesaid conventional preparations adhesive to the oral mucosa are not so high as demanded for an oral bandage, application of bases used in these preparations to an oral bandage can never satisfy the above-described requirements of an oral bandage. The conventional adhesive tapes which are intended to be applied to the skin cannot be, of course, used as an oral bandage because they have no adhesion to a wet surface such as oral mucosa.

Japanese Patent Application (OPI) No.186913/84 is directed to an invention that four components of gelatin or agar, gluten, carboxyvinyl polymer, and vinyl acetate resin or gum are essential. It is therefore apparent that the cited reference differs from the present application in which a homogeneous state is maintained by a two component system.

In the JPA document a water-soluble material and a water-insoluble material are mixed together with water in such a manner that a water content is 0.5-20 w/w%. From this fact, it is apparent that a homogeneous state cannot be obtained.

Even if a base material having such a state is adhered to the oral mucosa, water at the adhering portion is not absorbed uniformly with respect to the base material, resulting in an ununiform absorption, and as a result, the system of the base material tends to break, and its adhesion is not maintained for a long period of time.

On the other hand, in the homogeneous state as in the present invention, absorption of water from the adhering portion is uniformly conducted over the whole base material. Consequently, it is difficult to proceed breakage of the system, and the adhesion is sufficiently maintained over a long period of time.

An oral bandage is required to have not only strong and long-lasting adhesion to the oral mucosa as described above but also softness sufficient to be adhered to any desired site of complicated shape in the oral mucosa and, in addition, safety from worsening of the injury due to irritation. However, an oral bandage having such performance characteristics has not yet been developed.

The present invention is intended to meet the above-described situations.

Accordingly, an object of this invention is to provide an oral bandage having high adhesive strength for a prolonged period of time and softness with which to adhere to desired site of the oral mucosa or teeth.

Another object of this invention is to provide an oral preparation adhesive to the oral mucosa by which an active ingredient can be surely and effectively administered to the oral mucosa.

According to the invention we provide an oral bandage comprising a soft adhesive film consisting of a mixture of (a) an acrylic acid polymer, methacrylic acid polymer and/or maleic anhydride polymer and (b) a vinyl acetate polymer, the polymers (a) and (b) being uniformly dissolved in each other without regions of phase separation, so as to be substantially water-insolubilized; and optionally a basic substance capable of neutralizing said polymers (a) and an oral preparation comprising such an oral bandage having incorporated therein a topical drug.

The term "compatible state" as herein used means such a state that the polymers (a) and (b) (hereinafter simply referred to as "polycarboxylic acids") and the vinyl acetate polymer (hereinafter referred to as polyvinyl acetate) are uniformly dissolved in each other without forming small individual regions due to phase separation.

Water-soluble high-molecular compounds, such as polycarboxylic acids and polycarboxylic acid anhydrides have per se a shape-retention property. When they absorb a small amount of water, they exhibit strong adhesiveness but soon take up excess water to cause reduction in viscosity and degradation, thus resulting in losing their adhesiveness by being substantially dissolved in water. Moreover, since polycarboxylic acids in a dissolved state are acidic, they heavily irritate the sensitive injured part of the oral mucosa to cause worsening of the condition.

The present inventors have conducted extensive investigations on water-insolubilization of the above-described water-soluble high-molecular compounds, such as polycarboxylic acids, polycarboxylic acid anhydrides, etc., aiming at effective utilization of these compounds exhibiting excellent adhesion upon absorption of water as an oral bandage, while eliminating the above-described disadvantages, i.e., loss of adhesion due to over-absorption of water and irritation of the injured part. As a result, it has now been found that polycarboxylic acids and polyvinyl acetate are compatible with each other, and mixing of these two components in a compatible state substantially realizes water-insolubilization of the polycarboxylic acids without impairing the strong adhesion upon water absorption. Therefore, even if such a compatible mixture of the two components is shaped into a thin and soft film, it can exert strong adhesion for an extended period of time without undergoing degradation due to water absorption in a wet state.

It has further been found that incorporation of a basic substance (salt or base) capable of neutralizing the polycarboxylic acids into the above-described compatible mixture can further relieve the irritation on the injured part of the oral mucosa.

It has furthermore been found that incorporation of topical drugs into adhesive film and/or film support comprising the above-described compatible mixture can provide film-like oral preparations retaining the strong adhesion, by which the drug can be surely, simply and effectively administered to the oral mucosa, thus permitting prevention and treatment of oral diseases.

In the accompanying drawing:

The graph is a characteristic curve of (dissolved amount)/(total dissolved amount) of a drug, over a period of time.

A soft film comprising a compatible mixture of the polycarboxylic acids and polyvinyl acetate according to the present invention does not show adhesion in a dry state but comes to exhibit strong adhesion upon water absorption, such adhesion being substantially unchangeable even when immersed in water. Such a characteristic can first be manifested when the polycarboxylic acids and polyvinyl acetate are in a compatible state, not appearing when they are not in a compatible state.

As described above, the mixture of the polycarboxylic acids and polyvinyl acetate in a compatible state exhibit characteristics unpredictable from those of a mixture in a phase-separated state. More specifically, a film in a phase-separated state is turbid, whereas a film in a compatible state has such a high transparency that no independent small region is observed under an optical microscope. Further, when immersed in water, the polycarboxylic acids is dissolved out from the film in a phase-separated state, resulting in degradation as a whole; while the film in a compatible state only undergoes uniform swelling with very little elution of the polycarboxylic acids into water, which indicates that the polycarboxylic acids is substantially water-insolubilized. The compatible state (compatibility) of the polycarboxylic acids and polyvinyl acetate can be determined by making use of insolubilization of the polycarboxylic acids.

When a basic substance capable of neutralizing polycarboxylic acids is mixed with the above-described compatible mixture, the state of its mixing has no substantial influence on the adhesion property. Therefore, the basic substance may be mixed either in a compatible state or in a coarse dispersion.

Compatibility between the polycarboxylic acids and polyvinyl acetate can be clearly observed if the

mixture consists of only these two components as mentioned above. However, differrences in compatibility become unclear in those mixtures containing a basic substance having a neutralizing effect. In other words, in a mixture containing a basic substance, the mixing state of the basic substance being not restricted, even if the polycarboxylic acids and polyvinyl acetate are in a compatible state, the basic substance, if being mixed in a coarse dispersion, makes the film turbid. Thus, the mixing state of the polycarboxylic acids and polyvinyl acetate cannot always be observed visually or under an optical microscope.

Nevertheless, as described above, it has been confirmed that water-solubility of polycarboxylic acids can be markedly inhibited in a compatible mixture with polyvinyl acetate and that such a compatible mixture is uniformly swollen without degradation even when immersed in water for a considerably long period of time. This property can be recognized irrespective of whether a basic substance having a neutralizing effect be present or not.

Accordingly, this property can be made use of in determination of compatibility between polycarboxylic acids and polyvinyl acetate. This method of determination can be regarded reasonable from the fact that the oral bandage according to the present invention can be adhered to the oral mucosa for a long period of time owing to the limited water-solubility of the polycarboxylic acids.

In the present invention, the compatibility between polycarboxylic acids and polyvinyl acetate is determined from the amount of dissolved polycarboxylic acids. That is, the compatible state as herein referred to specifically means that the dissolution ratio of polycarboxylic acids as obtained by the following method is 40% by weight or less. In the case of an oral bandage containing a salt having a neutralizing effect, it means that the dissolution ratio of polycarboxylic acids as obtained by the following method is 50% by weight or less, taking into account dissolving of the salt.

Method of determing Dissolution Ratio:

A film comprising polycarboxylic acids and polyvinyl acetate is ground and weighed. The ground sample is put in a mesh bag and left to stand still in 300 times or more the weight of pure water at 20 °C for one hour. The bag is then taken out, and the amount of polycarboxylic acids dissolved out into the water is determined by neutralization titration or the like technique. This value is divided by the amount of the polycarboxylic acids initially contained in the film to obtain the dissolution ratio.

In the case when the film contains a basic substance, the dissolution ratio is obtained in the same manner as above except that the bag after the immersion is weighed to obtain the total amount of dissolved polycarboxylic acids and dissolved salt from, for example, weight reduction and this value is divided by the sum of the polycarboxylic acids and the basic substance initially contained in the film to obtain the dissolution ratio.

Since the oral bandage in accordance with the present invention comprises a soft film which is not adhesive in a dry state but shows adhesion only upon absorption of water, it can be stored as such without requiring any special storage conditions. On use, the oral bandage is stuck onto the oral mucosa whereupon it absorbs saliva or moisture of the mucous membrane to rapidly exerts strong adhesion to the mucous membrane. Thus, it firmly adheres to the affected part or injured part of the oral cavity that is less adherable due to the drug administered, stomatorrhagia, and the like. This adhesion lasts for a markedly prolonged period of time, which is a well-marked characteristic of the present invention. Such adhesion of long duration can first be attained by the adhesive film comprising the polycarboxylic acids and polyvinyl acetate in a compatible state as set forth above.

The mechanism accounting for the long-lasting adhesion is not clear, but it is believed that the polycarboxylic acids contributes to adhesiveness to the wet mucosa and the polyvinyl acetate contributes to water resistance in a compatible mixture thereof, thus functioning together to give adhesion of long duration.

The mixing state of the basic substance capable of neutralizing polycarboxylic acids has no influence on the adhesion, but the kind of the basic substance to be used exerts delicate influences on the adhesion and the like. For example, polyvalent metal salts, e.g., zinc oxide, calcium oxide, etc., function to reduce adhesion and to enhance water resistance, while monovalent metal salts, e.g., sodium acetate, etc., or a monovalent base, e.g., sodium hydroxide, triethanolamine, etc., functions to reduce water resistance and to enhance adhesion.

As described above, since the oral bandage in accordance with the present invention has adhesion of long duration, it can prevent the drug administered to the affected part of the oral cavity from running off to accelerate healing with a remarkably increased absorption of the drug and also give protection to the injured part of the oral cavity for a long period of time to expedite recovery.

Further, since the irritation due to eluted polycarboxylic acids can be reduced by adding a basic substance having a neutralizing effect to the adhesive film, a situation wherein the injured part of the oral

cavity becomes worse due to application of the oral bandage can be avoided.

In addition, the adhesive film according to the present invention is not merely composed of a water-soluble high-molecular substance but comprises a substantially water-insoluble soft film, in which polycarboxylic acids and polyvinyl acetate exist in a compatible state. Therefore, adhesion of long duration can be produced in a very thin film. In other words, too a thin film solely made of a water-soluble high-molecular substance is readily dissolved out in saliva in a short time to rapidly lose its adhesiveness so that a film made of such a material should have a considerably large thickness. However, a thick film produces a feeling foreign to the applied part and also reduces softness of the oral bandage. On the contrary, the oral bandage of the present invention does not require such a large thickness, thus giving no uncomfortable feeling.

The oral bandage according to the present invention can be produced by, for example, dissolving polycarboxylic acids and polyvinyl acetate in a solvent common to both and rapidly flow-casting the solution in a thin film, followed by drying.

The oral bandage containing a basic substance having a neutralizing effect according to the present invention can be produced by, for example, dissolving polycarboxylic acids and polyvinyl acetate in a solvent common to both, adding a basic substance capable of neutralizing the polycarboxylic acids to the solution, and rapidly flow-casting the mixture in a thin film, followed by drying. Incorporation of the basic substance may be carried out by dissolving in the solution or by dispersing a powderous basic substance in the solution. The above-described flow casting method is advantageous to easily produce a very thin film.

In the present invention, a topical drug can be incorporated into the oral bandage of the invention to obtain oral preparations. The method of incorporation is not particularly restricted, and usually comprises adding the topical drug directly or in the form of a solution to the solution of polycarboxylic acids and polyvinyl acetate, rapidly casting the composition in a thin film and drying. the acrylic polymers include an acrylic acid homopolymer and copolymers of acrylic acid and acrylic esters, e.g., butyl acrylate, 2-ethylhexyl acrylate,
methacrylic esters, e.g., methyl methacrylate,
or vinyl monomers, e.g., vinyl acetate, and copolymers, e.g., carboxyvinyl polymer. Examples of the methacrylic polymers include a methacrylic acid homopolymer and copolymers of methacrylic acid and comonomers as enumerated for the acrylic polymers. Specific examples of the maleic anhydride polymers include copolymers of maleic anhydride and methyl vinyl ether,

These compounds can be used either individually or in combination of two or more thereof. It is preferable that these Polycarboxylic acids contain 20% by weight or more of a -COOH group in case of methacrylic polymers or 16% by weight or more or a -CO-O-CO- group in case of maleic anhydride polymers.

The vinyl acetate polymer which can be used in the present invention typically includes a vinyl acetate homopolymer. In addition, copolymers of vinyl acetate and vinyl monomers, e.g., acrylic esters, and partial saponification products of a vinyl acetate homopolymer may also be employed. These vinyl acetate polymers may be used either individually or in combinations of two or more thereof. The polyvinyl acetate preferably has an average molecular weight (viscosity-average molecular weight) of not less than 60,000. Use of polyvinyl acetate having an average molecular weight less than 60,000 reduces water resistance of the adhesive, resulting in failing of the expected effects.

The basic substance which can be used for neutralizing polycarboxylic acids includes not only salts but bases. Typical examples of the salt include salts of metals and weak acids, metal oxides, metal hydroxides, amines, and mixtures thereof. Specific examples of the salt of metals and weak acids are salts of sodium, potassium, calcium, magnesium, etc. and carboxylic acids, e.g., acetic acid, lactic acid, citric acid, etc. Specific examples of the metal oxides are zinc oxide, calcium oxide, magnesium oxide, etc. Specific examples of the metal hydroxides are sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, etc. Specific examples of the amines are triethanolamine, diisopropanolamine, etc. These compounds can be used either alone or in combination. A preferred amount of the basic substance to be added varies widely depending on the kind thereof. In the case of using a polyvalent metal salt, for example, it is preferably added in an amount of from 0.2 to 0.8 equivalent based on the polycarboxylic acids. If its amount is less than 0.2 equivalent, the effect to relieve irritation on the injured part of the oral mucosa becomes insufficient. If it exceeds 0.8 equivalent, sufficient duration of adhesion can hardly be attained. In case of using a monovalent metal salt or a monovalent base, it is preferably added in an amount of from 0.03 to 0.2 equivalent based on the polycarboxylic acids. Amounts less than 0.03 equivalent reduce the effect of relieving irritation on the injured part, and amounts exceeding 0.2 equivalent reduce water resistance of the adhesive film, resulting in difficulty in obtaining sufficient adhesion.

The solvent common to the polycarboxylic acids and polyvinyl acetate includes lower alcohols, such as

methanol, ethanol, etc.; mixed solvents comprising a lower alcohol in a larger proportion and a compatible organic solvent, such as acetone, ethyl acetate, etc.; and mixed solvents comprising a lower alcohol or the above-described mixed solvent and water. The mixed solvent of a lower alcohol and an organic solvent preferably contains not more than 30% by weight of the organic solvent because the organic solvent of more than 30% by weight makes it difficult to dissolve polycarboxylic acids. The mixed solvent of a lower alcohol or a lower alcohol-organic solvent mixed solvent and water preferably contains not more than 30% by weight of water because a water content exceeding 30% by weight is liable to make it difficult to dissolve the polyvinyl acetate.

In the preparation of the oral bandage or oral; preparations of the invention, it is preferable that the polycarboxylic acids to polyvinyl acetate mixing ratio fall within such a range that the value A as obtained according to the following formula ranges from 15 to 45:

$$A = \frac{\left(\begin{matrix}\text{Weight of -COOH} \\ \text{in Adhesive Film}\end{matrix}\right) + \frac{5}{4}\left(\begin{matrix}\text{Weight of -CO-O-CO-} \\ \text{in Adhesive Film}\end{matrix}\right)}{\left(\begin{matrix}\text{Weight of Polycarboxylic Acids in Adhesive Film} \\ \text{+ Weight of Polyvinyl Acetate in Adhesive Film}\end{matrix}\right)} \times 100$$

As the value A becomes larger, the adhesion to the mucous membrane increases, but the duration of adhesion tends to decrease. To the contrary, the smaller the value A, the lesser the ahesion, but the duration of adhesion tends to increase. If the value A is less than 15, sufficient adhesion is hard to obtain. If it exceeds 45, it becomes difficult to obtain sufficient duration of adhesion. Accordingly, the mixing ratio of polycarboxylic acids and polyvinyl acetate is preferably adjusted so that the value A falls within a range of from 15 to 45. Taking the case of using polyacrylic acid as a polycarboxylic acid for instance, with the proportion of polyacrylic acid in the adhesive film being between 24 and 72% by weight, the value A falls within the above-recited range to obtain good results.

When the polycarboxylic acids and polyvinyl acetate are dissolved in a common solvent, care should be taken so as to sufficiently dissolve the both components. On this occasion, concentrations of the polycarboxylic acids, polyvinyl acetate, etc. are not particularly limited. However, too a high concentration of the high-molecular substance makes the resulting solution highly viscous, and such a viscous solution is difficult to flow-cast in a film. Therefore, it is preferable to give care that the concentrations of the high-molecular substances may not exceed 40% by weight.

In the preparation of the adhesive film according to the present invention, the solution comprising the polycarboxylic acids and polyvinyl acetate and, if necessary, a basic substance and/or a topical drug is cast on an appropriate film, such as polyethylene-laminated paper, having been subjected to releaseability-imparting treatment, and the casted film is rapidly dried with hot air in a drying oven or a drying tower. Suitable time and temperature in drying vary depending on the composition of a common solvent used, solid content of the solution, thickness of the cast film, the pressure and the like but, in general, preferably range from 60° to 120° C in temperature and from 1 to 20 minutes in time under an atmospheric pressure. A very thin film that can be, as such, used as an oral bandage can be thereby produced. The thickness of the resulting film is preferably be adjusted to a range of from 5 to 100 μm by controlling the amount of the casting solution, and the like. If a film thickness is less than 5 μm, it is difficult to obtain sufficient adhesion. A film having a thickness exceeding 100 μm tends to produce a feeling foreign to the mouth and to impair softness of the film.

As described above, the adhesive film in accordance with the present invention comprises a polycarboxylic acids and a vinyl acetate polymer not in a merely mixed state but in a compatible state with each other, in which the polycarboxylic acids is substantially water-insolubilized. Hence, even being very thin, it exerts strong adhesion for an extended period of time without suffering degradation due to water absorption. Besides, the film can easily be deformed according to the form of the oral mucosa and adhered thereto simply by pressing because of its softness.

The oral bandage and oral preparations according to the present invention may solely comprise the adhesive film but may further comprise a soft film support in combination.

A composite comprising the adhesive film and a support can be produced by laminating the adhesive film on a soft film support in a usual manner, such as hot pressing or by the use of an adhesive. Alternatively, the lamination can be carried out simultaneously with the preparation of the adhesive film by casting the film-forming composition on a soft film support, followed by drying. The latter process has an advantage over the former in simplifying the production procedure since hot pressing or adhesion with an adhesive is unnecessary.

The soft film support which can preferably be used in the present invention is substantially impermeable to water. Such a support typically includes plastic films, such as polyethylene, polyvinyl acetate resin, an ethylene-vinyl acetate copolymer, polyvinyl chloride, polyurethane, etc., metal foils, such as aluminum foil, tin foil, etc., laminates of cloth or paper and a plastic film, and the like. Of these, plastic films are preferred in view of safety and feeling in use. A preferred thickness of the film support is from 10 to 100 μm in view of handling properties and freedom from a foreign feeling on use. A thickness of the composite film, i.e., a total thickness of the adhesive film and the film support, is preferably in the range of from 30 to 150 μm. If it is less than 30 μm, handling properties and operation properties are deteriorated. A thickness exceeding 150 μm is liable to give a foreign feeling on use.

When the oral bandage of the invention contains a topical drug to obtain an oral preparation as described before, the topical drug may be incorporated into the adhesive film and/or the above-described film support. In the latter case, incorporation of the drug can be carried out by kneading with a resin material for the support, mixing the drug in the form of its solution with a resin material, absorbing onto a support, impregnating into a support, or a like method.

The topical drug which can be used in the present invention may be either solid or liquid at room temperature as long as it may be incorporated into the adhesive film or the film support by dissolving or dispersing.

Specific examples of the topical drugs to be used in the present invention are adrenal corticosteroids, e.g., Triamcinolone acetonide, Dexamethasone, Betamethasone, Prednisolone, Fluocinolone, Hydrocortisone, Beclomethasone, etc. and salts thereof; anti-inflammatory agents, e.g., Flurbiprofen, Ibuprofen, Diclofenac, Indomethacin, Bendazac, Flufenamic acid, Bufezamac, Cyclospoline, Clidanac, Glycyrrhizin, Ketoprofen, Piroxicam, Pranoprofen, Benzydamine, Ibuprofenpiconol, Etofenamate, Lysozyme, Chymotrypsin, Epidihydrocholesterine, Hinokitiol, α-Amylase, Azulene, Chlorophllin, Cromoglic acid, Tranilast, Serratiopeptidase, Pronase, Glucanase, Lithospermi Radix extract, etc. and salts thereof; antimicrobial agents, e.g., Acrynol, Cetyl pyridinium, Chlorhexidine, Domifen, Iodine, Monensin, Sanginalline, Metronidazol, Dequalinium, Tetracycline, Minocycline, Ofloxacin, Penicilline, Doxycycline, Oxycycline, Cefatrizin, Nystatin, Clindamycin, Fradiomycin, sulfate, etc. and salts thereof; analgesics, e.g., Ethyl aminobenziate, Camphor, Eugenol, Dibucaine, Phenol, Menthol, Creosote, Diphenhydramine, Lidocaine, Tetracaine, Procaine, Cocaine, Piprocaine, Mepivacaine, Promoxin, Dicronin, Guaiacol, etc. and salts thereof; hemostatics, e.g., Tranexamic acid, ε-Aminocapronic acid, Alginic acid, Bioflavonoide, Ascorbic acid, Thrombin, oxidized Cellulose, Cetraxate, Epinephrine, Ferric chloride, Fibrinogen, Carbazochrome, Adrenochrome, etc. and salts thereof; vasodilators, e.g., Inositol hexanicotinate, Cyclanderate, Cinnarizine, Tolazoline, Acetylcholine, etc. and salts thereof; agents activaing cellular function, e.g., Solcoseryl, Proglumide, Sucralfate, Gefarnate, Nicametate, Glutamine, Aceglutamide aluminum, Ethylcysteine, Chitin, Tocopherol nicotinate, Ubidecarenone, etc. and salts thereof; antiviral agents, e.g., Aciclovir, Idoxuridine, Betrabin, Amantadine, etc. and salts thereof; agents affecting calcium metabolism, e.g., Vitamin D, Endotoxin, Hydroxyapatite, Collagen, Cataboline, 2-Chloroadenosine, Norcardia, Calcitriol, Prostaglandins for alveolar bone, Osteoclast activating factors for alveolar bone, Parathormone for alveolar bone, Calcitonine for alveolar bone, etc. and salts thereof; astringents, e.g., Tannin, Tanninc acid, Zinc fluoride, Sodium fluoride, Strontium fluoride, Potassium nitate, Stannous fluoride, Aluminum potassium sulfate, Berberine, Bismuth compounds, Strontium chloride, Aluminum lactate, etc. and salts thereof.

The amount of these topical drugs to be incorporated in the oral preparation varies depending on the kind thereof, but from considerations of pharmacological effects and adhesion to the mucous membrane, it usually ranges from 0.0001 to 35% by weight, and preferably from 0.0002 to 20% by weight, based on the preparation. When positive administration of the drug to the oral mucosa is expected, the drug is preferably present in the adhesive film side. In the treatment of bad breath, and the like, it may be prevent in the support side.

The composite film composed of the adhesive film and the support has enhanced strength while retaining the excellent adhesion of long duration. As an additional effect, the composite film can present adhesion of foreign matters, such as foods, onto the back side of the oral bandage or oral preparations. Further, use of a substantially water-impermeable support effectively prevents permeation of water through the back side to thereby prolong the duration of adhesion.

The adhesive film or support of the oral bandage or oral preparations according to the present invention may further contain other additives, such as coloring matters, flavoring materials, softening agents, and the like, as long as they do not impair adhesiveness or pharmacological effects. For example, when both the adhesive film and the support are colorless, incorporation of a coloring matter in one of them makes it easy to distinguish the surface or back of the bandage or preparation.

According to the present invention, both of the adhesive film and the composite film composed of the

adhesive film and a support are very soft and, when applied to the oral mucosa, absorb water in the oral cavity to get further softened. Therefore, they can be easily fitted to any site of the oral cavity to thereby produce strong adhesion for an extended period of time. The adhesive strength of the adhesive film or the composite film of the invention was measured using a crosslinked collagen swollen with water as a substitute for the oral mucosa at a peel angle of 180° and, as a result, was found to be from 25 to 200 g/2.5 cm-width. Adhesive strength smaller than 25 g/2.5 cm-width cannot ensure adhesion to the oral mucosa for a long period of time, and that greater than 200 g/2.5 cm-width is liable to injure the mucous membrane upon peeling. Taking these facts into account, the oral bandage or preparations according to the present invention can be reasonably regarded as exhibiting the optimum adhesive strength.

The above-described adhesive strength is naturally subject to variations depending on the kind of adherends. That is, the adhesive film exerts sufficient adhesion to mucous membranes, the teeth, the skin, cross-linked collagen films, and the like, with the adhesive strength being not impaired even when immersed in water. But the adhesive film scarcely shows adhesion to plastics material or regenerated cellulose film, and the adhesion thereto is very weak and rapidly disappears in water. This property is entirely favorable for storage of prodducts. No special moisture-proof packaging is needed because the products do not adhere to packaging materials, storage cases, etc. Further, it is not necessary to cut the oral bandage or oral preparations into small lengths for storage, and they can be formed in a tape and wound on a spool without sticking to each other. They may be stored as they are, but if there is a fear of contamination, the surface that is to be adhered can be protected with paper or a plastic film.

The oral bandage and oral preparations containing a basic substance for neutralization according to the present invention are highly safe from harm to the injured part of the oral cavity due to the irritant polycarboxylic acids which are dissolved out when applied to the injured parts. That is, the adhesive film of the invention containing no basic substance for neutralization may be applied to the skin of shaved guinea pigs, the eye mucous membrane of rabbits, the oral mucosa of healthy persons, etc. without causing any substantial irritation. However, irritation is noted when it is applied to the injured skin of a shaved guinea pig caused by stripping the corneum with an adhesive tape. To the contrary, the products containing a basic substance for neutralization cause substantially no irritation on such an injured skin as well as on the normal mucous membranes.

The oral bandages or preparations according to the present invention possess excellent water resistance attributed to substantial water-insolubilization of the polycarboxylic acids constituting the adhesive film so that they are only swollen but not degraded even when immersed in water. Therefore, they retain adhesiveness for a long period of time, generally 3 to 4 hours or even more, e.g., for one day, onto the oral mucosa.

Further, the oral preparations comprising the oral bandage of the invention having incorporated therein a topical drug are effective in producing pharmacological effects and very easy to handle since they can be adhered to the wet surface of affected parts of the oral cavity simply by pressing thereonto for the prevention or treatment of oral diseases.

This invention will now be illustrated in greater detail with reference to the following examples, are not intended to limit the present invention. In these examples, all the parts and percents are given by weight unless otherwise indicated.

EXAMPLE 1

Five parts of a carboxyvinyl polymer as a polycarboxylic acid and 5 parts of polyvinyl acetate (degree of polymerization: ca. 1,500) were poured in 90 parts of methanol as a common solvent, followed by mixing to form a uniform solution. The resulting solution was flow-casted on a release paper, dried, and peeled off to obtain an adhesive film having a thickness of 30 μm. The value A of this film was 31.3. The dissolution ratio of the polycarboxylic acid, that is a criterion of the compatible state, was 9%, indicating that the film had a compatible state.

The adhesive film thus prepared was laminated on 15 μm thick aluminium foil by hot pressing to obtain an oral bandage.

COMPARATIVE EXAMPLE 1

Five parts of polyvinyl acetate (degree of polymerization: ca. 1,500) were dissolved in 20 parts of toluene, and to the solution was added 5 parts of a toluene-insoluble carboxyvinyl polymer, followed by thoroughly stirring to prepare a uniform suspension. The suspension was then flow-casted on a release paper, dried, hot pressed and peeled off to obtain an adhesive film having a thickness of 30 μm. The

resulting film had the same value A as in Example 1 but a ratio of dissolution of the polycarboxylic acid of 67%, which indicated that the carboxylvinyl polymer and polyvinyl acetate were in a phase-separated state.

The adhesive film thus prepared was laminated on 15 μm thick aluminum foil by hot pressing to obtain an oral bandage.

COMPARATIVE EXAMPLE 2

Five parts of a carboxyvinyl polymer were dissolved in 45 parts of pure water. Separately, 5 parts of polyvinyl acetate (degree of polymerization: ca. 1,500) was dissolved in 20 parts of toluene. The both solutions were mixed and then stirred in a small-sized stirrer at 5,000 rpm for 3 minutes to obtain a suspension. The resulting suspension was flow-casted on a release paper, dried and peeled off to obtain an adhesive film having a thickness of 30 μm. The value A of this film was the same as in Example 1, but the dissolution ratio of the polycarboxylic acid was 79%, indicating that the carboxyvinyl polymer and polyvinyl acetate were in a phase-separated state.

The resulting film was laminated on 15 μm thick aluminum foil by hot pressing to obtain an oral bandage.

The compatible state of each of the samples obtained in the foregoing examples was evaluated by macroscopic observation to see the appearance of the film and also under an optical microscope to observe whether small independent regions of the polycarboxylic acid or polyvinyl acetate were formed or not. Formation of such small regions indicates phase separation.

Further, each of the samples was cut in a size of 5 x 5 cm, immersed in water at 37° C for 10 minutes, dried and weighed to determine weight reduction. The weight reduction (%) as an average of 10 runs was taken as a parameter of solubility of the film.

Furthermore, the dissolution ratio of the polycarboxylic acid after 2 hour- and 4-hour immersion in the same manner as described above for the dissolution ratio after 1 hr-immersion.

The results obtained are shown in Table 1 below. In Table 1, the solubility (weight reduction) is an average of 10 sample pieces. The dissolution ratio after 1 hr-immersion as measured in the foregoing examples is also shown in Table 1.

TABLE 1

	Example 1	Comparative Example 1	Comparative Example 2
Compatible State:			
Appearance	trans-parent	turbid	turbid
Formation of Small Regions	no small regions observed	small regions observed	small regions observed
Solubility (%)	0.1	6.9	7.7
Dissolution Ratio (%):			
1 Hr-Immersion	9	67	79
2 Hr-Immersion	10	-	-
4 Hr-Immersion	12	-	-

As is apparent from Table 1 above, in the adhesive film of Example 1, the polycarboxylic acid and polyvinyl acetate are in a good compatible state, making a contrast to those of Comparative Examples 1 and 2. In particular, the results of polycarboxylic acid dissolution ratios reveal that the most of the

polycarboxylic acid, an adhesive component, in the films of Comparative Examples 1 and 2 is dissolved out into water through immersion for one hour, whereas the dissolution ratio of the film of Example 1 after 1 hour-immersion is as low as 9%, which increases only to 12% even by immersion for 4 hours, said ratio showing no further increase through additional immersion, though not shown in Table 1. It can be seen from these results that a major proportion of the total amount of the dissolved polycarboxylic acid is dissolved out during the first one-hour immersion. The change in the proportion of the dissolved amount to the total dissolved amount with time is shown in Figure 1.

Then, the oral bandages obtained in the foregoing examples were subjected to adhesion test and peel test at a peel angle of 180° C in accordance with the following test methods.

Adhesion Test:

A sample was cut out round to a diameter of 10 mm. The cut piece was attached to a crosslinked collagen film swollen with water which was fixed on a phenolic resin plate and immersed in water at 37° C to observe the state of the film.

Peel Test:

A sample was cut into a strip of 2.5 cm in width and 15 cm in length. The strip was attached to a collagen film and immersed in water in the same manner as in the adhesion test, and a peel strength at a peel angle of 180° C was measured by means of a Schopper type tensile strength tester.

The results obtained are shown in Table 2 below.

TABLE 2

	Example 1	Comparative Example 1	Comparative Example 2
State of Film And Adhesion in Water	No change observed except a swelling of the periphery. Firmly adhered for 5 hrs.	Remarkable swelling from the periphery. Spontaneously separated from the adherend in 0.5 to 1.5 hrs.	Gradual swelling all over the film. Still adhered for 30 mins but with little adhesion. Spontaneously separated from the adherend in 1.5 to 2.0 hrs.
Peel Strength (g/2.5cm-width): Immersion Time:			
10 mins	110	12	20
30 mins.	105	unmeasurable	unmeasurable
60 mins.	95	"	"
120 mins.	85	"	"
240 mins.	90	"	"

As can be seen from Table 2, the samples of Comparative Examples 1 and 2 peel apart from the adherend in the early stage of immersion in water, becoming unmeasurable for peel strength when immersed for 30 minutes. On the contrary, the sample according to the present invention exhibits excellent adhesion in water, with its peel strength after 4 hour-immersion showing about 80% of the initial value. These results prove that the oral bandage of the present invention exerts strong adhesion of extremely long

duration.

EXAMPLE 2

A 10% methanolic solution of a carboxyvinyl polymer (CVP) and a 10% methanolic solution of polyvinyl acetate (PVAc) (degree of polymerization: ca. 2,500) were mixed at a CVP to PVAc ratio as shown in Table 3. The mixed solution was flow-casted on a release paper and dried to obtain an adhesive film having a thickness of 20 μm. The value A of each sample thus prepared is shown in Table 3.

The resulting film was laminated on a 50 μm thick film of polyvinyl acetate (degree of polymerization: ca. 2,500) by hot pressing to obtain an oral bandage.

Each of the samples thus obtained was determined for the dissolution ratio of the polycarboxylic acid (immersion time: 1 hour), adhesiveness in water and peel strength at a peel angle of 180° C after 10 minutes-immersion in accordance with the methods as described in Example 1. The adhesiveness in water was expressed in terms of the time until the sample was spontaneously separated from the adherend. These test results are shown in Table 3.

TABLE 3

Mixing Ratio (CVP:PVAc)	2:8	3:7	5:5	7:3	8:2
Value A	12.5	18.8	31.3	43.8	50.0
Dissolution Ratio (%)	2	5	8	22	35
Adhesion Time (hr)	>8	>8	>8	3.2	1.5
Peel Strength (g/2.5 cm-width)	20	60	110	160	200

It can be seen from Table 3 above that when the value A falls within the range of from 15 to 45 with the CVP:PVAc ratio being from 3:7 to 7:3, the films are excellent in both adhesion time and peel strength as well as in dissolution ratio of the polycarboxylic acid, indicating usefulness as an oral bandage. However, the film having a CVP:PVAc ratio of 2:8 has the value A smaller than 15 and shows poor adhesion. On the other hand, the film having a CVP:PVAc ratio of 8:2 has a short adhesion time and a high polycarboxylic acid dissolution ratio due to the value A exceeding 45. Accordingly, these films out of the scope of the present invention are regarded as hard to use with exceptions for special purposes of use.

EXAMPLE 3

Four parts of an alternating copolymer of methyl vinyl ether and maleic anhydride and 6 parts of polyvinyl acetate (degree of polymerization: ca. 1,000) were dissolved in 90 parts of methanol. The resulting solution was flow-casted on a release paper, dried at 80° C and peeled to obtain an adhesive film having a thickness of 60 μm. The value A of this film was 23.0, and the dissolution ratio (immersion time: 1 hour) was 12%.

The oral bandage thus obtained was cut into a circle having a diameter of 10 mm. The cut piece was adhered to the palatine mucosa of 10 panel members, and the time until the sample was separated apart (peeling time) was determined. As a result, the average peeling time was 4.0 hours.

EXAMPLE 4

Six parts of polyacrylic acid (degree of polymerization: ca. 5000) and 14 parts of partially saponified polyvinyl acetate (degree of saponification: 20 mol%; degree of polymerization: ca. 1,500) were dissolved in 80 parts of methanol, and the resulting solution was flow-casted on a release paper, dried at 80° C and

peeled off to obtain an adhesive film having a thickness of 70 μm. The value A of this film was 37.5, and the dissolution ratio of the polycarboxylic acid (immersion time: 1 hour) was 37%.

Separately, an ethylene-vinyl acetate copolymer (vinyl acetate content: 30 mol%) was hot-pressed to form a film support having a thickness of 80 μm. The above obtained adhesive film and the film support were laminated by the use of a hot laminator to produce an oral bandage.

The resulting oral bandage was cut in a strip of 7 mm in width and 20 mm in length. The cut piece was adhered to the gingival mucosa of 10 panel members, and the time until the strip was separated therefrom (peeling time) was measured. As a result, the average peeling time was 7.6 hours.

EXAMPLE 5

Four parts of a carboxyvinyl polymer and 6 parts of polyvinyl acetate (degree of polymerization: ca. 2,000) were dissolved in 92 parts of isopropanol, and 2 parts of titanium dioxide was added thereto as a coloring matter was added thereto, followed by thoroughly mixing with stirring. The mixture was flow-casted on a release paper, dried at 90° C and peeled off to obtain an adhesive film having a thickness of 15 μm. The value A of this film was 25, and the dissolution ratio of the polycarboxylic acid (immersion time: 1 hour) was 6%. Separately, 0.1 part of Food Red 3 aluminum lake was added to 100 parts of a 20% ethyl acetate solution of polyvinyl acetate (degree of polymerization: ca. 2,000), followed by thoroughly mixing while stirring. The mixture was flow-casted on a release paper, dried at 180° C and peeled off to prepare a film support having a thickness of 30 μm. The above prepared adhesive film and the film support were laminated by hot pressing to obtain an oral bandage.

The thus obtained oral bandage was cut in a circle having a diameter of 20 mm. The cut piece was adhered to the buccal mucosa of 10 panel members, and the time until the bandage was separated therefrom (peeling time) was determined. As a result, an average peeling time was 5.6 hours.

The performance of the oral bandage to prevent running-off of a drug administered was evaluated using a food dye as a model of a drug and a crosslinked collagen film swollen with water as an adherend as follows. That is, 9.5 parts of lactose and 5 parts of Food Red 102 were ground in a mortar, and the mixture was pounched out into tablets of 5.0 mm in diameter and 0.5 mm in thickness. One of the tablets was placed on a water-swollen crosslinked collagen film that was fixed on a phenolic resin plate, and the oral bandage cut round to a diameter of 15 mm was adhered thereonto so as to cover the tablet. The sample was then immersed in water at 37° C. As a result, the time required for the dye in the tablet to be dissolved out into water was 4.1 hours as an average of 10 runs, indicating a sufficient performance property to prevent running-off of a drug administered.

Thereafter, the storage stability of the oral bandage was evaluated as follows. The oral bandage was cut in a tape of 18 mm in width and 3 m in length. The tape was rolled up, wrapped with a cellophane film, packed in a paper box of 6 cm x 6 cm x 2 cm and preserved under ambient conditions for 3 months. As a result, no change in shape or adhesion properties was noted, to confirm excellent storage stability of the oral bandage.

EXAMPLE 6

Three parts of a carboxyvinyl polymer, 2 parts of a methyl vinyl ether-maleic anhydride copolymer and 5 parts of polyvinyl acetate (degree of polymerization: ca. 2,000) were dissolved in 90 parts of methanol. The resulting mixed solution was flow-casted on a release paper, dried at 60° C and peeled off to obtain an adhesive film having a thickness of 15 μm. The value A of this film was 30.3, and the dissolution ratio of the polycarboxylic acid (immersion time: 1 hour) was 10%.

The thus obtained film was laminated on a 30 μm thick film support of polyvinyl acetate (degree of polymerization: ca. 1,500) by hot pressing to obtian an oral bandage.

The resulting oral bandage was cut round to a diameter of 10 mm, adhered to the gingival mucosa of 10 panel members, and the time until the bandage was separated therefrom (peeling time) was measured. As a result, the peeling time was 5.4 hours in average.

EXAMPLE 7

Into 90 parts of methanol were poured 4.7 parts of a carboxyvinyl polymer and 4.7 parts of polyvinyl acetate (degree of polymerization: ca. 1,500), and 0.6 part of diisopropanolamine was further added thereto, followed by mixing to form a uniform solution. The resulting solution was flow-casted on polyethylene-laminated paper dried in a drier at 80° C for 8 minutes and peeled off to prepare an adhesive film having a

thickness of 40 μm. The value A of this film was 31, and the dissolution ratio of the polycarboxylic acid was 12%, which value indicated the compatible state of the film.

The thus obtained adhesive film was laminated on a 40 μm polyvinyl acetate film (degree of polymerization: ca. 2,000) by hot pressing at 100 ° C to obtain an oral bandage.

COMPARATIVE EXAMPLE 3

In 30 parts of toluene were dissolved 4.7 parts of polyvinyl acetate (degree of polymerization: ca. 1,500) and 0.6 parts of diisopropanolamine, and 5 parts of a toluene-insoluble carboxyvinyl polymer powder was added to the solution, followed by sufficiently mixing while stirring to prepare a uniformly dispersed suspension. The resulting suspension was flow-casted on polyethylene-laminated paper dried in a drier at 100 ° C for 10 minutes and peeled off to obtain an adhesive film having a thickness of 40 μm. The value A of this film was equal to that of the adhesive film of Example 7, but the dissolution ratio of the polycarboxylic acid was 72%, indicating that the carboxyvinyl polymer and the polyvinyl acetate were in a phase-separated state.

The adhesive film thus obtained was laminated on a 40 μm thick polyvinyl acetate film by hot pressing at 100 ° C in the same manner as in Example 7 to obtain an oral bandage.

COMPARATIVE EXAMPLE 4

In 45 parts of pure water were dissolved 4.7 parts of a carboxyvinyl polymer and 0.6 part of diisopropanolamine. Separately, 4.7 parts of polyvinyl acetate (degree of polymerization: ca. 1,500) was dissolved in 30 parts of toluene. The two solutions were mixed and stirred in a small-sized stirrer at 5,000 rpm for 5 minutes to prepare a suspension. The resulting suspension was flow-casted on polyethylene-laminated paper, dried in a drier at 100 ° C and peeled off to obtain an adhesive film having a thickness of 40 μm. The value A of this film was equal to that of the film of Example 7, but the dissolution ratio of the polycarboxylic acid was 77%, indicating that the carboxyvinyl polymer and the polyvinyl acetate were in a phase-separated state.

The film thus obtained was laminated on a 40 μm thick polyvinyl acetate film by hot pressing at 100 ° C in the same manner as in Example 7 to obtain an oral bandage.

Each of the samples obtained in Example 7 and Comparative Examples 3 and 4 was evaluated for the compatible state, the adhesiveness (adhesion time) and the peel strength. The compatible state was observed in the same manner as in Example 1, and the adhesiveness and peel strength were determined in the same manner as in Example 2. Further, each sample cut round to a diameter of 10 mm was adhered to the palatine mucosa of 5 healthy male panel members, and the time until the sample was separated therefrom was measured. The adhesion was effected after lunch, and the panel members were allowed to drink and talk, ad lib. The results obtained are shown in Table 4 below.

TABLE 4

	Example 7	Comparative Example 3	Comparative Example 4
Compatible State:			
Appearance	trans-parent	turbid	turbid
Formation of Small Regions	no small regions observed	small regions observed	small regions observed
Adhesiveness (Adhesion Time) (min)	185[1)]	70[2)]	55[2)]
Peel Strength (g/2.5 cm-width)	35	10	12
Peeling Time (min)	210	25	40

Note: 1): Strong adhesion was retained for 60 minutes.

2): Only slight adhesion was noted with insubstantial adhesive strength after 60 minutes.

As is apparent from the results of Table 4, the polycarboxylic acid and the polyvinyl acetate in the film of Example 7 are in a good compatible state, making a contrast to the films of Comparative Examples 3 and 4. More specifically, the films of Comparative Examples 3 and 4 are separated from the adherend in the early stage of the adhesion test and undergo great reduction in adhesion through immersion in water for 10 minutes in the peel test. Further, these comparative samples are separated from the adherend in the test using a panel. To the contrary, the oral bandage according to the present invention exhibits excellent results in the adhesion test, peel test and panel test, demonstrating strong adhesion of long duration.

COMPARATIVE EXAMPLE 5

In order to ascertain high safety of the oral bandage of the present invention, a comparative adhesive film containing no diisopropanolamine was prepared as follows.

Carboxyvinyl polymer	5.0 parts
Polyvinyl acetate (degree of polymerization: ca. 2,000)	5.0 parts
Methanol	90.0 parts

The above components were mixed while stirring to prepare a uniform solution. The solution was flow-casted on polyethylene-laminated paper, dried in a drier at 80° C for 8 minutes and peeled off to obtain an

adhesive film having a thickness of 40 μm. The resulting film was laminated on a 40 μm thick polyvinyl acetate film (degree of polymerization: ca. 2,000) by hot pressing at 100 °C to obtain a comparative oral bandage.

Irritation of the oral bandage as obtained in Example 7 on the normal skin and injured skin of a guinea pig was determined as compared with the above obtained comparative sample in accordance with the following test method.

The back of female Hartley guinea pigs (body weight: 300 to 400 g) was shaved with an electric clipper and an electric shaver to expose the normal skin. An adhesive tape was attached to the normal skin followed by peeling 7 times, whereby the stratum corneum was removed therefrom to form injured skin.

The sample was cut round to a diameter of 10 mm, dipped in water and adhered to each of the normal skin and the injured skin. The adhered sample was covered with absorbent cotton and further closely covered thereon with an adhesive tape for tight covering. Six hours later, the sample was removed, and irritation score was judged after 1 hour and 24 hours from the removal according to the following four grades:

0 : No change
0.5: Slight Erythema
1 : Moderate Erythema
2 : Severe erythema with edema

The results obtained are shown in Table 5 below. Each score shown in Table 5 is an average of 6 runs.

TABLE 5

	Normal Skin		Injured Skin	
	1 Hr	24 Hrs	1 Hr	24 Hrs
Example 7	0.3	0.3	0.5	0.5
Comparative Example 5	0.3	0.4	0.4	2.0
Non-Treated Group	0.1	0.2	0.2	0.3

The results of Table 5 above demonstrate that the sample according to the present invention causes no irritation on not only the normal skin but the injured skin as compared with the comparative sample, although there is no difference in irritation on the normal skin between the sample of the invention and the comparative sample.

EXAMPLE 8

Carboxyvinyl polymer	8.0 parts
Polyvinyl acetate (degree of polymerization: ca. 1,500)	2.0 parts
ZnO	3.6 parts
Methanol	26.4 parts

The above components were kneaded to obtain a uniform mixture. The mixture was flow-casted on polyethylene-laminated paper having been subjected to releasability-imparting treatment, dried in a drier at 100 °C for 3 minutes and peeled off to obtain an adhesive film having a thickness of 10 μm. The value A of this film was 50. The resulting film was then laminated on a 40 μm thick film of a mixture of polyvinyl acetate (degree of polymerization: ca. 800) and polybutene (95:5) by hot pressing at 100 °C to obtain an oral bandage.

The sample was evaluated for peel strength, peeling time (panel test) and irritation on the injured skin in the same manner as for the sample of Example 7. The results obtained are as follows:

Peel Strength: 60 g/2.5 cm-width
Peeling Time: 186 minutes
Irritation Score: 0.6

EXAMPLE 9

Carboxyvinyl polymer	3.4 parts
Polyvinyl Acetate (Degree of polymerization: ca. 1,000)	8.4 parts
Sodium citrate ($Na_3C_6H_5O_7$)	0.2 part
Methanol	71.0 parts
Pure water	17.0 parts

The above components were mixed to obtain a uniform solution, and the solution was flow-casted on a polyethylene terephthalate film, dried in a drier at 80° C for 15 minutes and peeled off to obtain an adhesive film having a thickness of 80 μm. The value A of this film was 18. The resulting film was then laminated on 15 μm thick aluminum foil by hot pressing at 100° C to obtain an oral bandage.

The sample was evaluated for peel strength, peel time (panel test) and irritation on the injured skin in the same manner as for the sample of Example 7. The results obtained are as follows:

Peel Strength: 25 g/2.5 cm-width
Peeling Time: 258 minutes
Irritation Score: 0.3

EXAMPLE 10

Methyl vinyl ether/maleic anhydride alternating copolymer	4.0 parts
Polyvinyl acetate (degree of polymerization: ca. 1,500)	6.0 parts
Sodium hydroxide	0.5 part
Methanol	67.5 parts
Ethyl acetate	22.0 parts

The above components were mixed to prepare a uniform solution, and the solution was flow-casted on 15 μm thick aluminum foil and dried in a drier at 60° C for 15 minutes to obtain a composite oral bandage having a total thickness of 35 μm. The value A of the adhesive film constituting the composite oral bandage was 23.

The sample was evaluated for peel strength, peeling time (panel test) and irritation on the injured skin in the same manner as for the sample of Example 7. The results obtained are as follows:

Peel Strength: 54 g/2.5 cm-width
Peeling Time: 222 minutes
Irritation Score: 0.5

EXAMPLE 11

Polyacrylic acid	7.0 part
Saponified polyvinyl acetate (saponification degree: 20 mol%)	3.0 parts
ZnO	0.8 part
Methanol	89.2 parts

The above components were mixed to prepare a uniform solution. The solution was flow-casted on polyethylene-laminated paper, and dried in a drier at 80° C for 10 minutes to obtain a composite oral bandage having a thickness of 50 μm. The value A of the adhesive film constituting the composite was 44.

The sample was evaluated for peel strength, peeling time (panel test) and irritation on the injured skin in the same manner as for the sample of Example 7. The results obtained are as follows:

Peel Strength: 70 g/2.5 cm-width
Peeling Time: 166 minutes
Irritation Score: 1.0

EXAMPLE 12

Carboxyvinyl polymer	4.0 parts
Polyvinyl acetate (degree of polymerization: ca. 2,000)	6.0 parts
Diisopropanolamine	0.7 part
ZnO	1.4 parts
Methanol	87.9 parts

The above components were mixed to prepare a uniform solution. The solution was flow-casted on a polyethylene terephthalate film, dried in a drier at 80° C for 15 minutes and peeled off to obtain an adhesive film having a thickness of 30 μm. The value A of this film was 25.

Polyvinyl acetate (degree of polymerization: ca. 2,000)	80.0 parts
Titanium white	19.5 parts
Food Red 3 aluminum lake	0.5 part

The above components were mixed and formed into a film of 30 μm in thickness, and the above prepared adhesive film was laminated thereon by hot pressing at 100° C to obtain an oral bandage.

The resulting sample was evaluated for peel strength, peeling time (panel test) and irritation on the injured skin in the same manner as for the sample of Example 7. The results obtained are as follows:

Peel Strength: 35 g/2.5 cm-width
Peeling Time: above 300 minutes
Irritation Score: 0.4

EXAMPLE 13

Carboxyvinyl polymer	3.0 parts
Methyl vinyl ether/maleic anhydride alternating copolymer	2.0 parts
Polyvinyl acetate (degree of polymerization: ca. 1,500)	4.3 parts
Triethanolamine	0.7 part
Methanol	80.0 parts
Pure water	10.0 parts

The above components were mixed to prepare a uniform solution. The solution was flow-cast on polyethylene-laminated paper, dried in a drier at 80 °C for 10 minutes and peeled off to obtain an adhesive film having a thickness of 25 μm. The value A of this film was 33.

The resulting film was laminated on a 30 μm thick polyvinyl acetate film (degree of polymerization: ca. 1,500) by hot pressing at 100 °C to obtain an oral bandage.

The resulting sample was evaluated for peel strength, peeling time (panel test) and irritation on the injured skin in the same manner as for the sample of Example 7. The results are as follows:

Peel Strength: 42 g/2.5 cm-width
Peeling Time: 190 minutes
Irritation Score: 0.4

EXAMPLES 14 to 19

Oral preparations comprising an adhesive film or a composite of an adhesive film and a support, in which the adhesive film and/or the support contained a topical drug as shown in Table 6 below, were prepared using the materials shown in Table 6. In each example, the adhesive film and the support were prepared in the same manner as described in the corresponding example shown in the column of "material" in Table 6 except for film thickness.

TABLE 6

Example No.	Adhesive Film			Support		
	Material	Drug and Its Content (wt%)	Thickness (μm)	Material	Drug and Its Content (wt%)	Thickness (μm)
14	Example 1	Mepivacaine 5	30	Example 1	-	15
15	Example 2 (CVP/PVAc= 5/5)	-	20	Example 2	Cetylpyridinium chloride 2 ℓ-Menthol 3	50
16	Example 3	Lithospermi Radix extract	60	PVAc*	-	30
17	Example 4	Chlorhexidine-hydrochloride 2	100	-	-	-
18	Example 5	Predonisolone 0.2	40	Example 5	-	30
19	Example 6	Sodium azulene-sulfonate 0.5	20	Example 6	-	30

Note: *: Polyvinyl acetate having a degree of polymerization of about 2,000.

EXAMPLES 20 to 37

Oral preparations comprising an adhesive film and a support, in which the adhesive film or both the adhesive film and the support contained a topical drug as shown in Table 7 below, were prepared using the film materials shown in Table 7. In each example, the adhesive film and the support were prepared in the same manner as described in the corresponding example shown in the column of "material" in Table 7 except for film thickness.

TABLE 7

Example No.	Adhesive Film			Support		
	Material	Drug and Its Content (wt%)	Thickness (μm)	Material	Drug and Its Content (wt%)	Thickness (μm)
20	Example 7	Triamcinolone acetonide 0.05	30	Example 7	-	40
21	Example 7	Dipotassium glycyrrhetinate 1.0	30	Example 7	-	40
22	Example 7	Fradiomycin sulfate 1.0 Hydrocortisone acetate 0.5	30	Example 7	-	40
23	Example 7	Ethyl aminobenzoate 10.0	30	Example 7	-	40
24	Example 7	Tocopherol nicotinate 2.0 Cetylpyridinium chloride 0.2	30	Example 7	-	40
25*	Example 8	Tetracycline hydrochloride 3	20	Example 8	-	30
26*	Example 8	Strontium chloride 5	20	Example 8	-	30
27*	Example 8	Tranexamic acid 0.1	20	Example 8	-	30

* Dried at 70°C for 15 minutes

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TABLE 7 (cont'd)

Example No.	Adhesive Film: Material	Adhesive Film: Drug and Its Content (wt%)	Adhesive Film: Thickness (μm)	Support: Material	Support: Drug and Its Content (wt%)	Support: Thickness (μm)
28	Example 9	Dexamethasone 0.1	60	Example 9	-	9
29	Example 9	Sodium fluoride 5	60	Example 9	-	9
30	Example 9	Lysozyme chloride 0.5	60	Example 9	-	9
31	Example 11	Lidocaine 5	50	Ethylene-vinyl acetate copolymer (vinyl acetate content: 28 wt%)	-	60
32	Example 12	Aluminum lactate 5	60	Example 12	-	30
33	Example 13	Dibucaine hydrochloride 0.5	30	Example 13	Dibucaine hydrochloride 0.5	30
34	Example 13	Dequalinium hydrochloride 2	30	Example 13	Dequalinium hydrochloride 2	30
35	Example 13	Calcitriol 0.001	40	Example 13	-	30
36	Example 13	1α,(OH)-vitamin D_3 0.005	40	Example 13	-	30
37	Example 13	1α,24(R)-(OH)$_2$-vitamin D_3 0.005	40	Example 13	-	30

The effects of the oral preparations obtained in Example 14 to 37 were evaluated by the following clinical examples.

CLINICAL EXAMPLE 1

Effect on Stomatitis

A patient (50-year-old, female) suffered from stomatitis of 5 mm in diameter on her buccal mucosa. The oral preparation of Example 20 was applied on the affected part three times a day. The inflammation subsided on the third day.

CLINICAL EXAMPLE 2

Effect on Stomatitis

A patient (27-year-old, male) with stomatitis of 6 mm in diameter on his gingival mucosa had much pain at meals. The oral preparation of Example 3 was prescribed to him with a direction to apply to the affected part at meals. He had no pain on the injured site during a meal.

CLINICAL EXAMPLE 3

Effect on the injured site by toothbrushing

A patient (8-year-old, female) had a injured site on her gingival mucosa due to brushing with a toothbrush. The oral preparation of Example 21 was applied to the injured part three times a day, while toothbrushing instructions were given to the patient. The wound healed on the 2nd day.

CLINICAL EXAMPLE 4

Effect on Halitosis

A patient (21-year-old, female) complained of bad breath. Ten oral bandages of Example 15 were prescribed to her with directions to apply to the cervix dentis of the jaw twice a day. On re-examination after 1 week, subjective symptoms disappeared.

CLINICAL EXAMPLE 5

Prophylactic Effect on Infection

⌊456 Flap operation was performed on a patient (39-year-old, male) with adult periodontitis having deep pockets. The oral preparation of Example 22 was applied on the operated part, and a pack was further applied thereon. When the pack was removed on the third day, granulation was found to be normal. The patient further received only the oral preparation twice a day for 4 days, and the postoperative course was uneventful.

CLINICAL EXAMPLE 6

Effect on Periodontal Disense

The oral preparation of Example 24 was applied to ⌊345 of a patient (45-year-old, male) with adult periodentitis having deep pockets once a day for 4 weeks. As a control, ⌊345 were not treated with the oral preparation.

As a result, in the treated part, the gingival index decreased from 2 to 1 and the pocket depth decreased from 5.5 mm to 4.0 mm. On the other hand, almost no improvement of symptoms was noted in the control part.

CLINICAL EXAMPLE 7

Effect on Dentin Hyperesthesia

A patient (36-year-old, female) complained of dentin hyperesthesia accompanied by sharp pain in ⌊4. Thirty units of the oral preparation of Example 26 were prescribed to her with a direction to apply to the affected part twice a day.

On re-examination after 3 weeks, the symptoms completely disappeared.

CLINICAL EXAMPLE 8

Effect on dentin hyperesthesia

A patient (56-year-old, female) complained of dentin hyperesthesia accompanied by sharp pain in ⌊2. The oral preparation of Example 9 were applied to the affected part twice a day.

On re-examination after four weeks, the symptoms completely disappered.

CLINICAL EXAMPLE 9

Local Anesthetic Effect

The oral preparation of Example 31 was preoperatively applied to the gingiva of a patient (41-year-old, female) with proliferative gingivitis. Thereafter, gingivectomy was performed on the patient, but the patient experienced neither pain during the operation nor paresthesia in the part where the oral preparation was not administered. Further, the postoperative course was uneventful.

Claims

1. An oral bandage comprising a soft adhesive film consisting of a mixture of (a) an acrylic acid polymer, methacrylic acid polymer and/or maleic anhydride polymer and (b) a vinyl acetate polymer, the polymers (a) and (b) being uniformly dissolved in each other without regions of phase separation, so as to be substantially water-insolubilized; and optionally a basic substance capable of neutralizing said polymers (a).

2. An oral bandage as claimed in Claim 1, wherein the weight ratio of the polymer(s) (a) to polymer (b) in the film is such that the value obtained from the following formula is from 15 to 45:

$$\frac{(\text{weight of } -COOH) + \frac{5}{4}(\text{Weight of } -CO-O-CO-)}{\text{Total weight of polymers (a) and (b)}} \times 100$$

3. An oral bandage as claimed in Claim 1 or 2, wherein said vinyl acetate polymer has an average molecular weight determined by viscosity of at least 60,000.

4. An oral bandage as claimed in any preceding claim, wherein said acrylic or methacrylic polymer contains 20% by weight or more of -COOH group and said maleic anhydride polymer contains 16% by weight or more of -CO-O-CO- group.

5. An oral bandage as claimed in any preceding claim, wherein said mixture was obtained by dissolving the polymers (a) and (b) in a solvent common to both.

6. An oral bandage as claimed in Claim 5, wherein said solvent is selected from lower alcohols, mixtures of a lower alcohol in a larger proportion and a compatible organic solvent, mixtures of a lower alcohol in a larger proportion and water, and mixtures of a lower alcohol in a larger proportion, a compatible organic solvent and water.

7. An oral bandage as claimed in Claim 6, wherein said mixture of a lower alcohol and an organic solvent contains not more than 30% by weight of the organic solvent.

8. An oral bandage as claimed in Claim 6, wherein said mixture of a lower alcohol and water or of a lower alcohol, an organic solvent and water contains not more than 30% by weight of water.

9. An oral bandage as claimed in any preceding claim wherein said basic substance (c) is at least one salt or base.

10. An oral bandage as claimed in Claim 9, wherein said basic substance is a monovalent metal salt or monovalent base and is present in an amount of from 0.03 to 0.2 equivalent based on the said

polymers (a).

11. An oral bandage as claimed in any preceding claim, wherein said oral bandage further comprises a soft film support.

12. An oral preparation comprising an oral bandage as defined in any preceding claim and a topical drug incorporated therein.

Revendications

1. Emplâtre pour la cavité buccale comprenant un film adhésive souple consistant en un mélange de (a) un polymère d'acide acrylique, un polymère d'acide méthacrylique et/ou un polymère d'anhydride maléique et (b) un polymère d'acétate de vinyle, les polymères (a) et (b) étant uniformément dissous l'un dans l'autre sans régions de séparation de phase de manière à être substantiellement rendus insolubles dans l'eau, et à choix une substance basique capable de neutraliser les dits polymères (A).

2. Emplâtre buccal selon la revendication 1, dans lequel le rapport du poids du/des polymère(s) (a) au polymère (b) dans le film est tel que la valeur obtenue par la formule ci-jointe va de 15 à 45:

$$\frac{(\text{poids du } -COOH) + \frac{5}{4}(\text{poids du } -CO-O-CO-)}{\text{poids total des polymères (a) et (b)}} \times 100$$

3. Emplâtre buccal selon la revendication 1 ou 2, dans lequel le dit polymère d'acétate de vinyle a un poids moléculaire moyen déterminé par la viscosité d'au moins 60'000.

4. Emplâtre buccal selon l'une quelconque des revendications précédentes, dans lequel le dit polymère acrylique ou méthacrylique contient 20% en poids ou plus du groupe -COOH et le dit polymère d'anhydride maléique contient 16% en poids ou plus du groupe -CO-O-CO.

5. Emplâtre buccal selon l'une quelconque des revendications précédentes, dans lequel le dit mélange a été obtenu par dissolution des polymères (a) et (b) dans un solvant qui leur est commun à tous deux.

6. Emplâtre buccal selon la revendication 5, dans lequel le dit solvant est sélectionné parmi les alcools inférieurs, les mélanges d'un alcool inférieur dans une proportion plus grande et d'un solvant compatible, les mélanges d'un alcool inférieur dans une proportion plus grande et d'eau, et les mélanges d'un alcool inférieur dans une portion plus grande, d'un solvant organique compatible et d'eau.

7. Emplâtre buccal selon la revendication 6, dans lequel le dit mélange d'un alcool inférieur et d'un solvant organique ne contient pas plus de 30% en poids de solvant organique.

8. Emplâtre buccal selon la revendication 6, dans lequel le dit mélange d'un alcool inférieur et d'eau ou d'un alcool inférieur, d'un solvant organique et d'eau ne contient pas plus de 30% en poids d'eau.

9. Emplâtre buccal selon l'une quelconque des revendication précédentes, dans lequel la substance basique (c) est au moins un sel ou une base.

10. Emplâtre buccal selon la revendication 9, dans lequel la dite substance basique est un sel de métal monovalent ou une base monovalente et est présente dans une quantité allant de 0,03 à 0,2 équivalente sur la base des dits polymères (a).

11. Emplâtre buccal selon l'une des revendications précédentes, dans lequel le dit emplâtre buccal comprend de plus un support souple de film.

12. Préparation pour la cavité de la bouche comprenant un emplâtre buccal selon l'une quelconque des revendications précédentes et un médicament topique qui lui est incorporé.

Patentansprüche

1. Oraler Verband, enthaltend einen weichen Klebefilm, bestehend aus einer Mischung von (a) einem Acrylsäurepolymer, Methacrylsäurepolymer und/oder Maleinanhydridpolymer und (b) einem Vinylacetatpolymer, wobei die Polymere (a) und (b) einheitlich ineinander aufgelöst sind, ohne Zonen von Phasentrennung, so dass sie im wesentlichen wasserinsolubilisiert sind; und gegebenenfalls eine basische Substanz, die fähig ist, die genannten Polymere (a) zu neutralisieren.

2. Oraler Verband gemäss Anspruch 1, worin das Gewichtsverhältnis des (der) Polymer(e) (a) zu Polymer (b) im Film so ist, dass der Wert, der von folgender Formel erhalten wird, 15 bis 45 ist:

$$\frac{\text{(Gewicht von -COOH)} + \frac{5}{4}\text{ (Gewicht von -CO-O-CO)}}{\text{Gesamtgewicht der Polymere (a) und (b)}} \times 100$$

3. Oraler Verband gemäss Anspruch 1 oder 2, worin das genannte Vinylacetatpolymer ein mittleres durch Viskosität bestimmtes Molekulargewicht von mindestens 60'000 besitzt.

4. Oraler Verband gemäss einem der vorhergehenden Ansprüche, worin das genannte Acryl- oder Methacrylpolymer 20 Gew.-% oder mehr -COOH-Gruppen aufweist und das genannte Maleinanhydridpolymer 16 Gew.-% oder mehr -CO-O-CO-Gruppen aufweist.

5. Oraler Verband gemäss einem der vorhergehenden Ansprüche, worin die genannte Mischung durch Auflösen der Polymere (a) und (b) in einem für beide üblichen Lösungsmittel erhalten wurde.

6. Oraler Verband gemäss Anspruch 5, worin das genannte Lösungsmittel ausgewählt ist aus niederen Alkoholen, Mischungen von niederen Alkohlen in einem grösseren Anteil und einem verträglichen organischen Lösungsmittel, Mischungen eines niederen Alkoholes in einem grösseren Anteil und Wasser, Mischungen eines niederen Alkoholes in einem grösseren Anteil, einem verträglichen organischen Lösungsmittel und Wasser.

7. Oraler Verband gemäss Anspruch 6, worin die genannte Mischung eines niederen Alkohols und einem organischen Lösungsmittel nicht mehr als 30 Gew.-% des organischen Lösungsmittels enthält.

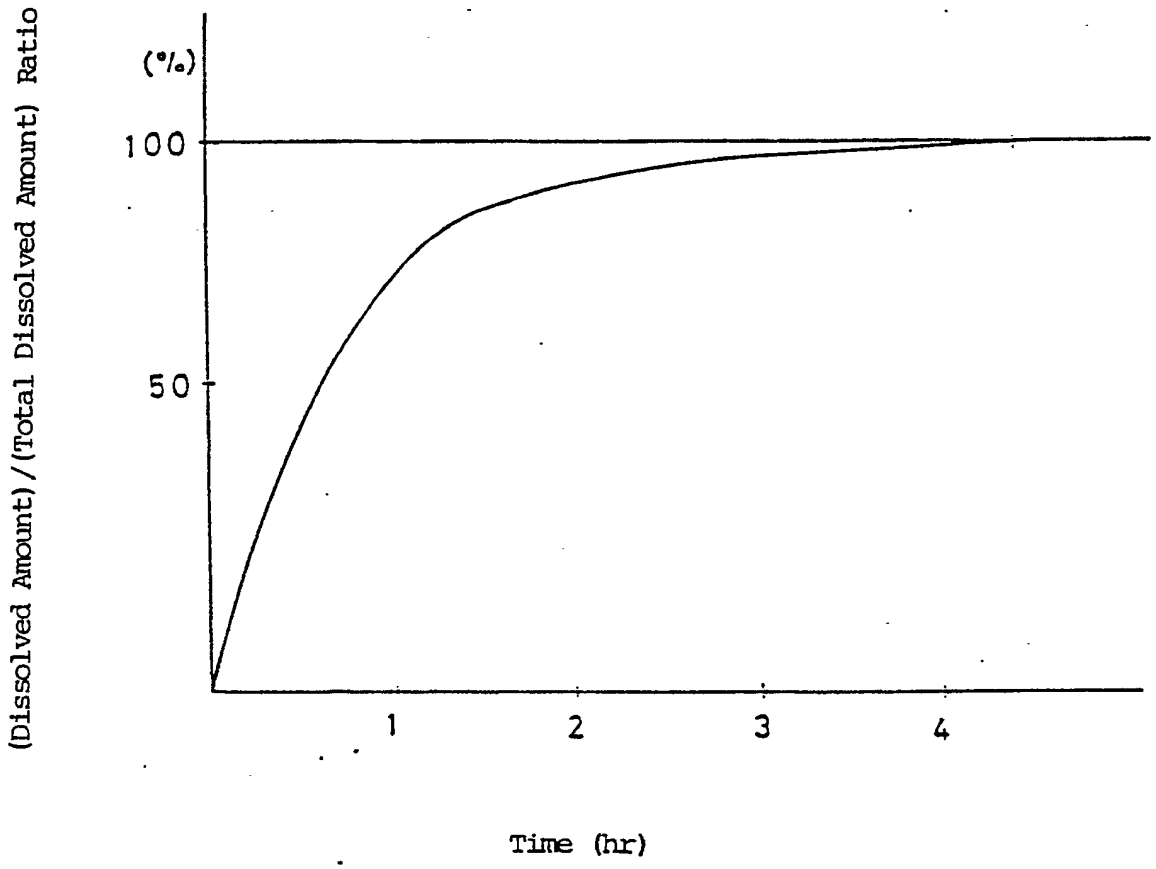
8. Oraler Verband gemäss Anspruch 6, worin die genannte Mischung eines niederen Alkohols und Wasser oder eines niederen Alkohols, eines organischen Lösungsmittels und Wasser nicht mehr als 30 Gew.-% Wasser enthält.

9. Oraler Verband gemäss einem der vorhergehenden Ansprüche, worin die genannte basische Substanz (c) mindestens ein Salz oder eine Base ist.

10. Oraler Verband gemäss Anspruch 9, worin die genannte basische Substanz ein monovalentes Metallsalz oder eine monovalente Base ist und in einem Anteil von 0,03 bis 0,2 Aequivalenten auf Basis des genannten Polymers (a) vorhanden ist.

11. Oraler Verband gemäss einem der vorhergehenden Ansprüche, worin der genannte orale Verband im weiteren einen weichen Trägerfilm aufweist.

12. Orale Zubereitung, enthaltend einen oralen Verband gemäss der Definition eines der vorhergehenden Ansprüche und eines einverleibten topischen Medikamentes.



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(54) **Verfahren zur Herstellung einer Darreichungs- und Dosierungsform für Arzneimittel-Wirkstoffe, Reagentien oder andere Wirkstoffe.**

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Beschreibung

Arzneimittel können in Form von Pulvern, Tropflösungen oder Säften oral verabreicht werden. Da bei diesen Abgabeformen eine genaue Dosierung jedoch schwierig ist, werden vom Hersteller dosierte Applikationsformen wie Tabletten, Dragees oder Kapseln generell bevorzugt. Auch Reagentien und andere Wirkstoffe, z.B. Süßstoffe oder Aromastoffe, werden für eine genaue dosierte Anwendung häufig tablettiert. Die Herstellungstechnik für Tabletten, Dragees, Kapseln und dergleichen ist zwar weitgehend ausgereift, doch sind eine Reihe von systembedingten Nachteilen nicht zu übersehen.

Für niedrig dosierte Wirkstoffe muß ein großer Anteil an Hilfsstoffen zugesetzt werden, um zu einer handhabbaren Größe der Einzeldosis zu gelangen. Weiterhin ist eine genaue Kennzeichnung einzelner Tabletten oder Dragees praktisch nicht möglich. Es haben sich deshalb Durchdrückpackungen durchgesetzt, welche eine Mehrzahl von Tabletten, Dragees oder auch Kapseln enthalten und welche mit den notwendigen Informationen, insbesondere dem Namen des Präparates bedruckt sind. Die Herstellung solcher Verpackungen erfordert naturgemäß einen zusätzlichen Arbeitsgang und es werden Umverpackungen in Form von Faltschachteln benötigt, welche ein beträchtliches Leervolumen aufweisen und dadurch zusätzlich Lagerraum beanspruchen. Ein besonders gravierender Nachteil von Dragees und Kapseln besteht darin, daß eine Zerteilung praktisch unmöglich ist, die kleinste Dosis somit vorgegeben ist. Auch bei Tabletten ist eine genaue Zerteilung schwierig, lediglich größere Tabletten mit einer Kerbe als Sollbruchstelle lassen sich allenfalls teilen, wobei häufig ungleichgroße Bruchstücke entstehen.

Es sind bereits Versuche zur Schaffung einer neuen Darreichungsform für die orale Verabreichung von Arzneimitteln bekannt geworden, welche aus wirkstoffhaltigen Folien bestehen. Gemäß der BE-A 637 363 wird ein papierartiges Trägermaterial aus unlöslichen Zellulosefasern mit einer Wirkstofflösung getränkt bzw. durch Auftragen oder -streuen beschichtet und eine Dosierung durch Perforation der Trägerfolie nach Art eines Briefmarkenbogens erreicht. Die Wirkstoffdosierung ist dabei zwangsläufig äußerst ungenau. Aus den DE-A 2 432 925 und DE-A 2 449 865 ist es bekannt, Arzneimittelwirkstoffe in Folienbildner einzuarbeiten, bei denen es sich vorzugsweise um wasserlösliche Verbindungen wie Methyl- und Ethylzellulose, insbesondere aber Hydroxypropylzellulose, Hydroxyethylzellulose oder Methylhydroxypropylzellulose handelt. Daneben können die Folien Füllstoffe und Trennmittel enthalten. Die DE-A 2 746 414 beschreibt ebenfalls die Verarbeitung von wirkstoffhaltigen Folienmassen auf Basis von beispielsweise Gelatine oder Zellulosederivaten und weiteren Zusätzen wie Stärke zu Folien, in die der Wirkstoff eingearbeitet ist. Die erhaltenen wirkstoffhaltigen Folien lassen sich zur Dosierung durch Perforation in einzelne Abschnitte aufteilen.

Aus der GB-A 1 061 557 ist es bekannt, Gelatinefolien oder Reispapier mit einer Wirkstofflösung zu imprägnieren oder mit einer Wirkstofflösung bzw. -schmelze zu beschichten. Die Beschichtung erfolgt durch Besprühen mit der Lösung oder durch Laminieren von zwei Trägerfolien mit der dazwischen liegenden Wirkstoffschmelze. Diese Herstellungsverfahren ermöglichen keine exakte Dosierung des Wirkstoffes: Beim Aufsprühen einer Wirkstofflösung kann ebenso wie beim Beschichten mit einer Schmelze eine völlig gleichmäßige Schichtdicke nicht sichergestellt werden. Darüber hinaus haftet die nur aus dem Wirkstoff bestehende Beschichtung häufig schlecht auf der Trägerfolie.

Die JA-A 76/54 917 erwähnt die Möglichkeit, eßbare Folien, z.B. Gelatinefolien, mit Wirkstofflösungen zu bedrucken, welche Verdickungsmittel wie Hydroxylpropylzellulose enthalten. Auch bei dieser Vorgehensweise erhält man häufig nur schlecht haftende Beschichtungen.

Alle diese Vorschläge haben keinen Eingang in die Praxis gefunden und in dem neuesten Lehrbuch der "Arzneiformenlehre" von P.H. List, 4. Auflage, Stuttgart, 1985, finden sie keine Erwähnung. Dies beruht ersichtlich darauf, daß die bislang bekanntgewordenen Vorschläge es nicht ermöglichen, die geforderte Gewichtskonstanz und gleichmäßige Wirkstoffverteilung zu erreichen, welche heute gefordert werden. Die Pharmakopoea Europae setzt zum Beispiel Maßstäbe für die Gleichförmigkeit des Gewichtes einzeldosierter Arzneiformen, wobei diese dem jeweiligen Durchschnittsgewicht entsprechend nach höchstzulässigen Abweichungen in % gestattelt sind. Die Forderung liegt im allgemeinen bei +/– 5 bis max. 10%. Entsprechende Werte für feste Arzneiformen bestehen auch hinsichtlich anderer Parameter wie Zerfallzeit und Lösungsgeschwindigkeit.

Die oben erwähnten Vorschläge des Standes der Technik führen zu Produkten ungenügender Akzeptanz durch die Patienten (z.B. lassen sich Papierabschnitte nur schlecht einnehmen) und erlauben keine exakte Dosierung pro Flächeneinheit, wie sie unbedingt gefordert werden muß. Bei Inkorporieren des Wirkstoffes in eine Folie bereitet nicht nur die genaue Dosierung Schwierigkeiten, sondern ein wesentlicher weiterer Nachteil besteht darin, daß für jeden Wirkstoff eine entsprechende Folie gesondert hergestellt werden muß, so daß die Wirtschaftlichkeit des Herstellungsverfahrens nicht gegeben ist.

Der Erfindung liegt demgegenüber die Aufgabe zugrunde, eine "zweidimensionale" Darreichungs- und Dosierungsform zu schaffen, welche die genannten Nachteile nicht aufweist, sich leicht herstellen läßt und mit großer Flexibilität an die Anforderungen des Marktes und verschiedener Wirkstoffe angepaßt werden kann.

Gegenstand der Erfindung ist ein Verfahren zur Herstellung einer Darreichungs- und Dosierungsform für Arzneimittelwirkstoffe, Reagentien oder andere Wirkstoffe in Form einer wasserlöslichen Folie auf Basis von Stärken, Gelatinen, Glycerin und/oder Sorbit sowie gegebenenfalls natürlichen und/oder synthetischen Harzen und Gummen, welches dadurch gekennzeichnet ist, daß man

a) eine wäßrige Zusammensetzung, deren Rezeptur derjenigen der Trägerfolie entspricht, aus dem Wirkstoff sowie Stärken, Gelatinen, Glycerin und/oder Sorbit sowie gegebenenfalls natürlichen und/oder synthetischen Harzen und Gummen herstellt, und

b) diese Beschichtungsmasse kontinuierlich mittels eines Walzenauftragsverfahrens in genau vorbestimmter Menge (Schichtdicke) auf mindestens eine Seite der wasserlöslichen wirkstofffreien Folie aufbringt.

Die erfindungsgemäß hergestellte Darreichungsform weist eine Reihe wesentlicher Vorteile auf:

– Eine Trägerfolie kann für die verschiedensten Wirkstoffe verwendet werden und somit in größerer Menge wirtschaftlich produziert werden,

– die wirkstoffhaltige Schicht kann bei hochwirksamen Arzneimitteln sehr dünn sein, da das Trägermaterial die ausreichende mechanische Festigkeit gewährleistet,

– die Beschichtung haftet hervorragend auf der Trägerfolie, weil beide dieselbe Rezeptur aufweisen,

– mit Hilfe der modernen Walzen-Auftragverfahren läßt sich die wirkstoffhaltige Beschichtung mit konstanter Schichtdicke aufbringen, so daß die erforderlichen Toleranzen eingehalten werden können,

– falls eine Sterilisierung erforderlich ist, kann diese wegen der geringen Schichtdicke problemlos mittels Strahlenbehandlung erreicht werden,

– der Träger läßt sich auf der Vorder- und insbesondere der Rückseite unter Verwendung physiologisch verträglicher Druckfarben mit verschiedenen Informationen bedrucken,

– aufgrund der relativ großen Fläche von beispielsweise 4 bis 10 cm^2 lassen sich ausführliche Informationen für den Benutzer auf das unbeschichtete Trägermaterial oder auch nachträglich aufdrucken,

– die Dosiereinheiten lassen sich durch entsprechende Vorzerteilung, z.B. eine Perforierung, flexibel gestalten, so daß für verschiedene Dosierungen (z.B. für Erwachsene und Kinder) nur ein Produkt hergestellt werden muß; die Vorzerteilung kann ggf. auch erst in der Apotheke oder im Krankenhaus nach ärztlichen Angaben vorgenommen werden.

Mit den früher beschriebenen Darreichungsformen in Folienform hat die erfindungsgemäße darüberhinaus den Vorteil des äußerst geringen Platzbedarfes gemeinsam. Statt Faltschachteln können daher beispielsweise Taschen oder Beutel aus Kunststoffolie oder kunststoffbeschichtetem Papier verwendet werden, in welche das Produkt eingesiegelt wird, ähnlich wie feuchte Erfrischungstücher.

Die Herstellung der Trägerfolie erfolgt in an sich bekannter Weise mit einer kontinuierlich arbeitenden Folienmaschine auf Rollenbasis. Das Streichverfahren zur Herstellung der Trägerfolie arbeitet nach dem Walzenprinzip, d.h. die wasserhaltige Zusammensetzung für die Trägerfolie wird mittels Rollen und Rakel angetragen und zu dünnen Bahnen ausgestrichen, auf der Rolle vorgetrocknet und im Haupttrockengang auf die gewünschte Endfeuchte nachgetrocknet. Das erhaltene Endprodukt ist so fest und elastisch, daß es auf Rollen gewickelt werden kann und lagerfähig ist, wenn die Restfeuchtigkeit nicht zu hoch ist (Gefahr der Schimmelbildung).

Die Folienbreite kann beliebig sein und wird günstigerweise auf die Breite der Beschichtungsmaschine zugeschnitten. Es bietet sich jedoch an, bereits bei der Herstellung beide Breiten aufeinander abzustimmen.

Es ist technisch auch möglich, die Folienherstellung und die Beschichtung zeitlich nacheinander auf derselben Anlage vorzunehmen, wodurch die Wirtschaftlichkeit wesentlich erhöht werden kann.

Die verwendete Zusammensetzung wird unter Umpumpen bei der gewünschten Temperatur, Viskosität und Homogenität gehalten. Die Trocknung der Folie erfolgt anschließend in einem Wärmetunnel. Die so gewonnene Trägerfolie stellt den indifferenten Träger für die spätere Beschichtung mit verschiedene Wirkstoffe enthaltenden Beschichtungsmassen dar.

Zur Herstellung der wasserlöslichen Trägerfolie dient eine physiologisch unbedenkliche Zusammensetzung. Die "Wasserlöslichkeit" soll dabei so definiert sein, daß die Herstellung der Folie aus einer wäßrigen Zusammensetzung erfolgt und daß sich die fertige Folie später bei der Anwendung wiederum in Wasser bzw. im Magensaftmilieu löst oder darin quillt.

Als Folienbildner kommen insbesondere Gelatinen sowie Stärken (Kartoffelstärke, Weizenstärke, Maisstärke) sowie ferner Poly-N-vinylpyrrolidon (PVP), Methyl- und Ethylzellulose sowie Polyvinylalkohol (PVA) infrage. Ferner können wässerlösliche Acrylharzdispersionen Verwendung finden. Geeignete Weichmacher sind insbesondere polyfunktionelle Alkohole wie Glycerin und Sorbit (Karion®).

Die Komponenten werden in geeigneter Weise mit Wasser kalt angemischt und unter leichtem Erwärmen und ständigem Rühren zu einem streichfähigen Schleim verarbeitet. Das Einrühren von Luft muß soweit wie möglich vermieden werden, um eine klare, allenfalls leicht opaleszierende Masse zu erhalten.

Die Stärke der Trägerfolie beträgt vorzugsweise zwischen etwa 50 und 250 µm. Sie ist in weitem Maße steuerbar. Auch die Eigenschaften der Trägerfolie lassen sich durch entsprechende Kombination der Folienbildner und Weichmacher qualitativ stark beeinflussen. Die Trägerfolie soll eine möglichst gleichmäßige Stärke aufweisen (vorzugsweise z.B. 100 µm), leicht elastisch und knickfähig sein, ohne zu brechen. Dabei sollte der Stärkeanteil ausreichend hoch sein, damit beim Aufbringen der Beschichtungsmasse Feuchtigkeit aufgenommen wird, ohne daß es zu einem Kleben der Oberfläche oder zum Erweichen der ganzen Folie kommt.

Folgende Rahmenrezeptur hat sich für die Trägerfolie bewährt:

Gelatine 8 bis 10 g
Stärke 4 bis 8 g
Glycerin 1 bis 2 g

Polyvinyl-pyrrolidon 1 bis 2 g
Wasser 30 bis 50 g

Wasserlösliche natürliche und/oder synthetische Harze, z.B. Acrylharze, und Gumme sind ebenfalls geeignet. Ggf. können der Masse noch übliche weitere Stoffe zugefügt werden, z.B. Konservierungsmittel wie p-Hydroxybenzoesäure-Ester, inerte lösliche oder unlösliche Füllstoffe, Geschmackstoffe, Zucker oder andere Süßungsmittel, weitere Weichmacher, insbesondere Polyole, Wachse oder Farbstoffe.

Die Möglichkeit der vorder- und rückseitigen Bedruckung der Trägerfolie ist ein besonderer Vorteil der erfindungsgemäßen Darreichungsform. Beispielsweise können die Kennzeichnung, Angaben über die Inhaltsstoffe sowie Dosierungsangaben aufgedruckt werden. Gegebenenfalls läßt sich sogar der ganze Inhalt eines Beipackzettels rückseitig aufdrucken mit der Folge, daß ein separater Beipackzettel, der auch häufig verlorengeht, überflüssig wird. Bei Arzneimitteln, welche regelmäßig genommen werden müssen, beispielsweise bei hormonalen Contrazeptiva, kann der gesamte Verabreichungsplan so angebracht werden, daß eine einfache Einnahmekontrolle gewährleistet ist. Zur Bedruckung müssen physiologisch verträgliche Farben (Lebensmittelfarben) verwendet werden, da die Trägerfolie einen Teil der oral verabreichten Darreichungsformen bildet.

Für die wirkstoffhaltige Beschichtungsmasse findet eine wäßrige Zusammensetzung Verwendung, die physiologisch inert ist und deren Einzelkomponenten für Arzneimittel bzw. Lebensmittel geeignet sind. Wesentlich ist die gegenseitige physikalisch-chemische Affinität und Verträglichkeit zwischen Beschichtungsmasse und Trägerfolie, welche besonders gut ist, weil die verwendeten Komponenten gleich sind bzw. sehr ähnliche Eigenschaften besitzen. Unter Berücksichtigung des zugeführten Wirkstoffes entspricht die Rezeptur der Beschichtungsmasse demgemäß der oben für die Trägerfolie genannten, wobei die genaue Einstellung auf Feststoffgehalt und Viskosität mittels indifferenter Quell- und Füllstoffe erfolgt.

Die Masse enthält somit einmal polymere Filmbildner, vorzugsweise Gelatine und quellende oder lösliche Stärken sowie ggf. Zellulosen oder Hemizellulosen. Ferner werden Weichmacher zugesetzt, insbesondere mehrwertige Alkohole wie Glycerin oder Sorbit. Zur Einstellung der erwünschten Viskosität der Beschichtungsmasse, welche die Konsistenz eines Schleimes aufweist, finden polymere Quellstoffe Verwendung, vorzugsweise Alginate, Pectine, Chitine, Lecithine oder Polyethylenglykole. Diese letzteren Stoffe können gleichzeitig als Haftvermittler dienen. Andererseits können auch wasserlösliche synthetische oder natürliche Harze oder Gumme oder Gummi arabicum zugesetzt werden, um die Haftung der Beschichtung auf dem Trägermaterial zu verbessern. Schließlich können noch Konservierungsmittel wie z.B. p-Hydroxybenzoesäureester, Farbstoffe (Lebensmittelfarbstoffe), Pigmente wie Titandioxid oder Aroma- und Süßstoffe zugesetzt werden.

Coatingmassen mit einem Wassergehalt von ungefähr 50% und einer Viskosität von etwa 30 bis zu 10 000 cPs haben sich als besonders geeignet erwiesen. Die Rezeptur und Herstellung ähnelt derjenigen eines Arzneimittelsaftes, in welchem der Wirkstoff bzw. die Wirkstoffkombination gelöst oder gleichmäßig dispergiert wird. Die Beschichtungsmasse muß ausreichende Homogenität und galenische Stabilität aufweisen, damit ein gleichmäßiger Wirkstoffgehalt der fertigen Beschichtung sichergestellt ist.

In dieser Grundmasse wird der Wirkstoff gelöst bzw. dispergiert. Im Fall der Verwendung einer Dispersion muß der Wirkstoff für eine gleichmäßige Verteilung äußerst feinteilig sein. Vorzugsweise liegt die mittlere Teilchengröße im Bereich von etwa 1 bis 20 µm.

Die gewünschte Dosis des Wirkstoffes und die angestrebte Fläche der Dosiseinheiten bestimmen letztlich die Dicke der Schicht, wobei der Feuchtigkeitsgehalt der Beschichtungsmasse und der fertigen Beschichtung zu berücksichtigen sind.

Die erfindungsgemäße Darreichungsform ist besonders geeignet für Arzneimittel, welche niedrig dosiert verabreicht werden, d.h. bei welchen die Einzeldosis für die orale Applikation zwischen 0 mg (Placebo) und etwa 20 mg liegt. Geeignete Arzneimittelwirkstoffe finden sich in allen Bereichen der oralen Therapie; hervorzuheben sind u.a. Analeptika, Antibiotika, Antidiabetika, Antiemetika, Antiepileptika, Antihypertonika, Cortikoide, Geriatrika, Hypnotika, Cardiaka, Hypostatika und Biowirkstoffe.

In einem Beschichtungsgang lassen sich ca. 4 bis 20 g Wirkstoff je m^2 (= 10.000 cm^2) Trägerfolie aufbringen, so daß 10 cm^2 (= 2 übliche Briefmarken) bis zu 20 mg Wirkstoff aufnehmen können.

Die Beschichtungsmasse wird normalerweise auf eine Seite der Trägerfolie aufgebracht, doch ist auch eine beidseitige Beschichtung, insbesondere bei zwei verschiedenen Wirkstoffen möglich. Jede Beschichtung kann einen oder mehrere Arzneimittelwirkstoffe enthalten. Falls bei Verwendung mehrerer Wirkstoffe diese nicht ohne weiteres miteinander verträglich sind und in einer Beschichtungsmasse enthalten sein können, ist es bei der erfindungsgemäßen Darreichungsform möglich, die Beschichtung in mehreren Schichten unterschiedlicher Zusammensetzung aufzubringen und die Wirkstoffe dadurch voneinander zu trennen, wobei erforderlichenfalls eine wirkstofffreie Zwischenschicht vorgesehen werden kann. Weiterhin ist es möglich, über der wirkstoffhaltigen Schicht noch eine weitere Schutzschicht vorzusehen, welche den/die Wirkstoff(e) genen eine Berührung mit der Atmosphäre und/oder gegen Licht schützt. In diesen Fällen muß die Schutzschicht demgemäß luft- und feuchtigkeitsundurchlässig und/oder durch Zusatz entsprechender Farbstoffe bzw. Pigmente lichtundurchlässig sein.

Weiterhin kann durch entsprechenden Aufbau der Beschichtung die Wirkstoffabgabe nach Verabreichung des Arzneimittels gesteuert werden. Beispielsweise ist es möglich, eine Wirkstoffschicht zwischen mindestens zwei weiteren Schichten anzuordnen, welche die Wirkstoffresorption im Magen/Darmtrakt in an sich bekannter Weise steuern.

Dabei kann die Wirkstoffschicht z.B. zwischen zwei säureunlöslichen Schichten angeordnet werden, so daß bei Verabreichung der Magen passiert wird und die Resorption erst im Darmtrakt erfolgt. In ähnlicher Weise können unterschiedliche Wirkstoffe in verschiedenen Schichten übereinander auf die Trägerfolie aufgebracht werden, damit die Resorption nacheinander und/oder verzögert erfolgt.

Ähnliche pharmakokinetische Effekte lassen sich durch das Einarbeiten (z.B. Suspendieren) von unterschiedlich vorbehandelten mikroverkapselten Wirkstoffen erzielen.

Die Beschichtung des Trägermaterials mit der wirkstoffhaltigen Beschichtungsmasse erfolgt mittels eines Walzenauftragverfahrens. Dieses für die quantitative Beschichtung besonders geeignete Verfahren arbeitet nach einem dem Tiefdruck ähnlichen Verfahren, welches als "Akkugravur" bezeichnet wird. Hierfür geeignete Maschinen sind im Handel (Fa. Pagendarm, Hamburg) und erlauben Auftragsgewichte bis zu 80 g/m² bei Bahngeschwindigkeiten von mehreren 100 m/min. Die reproduzierbare Gewichtskonstanz liegt für 20 g/m² bei nur +/- 2,5% für 1 g/m² und für ca. +/- 10% über die gesamte Fläche. Der Auftrag der Beschichtungsmasse erfolgt kontinuierlich über Walzen mit spezieller Feingravur, wobei die eingravierten Rillen zur Laufrichtung der Trägerfolie vorzugsweise einen Winkel von 30 bis 60, insbesondere 45° bilden. In die Walzen können 27 bis 80 Rillen/cm eingeätzt sein. Entsprechend ihrer Form und Tiefe kann die Gravur eine definierte Menge der Beschichtungsmasse aufnehmen und anschließend an die Trägerfolie weitergeben. Durch Variation der Vorlaufgeschwindigkeit, der Laufrichtung und der Gravur sowie durch indirektes Auftragen über eine weitere geschwindigkeitsvariable Walze lassen sich die Beschichtungsmengen sehr exakt einstellen.

Eine zweiseitige Beschichtung ergibt häufig Vorteile, da Probleme durch Verwerfen des Trägermaterials und durch unterschiedliche Hygroskopizität ausgeglichen werden. Mehrfach- und auch Streifenbeschichtungen, ja sogar Druckbildbeschichtungen, sind möglich und bieten bei der Verarbeitung von inkompatiblen Wirkstoffen eine große Variabilität.

Ein anderes geeignetes Auftragverfahren entspricht dem Streichen von Papier oder von Folien. Dabei werden Rohpapiere dadurch verbessert, daß sie ein- oder zweiseitig mit Coatingmaterialien beschichtet werden. Die wässrigen Beschichtungsmassen gelangen zunächst auf ein Walzwerk, welches sie mittels einer rotierenden Walze aufnimmt, mit einen Rakel bestimmten Abstandes auf eine definierte Schichtdicke abstreift, worauf die Walze die Beschichtungsmasse auf den Träger abgibt. Die Trägerfolie, welche 0,30 bis 7,50 m breit sein kann, durchläuft anschließend einen Trockentunnel und wird dann auf Rollen aufgewickelt. Dieser Vorgang ist in einem oder mehreren Schritten ein- oder zweiseitig wiederholbar, wobei auch eine bereits beschichtete Fläche nochmals beschichtet werden kann. Das Gewicht des Trägermaterials nimmt um das der Trockenmasse zu. Die Genauigkeit des Auftragverfahrens mittels dieses Rakel-Verfahrens liegt reproduzierbar bei +/- 5%. Sie ist abhängig von der jeweiligen Schichtdicke, die variabel zwischen 4 und 40 g/m² betragen kann. Innerhalb der einzelnen Fertigungen kann eine Gewichtstoleranz pro Flächeneinheit bis unter +/- 1 % erreicht werden.

Bei Aufbringung mehrerer Schichten, wie dies oben bereits beschrieben wurde, werden diese nacheinander aufgebracht, wobei ggf. jede Beschichtung zuvor eine Trocknungsstation durchläuft. Diese kann beispielsweise aus einem temperierten Walzenpaar und einem in Sektionen steuerbaren Trockentunnel bestehen. Nach dem letzten Beschichtungsvorgang wird das beschichte Material auf Rollen aufgewickelt.

Die wirkstoffbeschichtete Trägerfolie wird anschließend in Dosiseinheiten vorzerteilt, welche ähnlich wie Briefmarken abtrennbar sind. Normalerweise wird diese Vorzerteilung beim Arzneimittelhersteller erfolgen, es ist jedoch auch denkbar, das beschichtete Material beispeilsweise an Krankenhäuser oder Apotheken auszuliefern, wo dann die Vorzerteilung dosisabhängig oder auch individuell nach ärztlicher Vorgabe durchgeführt werden kann.

Die Vorzerteilung erfolgt in besonders einfacher Weise durch Perforierung oder Stanzung, wobei es möglich ist, diesen Schritt mit der Bedruckung des Trägermaterials zu kombinieren. In vielen Fällen wird es allerdings günstiger sein, die Bedruckung des Trägermaterials vor der Beschichtung vorzunehmen.

Vor oder besser nach Vorzerteilung der wirkstoffhaltigen Beschichtung in Dosiseinheiten wird das beschichtete Trägermaterial zu gebrauchsfertigen Abschnitten zerschnitten, welche eine bestimmte Anzahl von Dosiseinheiten enthalten. Es ist auch denkbar, das Material auf Rollen zu schmalen Bändern zu zerschneiden. Von einer solchen Einzelrolle können dann die einzelnen Dosiseinheiten ähnlich wie einzelne Briefmarken abgetrennt werden.

Da als Grundstoffe für die Herstellung der erfindungsgemäßen Darreichungsform überwiegend Naturstoffe wie Stärken und Gelatine verwendet werden, erhält man insgesamt Produkte, welche den bekannten Oblaten ähneln und deren orale Einnahme keinerlei Schwierigkeiten bereitet. Wichtig ist, daß das Fertigprodukt weitgehend von Wasser befreit ist, d.h. einen Wassergehalt von wengier als 10 und vorszugsweise von weniger als 2% aufweist, da sonst Schimmelbildung auftreten kann.

Vorstehend wurde die Erfindung im wesentlichen im Zusammenhang mit Arzneimitteln beschrieben, worauf sie jedoch keineswegs beschränkt ist. Beispielsweise lassen sich in derselben Weise auch Dosierungsformen für chemische Reagentien, Aromastoffe und dergleichen herstellen.

Zur näheren Erläuterung der Erfindung soll das nachfolgende Ausführungsbeispiele dienen.

Beispiel

Herstellung einer Arzneimittel-Darreichungsform in Form einer beschichteten Folie.

Zur Herstellung einer wasserlöslichen Trägerfolie wurde von folgender Zusammensetzung ausgegangen:
Gelatine 10,0 Gew.-Teile = 25%
Kartoffelstärke 8,0 Gew.-Teile = 20%
Glycerin 1,5 Gew.-Teile = 3,75%
gereinigtes Wasser 20,5 Gew.-Teile = 51,25%

Die Viskosität der schleimartigen Zusammensetzung betrug bei 50°C ca. 3000 cPs. Mit Hilfe des Streichverfahrens wurde die Masse zu einer Folie verarbeitet, welche nach dem Trocknen noch 9,3% Restwasser enthielt.

Unter Verwendung derselben Grundstoffe wie für die Trägerfolie wurde die Beschichtungsmasse gemäß folgender Rezeptur hergestellt:
Gelatine 10,0 Gew.-Teile = 18,2%
Kartoffelstärke 5,0 Gew.-Teile = 9,1%
Glycerin 1,0 Gew.-Teile = 1,8%
Wirkstoff 5,0 Gew.-Teile = 9,1%
gereinigtes Wasser 34,0 Gew.-Teile = 61,8%

Die Viskosität der schleimartigen Zusammensetzung betrug temperatur- und wirkstoffabhängig zwischen 4.000 und 10.000 cPs. Zur Herstellung der Beschichtungsmasse wurde zunächst die Gelatine in einer ausreichenden Menge Wasser gelöst. Dazu wurde Wasser von 90 bis 95°C vorgelegt, in das die Gelatine unter Rühren eingetragen wurde. In einem getrennten Ansatz wurde der Wirkstoff zusammen mit dem Glycerin in Wasser gelöst. Schließlich wurde die Kartoffelstärke bei 50 bis 60°C unter Rühren in einer ausreichenden Menge Wasser angerührt. Die Gelatinelösung und die Kartoffelstärkesuspension wurden zusammengegeben und die Wirkstoffsuspension wurde in die Mischung langsam eingerührt, wobei Lufteinschlüsse vermieden wurden. Die Temperatur wurde auf 55 bis 60°C gehalten. Zuletzt wurde der gewünschte Wassergehalt durch Zugabe von weiterem Wasser eingestellt.

Die Beschichtungsmasse wurde mittels Akkugravur mit einem Naßbeschichtungsgewicht von 55 g/m² auf die Trägerfolie aufgebracht. Nach dem Trocknen betrug das Beschichtungsgewicht 23 g/m² entsprechend einem Wirkstoffgehalt von 5 g/m². Die wirkstoffbeschichtete Folie wurde anschließend kastenartig perforiert, so daß die einzelnen Abschnitte bei Abmessungen von 2 x 2,5 cm eine Fläche von 5 cm² aufwiesen. Ein solcher Abschnitt enthielt 2.5 mg Wirkstoff.

Nach dem Trocknen lag die Restfeuchtigkeit des Produktes bei 8,6%.

Es wurde eine Darreichungsform erhalten, welche bei oraler Einnahme im Mund rasch quillt und zergeht und sich demgemäß leicht schlucken läßt.

Patentansprüche

1. Verfahren zur Herstellung einer Darreichungs- und Dosierungsform für Arzneimittelwirkstoffe, Reagentien oder andere Wirkstoffe in Form einer wasserlöslichen Folie auf Basis von Stärken, Gelatinen, Glycerin und/oder Sorbit sowie gegebenenfalls natürlichen und/oder synthetischen Harzen und Gummen, dadurch gekennzeichnet daß man
a) eine wässrige Zusammensetzung, deren Rezeptur derjenigen der Trägerfolie entspricht, aus dem Wirkstoff sowie Stärken, Gelatinen, Glycerin und/oder Sorbit sowie gegebenenfalls natürlichen und/oder synthetischen Harzen und Gummen herstellt, und
b) diese Beschichtungsmasse kontinuierlich mittels eines Walzenauftragsverfahrens in genau vorbestimmter Menge (Schichtdicke) auf mindestens eine Seite der wasserlöslichen wirkstofffreien Folie aufbringt.

2. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß man der Zusammensetzung für die Trägerfolie und die Beschichtung zusätzlich inerte lösliche und/oder unlösliche Füllstoffe, Zucker und/oder andere Süßungsmittel, weitere Weichmacher, insbesondere Polyole, Wachse, Farbstoffe, Geschmacksstoffe und/oder Konservierungsmittel zusetzt.

3. Verfahren nach einem der Ansprüche 1 oder 2, dadurch gekennzeichnet, daß man für die Herstellung der Trägerfolie und der Beschichtungsmasse eine Zusammensetzung verwendet, die 8 bis 10 Gew.-Teile Gelatine, 4 bis 8 Gew.-Teile Stärke, 1 bis 2 Gew.-Teile Glycerin und 20 bis 50 Gew.Teile Wasser enthält.

4. Verfahren nach Anspruch 3, dadurch gekennzeichnet, daß man eine Beschichtungsmasse einsetzt, die bis zu 10 Gew.-Teile des Wirkstoffes enthält.

5. Verfahren nach einem der Ansprüche 1 bis 4, dadurch gekennzeichnet, daß man der Beschichtungsmasse zur Einstellung der Viskosität indifferente Quell- und Füllstoffe zusetzt.

6. Verfahren nach einem der Ansprüche 1 bis 5, dadurch gekennzeichnet, daß man die Beschichtungsmasse kontinuierlich mittels Rasterwalzen, welche eine genau definierte Menge der Beschichtungsmasse aufnehmen und wieder abgeben, auf die Trägerfolie aufbringt.

7. Verfahren nach einem der Ansprüche 1 bis 5, dadurch gekennzeichnet, daß man die Beschichtungsmasse kontinuierlich mittels glatter Walzenpaare, welche in geschwindigkeitsversetztem Gleichlauf die Masse aufnehmen und in definierter Menge abgeben, auf die Trägerfolie aufbringt.

8. Verfahren nach einem der Ansprüche 1 bis 7, dadurch gekennzeichnet, daß man zur Herstellung eines Kombinationspräparates auf die Ober- und die Unterseite der Trägerfolie unterschiedliche Wirkstoffe aufbringt.

Claims

1. Process for the manufacture of a presentation and dosage form for pharmaceutical active substances, reagents or other active substances in the form of a water-soluble foil based on starches, gelatines, glycerin and/or sorbite and also in some cases on natural and/or synthetic resins and gums, characterized in that
a) an aqueous composition, the formulation of which corresponds to that of the carrier foil, is manufactured from the active substance and from starches, gelatines, glycerin and/or sorbite and also in some cases from natural and/or synthetic resins and gums, and that

b) this coating substance is applied continuously in a precise pre-determined quantity (layer thickness) to at least one side of the active-substance-free-water-soluble foil by means of a roller coating process.

2. Process according to claim 1, characterized in that inert, soluble and/or insoluble fillers, sugars and/or other sweeteners, other softeners, particularly polyols, waxes, colorants, flavouring agents and/or preservatives are also added to the composition for the carrier foil and the coating.

3. Process according to one of claims 1 or 2, characterized in that, for the manufacture of the carrier foil and the coating substance, a composition is used which contains 8 to 10 parts by weight of gelatine, 4 to 8 parts by weight of starch, 1 to 2 parts by weight of glycerin and 20 to 50 parts by weight of water.

4. Process according to claim 3, characterized in that a coating substance is used which contains up to 10 parts by weight of the active substance.

5. Process according to one of claims 1 to 4, characterized in that inert swelling agents and fillers are added to the coating substance to regulate the viscosity.

6. Process according to one of claims 1 to 5, characterized in that the coating substance is continuously applied by means of grid rollers which take up and then release a precisely defined quantity of the coating substance.

7. Process according to one of claims 1 to 5, characterized in that the coating substance is applied to the carrier foil continuously by means of smooth pairs of rollers synchronized but out of phase which take up the substance and release a pre-defined quantity.

8. Process according to one of claims 1 to 7, characterized in that different active substances are applied to the top and bottom of the carrier foil for the manufacture of a compound preparation.

Revendications

1. Procédé de fabrication d'une forme d'administration et de dosage pour des principes actifs de médicaments, des réactifs ou d'autres substances actives, sous forme d'une feuille hydrosoluble à base d'amidons, de gélatines, de glycérol et/ou de sorbitol, et éventuellement de résines et gommes naturelles et/ou synthétiques, procédé caractérisé en ce que l'on

a) fabrique une composition aqueuse, dont la formulation correspond à celle de la feuille support, à partir de la substance active ainsi que d'amidons, de gélatines, de glycérol et/ou de sorbitol, et éventuellement de résines et gommes naturelles et/ou synthétiques, et

b) dépose en continu, à l'aide d'un cylindre d'enduction, cette masse, en quantité exactement prédéterminée (épaisseur de couche), sur au moins une des faces de la feuille hydrosoluble dépourvue de substance active.

2. Procédé selon la revendication 1, caractérisé en ce que l'on ajoute en plus, à la composition pour la feuille support et le revêtement, des charges inertes solubles et/ou insolubles, des sucres et/ou d'autres édulcorants, en outre des plastifiants, en particulier des polyols, des cires, des colorants, des aromatisants et/ou des conservateurs.

3. Procédé selon l'une des revendications 1 ou 2, caractérisé en ce que, pour la fabrication de la feuille support et du revêtement, on utilise une composition qui renferme de 8 à 10 parties en poids de gélatine, 4 à 8 parties en poids d'amidon, 1 à 2 parties en poids de glycérol et 20 à 50 parties en poids d'eau.

4. Procédé selon la revendication 3, caractérisé en ce que l'on met en œuvre une masse d'enduction qui renferme jusqu'à 10 parties en poids de la substance active.

5. Procédé selon l'une des revendications 1 à 4, caractérisé en ce que l'on ajoute des agents gonflants et charges inertes à la masse d'enduction, pour ajuster la viscosité.

6. Procédé selon l'une des revendications 1 à 5, caractérisé en ce que l'on dépose en continu la masse d'enduction sur la feuille support, à l'aide de cylindres à trame, qui prennent puis rétrocèdent une quantité exactement définie de la masse d'enduction.

7. Procédé selon l'une des revendications 1 à 5, caractérisé en ce que l'on dépose en continu la masse d'enduction sur la feuille support, à l'aide de paires de cylindres lisses, qui prennent la masse avec un syndrome décalé de la vitesse et la rétrocèdent en quantité définie.

8. Procédé selon l'une des revendications 1 à 7, caractérisé en ce que, pour fabriquer une préparation combinée, on dépose différentes substances actives sur la face supérieure et sur la face inférieure de la feuille support.

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Description

This invention relates to a pharmaceutical composition which is applied to a periodontal pocket or paradentium for the purpose of treating periodontal diseases. The pharmaceutical composition may be provided in the form of gel, sheet, film or bar-like formulation to release a controlled and effective amount of an active ingredient at the periodontal pocket or paradentium.

The "periodontal diseases" is a general term of various inflammatory diseases of paradentium. The diseases include a series of diseases exhibiting various syndromes which vary from each other according to the stage or situation of the diseases or the age of the patient, and have not been definitely subclassified. Since, however, the term "periodontal diseases" is given to any inflammatory disease which initially occurs at a marginal gingiva area and finally reaches an alveolar bone, the diseases can be roughly divided, on the basis of the degree of the inflammation, into "gingivitis" in which the inflammation is limited to the gingiva tissue, and "paradentitis" in which the inflammation is chronic and found even in an alveolar bone. However, peculiar diseases such as "juvenile paradentitis" and "acute necrotizing ulcerative gingivitis" are also included in the periodontal diseases.

The paradentitis, which was once called "alveolar pyorrhea", is characterized by remarkable symptoms such as inflammation of gingiva, formation of periodontal pockets, bleeding and pus discharge from said periodontal pockets, and it brings about resorption of alveolar bone, loose teeth, and shedding of teeth.

The consensus of most investigators is that periodontal diseases are caused by bacteria present in dental plaques formed in periodontal pockets. Efforts have been concentrated on the discovery of pathogenic bacteria responsible for said diseases. At the present time, an attributable major pathogen is recognized to be certain nigral pigment-producing bacteria, such as genus Bacteroides. However, other genera of bacteria including Actinobacillus, Capnocytophaga, Fusobacterium and Spirochetes may be included in the causative pathogens. In any case, it is an established theory that the periodontal diseases should not be attributed to all bacteria present in the dental plaque.

The periodontal diseases have previously been treated in several ways, such as exhaustive scaling of plaques in periodontal pockets, root planing, gingivectomy to eliminate the periodontal pocket, or surgical curettage to excise inflammatory tissues. These treatments have been effective to some extent but not satisfactory.

On the other hand, pharmacotherapy has also been conducted using drugs, for example germicides, antiinflammatory agents, plaque solubilizing agents, and hemostyptics. These drugs are used in the form of formulations suited for internal use or massotherapy (e.g., dentifrices and ointments). However, they are not satisfactory for the purpose of treatment of periodontal diseases because the internal use hardly permits the selective migration of the drug to the lesional region, and the massotherapy is not successful in solubilizing the plaques which are present beneath the gingival margin.

Recently, strips which comprise polymers and active ingredients for treatment of periodontal diseases have been developed. These strips are said to be useful for the treatment of plaques and inflammation beneath the gingival margin. The strips can be applied directly to the lesional region to be treated, and therefore, the active ingredient can be concentrated to the desired site selectively. This modified therapeutic method has been proved to be more effective than any conventional pharmacotherapy. For instance, J. M. Goodson et al. disclose the implantation of "hollow fiber", which contains germicides, into the gingival region (J. Clinical Periodontology, 1979: 6: 83-92). M. Addy et al. have reported the insertion of strips, which were prepared from a mixture of an insoluble polymer such as polyethylmethacrylate and germicides, into periodontal pockets (J. Periodontal, 693, Nov. 1982). In addition, insertion of the strips, prepared from a mixture of a soluble polymer and a drug, into the lesional region, such as periodontal pockets, is also reported (Japan Patent Publication No. 59-222406).

The formulations mentioned above comprise a mixture of an active ingredient and a homogeneous polymer base. Accordingly, where such formulation is designed to contain two or more active ingredients which differ from each other in terms of pharmacological activity and therapeutically effective dose, it has been impossible to prepare a formulation in which each of the plural ingredients may release independently and provide its suitable concentration as desired.

The use of the hollow fiber or insoluble polymer, as a base, causes irritation or pain to patients, and moreover, it necessitates the removal of the base after release of an active ingredient, which is often annoying. On the other hand, the strip which comprises a soluble polymer as a base or carrier permits a rapid release of an active ingredient. Accordingly, it does not afford a constant therapeutic effect and, therefore, has a poor practical use.

As the result of an extensive study for seeking a novel therapeutical composition for periodontal diseases, which suitably controls the release of one or more active ingredients and which does not give any uncomfortable feelings to patients, it has been

found that the use of a two-phase carrier base, which consists of particles comprising a polymer having a limited solubility in water and a water soluble polymer used for dispersing such particles, meets the requirements just mentioned above.

DE-A-3 432 573 and US-A-4 693 887 disclose pharmaceutical composition having two polymeric phases, one hydrophobic and one hydrophilic, the combination being insoluble in water and thus suitable for water-insoluble implants. A drug partitions itself between the phases. The hydrophilic phase has a different composition from the discontinuous phase employed in the present

Thus the present invention provides:

a controlled-release pharmaceutical composition in the form of gel, sheet, film, or bar to be inserted or placed into a periodontal pocket for treating a periodontal disease, said composition comprising a therapeutically effective amount of at least one active ingredient effective for the treatment of the periodontal disease, said active ingredient being dispersed in a two-phase carrier consisting of

(a) a continuous phase consisting of a water-soluble polymer capable of dissolving in water at a concentration of more than 1% by weight irrespective of pH, and

(b) a discontinuous phase consisting of solid particles composed of a polymer capable of dissolving in water at a concentration of at least about 0.1% and not more than about 1.0% by weight; or solid particles composed of a polymer capable of dissolving in water at a concentration of more than 1% by weight only at a pH higher than 4 or lower than 6

said particles having an average size ranging from 1 μm to 500 μm and being dispersed in said water-soluble polymer, with the weight ratio of said particles to said water-soluble polymer ranging from 1:99 to 99:1 on a dry weight basis, said water-soluble polymer being selected from the

methyl cellulose, hydroxypropyl cellulose, sodium carboxymethyl cellulose, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, sodium alginate, propylene glycol alginate, pullulan, tragacanth, xanthan gum, chitosan, polyethylene oxide, polyvinyl alcohol, polyacrylic acid, polymethacrylic acid, and salts thereof, and said solid particles being selected from

poly(glycolic acid), poly(lactic acid), polytetramethylglycolide, polydiethylglycolide, poly-ε-caprolactone, poly(DL-decalactone), poly(alkyleneadipate), methylacrylate/ methacrylic acid copolymer, methylacrylate/ methacrylic acid/ octylacrylate copolymer, ethylacrylate/ methacrylic acid copolymer, methylacrylate/ methacrylic acid/ methylmethacrylate copolymer, methylmethacrylate/ methacrylic acid copolymer, cellulose acetate phthalate, cellulose acetate succinate, cellulose acetate maleate, starch acetate phthalate, amylose acetate phthalate, methyl cellulose phthalate, hydroxypropylmethyl cellulose phthalate, hydroxyethyl ethylcellulose phthalate, hydroxypropylmethyl cellulose acetate succinate, carboxymethylethyl cellulose, polyvinylalcohol phthalate, polyvinyl acetate phthalate, polyvinylacetal phthalate, polyvinylbutylate phthalate, methylmethacrylate/ dimethylaminoethyl methacrylate copolymer, and polyvinylacetal/ dimethylamino acetate.

Brief Description of the Drawing

Fig. 1 shows the dissolution profile of two active ingredients contained in the pharmaceutical composition of the invention which is in the form of a film. Fig. 2 shows the dissolution profile of two active ingredients contained in a conventional composition.

"Water soluble polymer" or "soluble polymer" denotes any polymer which dissolves in an aqueous medium, particularly in water, in a concentration of more than 1% by weight, irrespective of pH.

For the purpose of simplicity, the polymers usable for the discontinuous phase are hereinafter referred to as "non-soluble polymer" as a whole.

The soluble polymer used in the present invention must be fabricated into a semi-solid or a solid material. The non-soluble polymer should have a property suitable for being fabricated into particles. Both soluble and non-soluble polymers employed in the present application should be, of course, physiologically acceptable.

The pharmaceutical composition of the present invention may be prepared by dispersing one or more of active ingredients into a non-soluble polymer, or both of a soluble polymer and a non-soluble polymer, and mixing these polymers, and finally forming the resultant mixture into a solid material of a film, sheet or bar-like shape, or into a semi-solid material such as gel or ointment.

In more detail, one or more non-soluble polymers is dissolved, as the first step, in an appropriate organic solvent. To the resultant solution is dissolved or dispersed one or more active ingredients, and the mixture is formed into film or sheet by casting method. The resultant solid material is ground into particles.

The particles are also obtainable by spray drying, Wuster coating, Coacervation, or Drying in liquid phase. The average particle size may range from 1μm to 500μm depending on the contemplated release pattern of the active ingredient. However, the size range between 1μm and 300μm is generally preferred.

On the other hand, one or more water soluble

polymers are dissolved in a suitable solvent. The solvent may contain, if desired, one or more active ingredients. Subsequently, the pH of the mixture is adjusted, if necessary, and the particles obtained above are uniformly suspended in the mixture. The pharmaceutical composition of the invention in the form of gel is thus obtained.

The composition of the invention in the form of film or sheet is obtained by deaerating the just mentioned gel, and subjecting the same to the casting process. The film or sheet may also be prepared by compression molding, extrusion or calendering. The most suitable forming process among others is selected depending on the physico-chemical properties of the polymers employed.

The bar-like composition of the invention is prepared in the similar manner as the film or sheet, but through extrusion.

The weight ratio of the particles to the soluble polymer ranges from 1:99 to 99:1 on the basis of dry weight. The composition of the particles: soluble polymer in a ratio of 10:90-70:30 is preferred.

Therapeutically active ingredient or ingredients used for the preparation of the composition of the invention are selected from those effective for prevention or treatment of periodontal diseases, for example, germicides, such as chlorhexidine, Ag protein, glyceryl iodide, phenol, benzalkonium chloride, and cetylpyridinium chloride; antimicrobial agents, such as ampicillin, tetracycline, benzylpenicillin, clindamycin, cefalexin, erythromycin, chloramphenicol, and fragiomycin sulfate; anti-inflammatory agents, such as ibuprofen, indomethacin, ketoprofen, mefenamic acid, antipyrine, pranoprofen, ibufenac, tiaramide hydrochloride, prednisolon, dexamethasone, triamcinolone acetonide, and prostaglandine; plaque solubilizing agents, such as dextranase, protease, and amylase; collagenase inhibitors obtained from the extraction of crude drugs, such as gambir-catechu known by the name of "asenyaku"; local anesthetics, such as tetracaine hydrochloride and ethyl aminobenzoate; antihistaminic agents, such as chlorphenilamine maleate and diphenhydramine; and hemostatic agents such as tranexamic acids.

The solid composition of the invention in the form of film, sheet or bar can be prepared in different sizes. However, the convenient size of the film or sheet may be 0.1-0.5 mm in thickness, 0.5-3 mm in width, and 10-50 mm in length. The size of the bar may generally range from 0.5 to 1.5 mm in diameter and from 10 to 50 mm in length. Furthermore, the composition of the invention may be cut in suitable size by the user depending on several factors, such as severity of the disease, and the width and depth of the locus to be applied. The composition of the invention can be applied to the periodontal pocket or paradentium by insertion, injection, or rubbing according to the type of formulation.

The pharmaceutical composition of the invention exhibits a desirably controlled release pattern of the active ingredient(s). Such controlled release is attained by careful selection of a particular condition with respect to the following variables.

(1) Distribution ratio of an active ingredient between the particles and the soluble polymer.

(2) The particle size to be dispersed in the soluble polymer.

(3) Selection of non-soluble polymer or polymers which permits the modification of both the solubility of particles and diffusion velocity of an active ingredient in the particles in the manner as desired.

(4) The use of one or more kind(s) of particles which differ from each other in their solubilities.

(5) The ratio of the amounts of particles and soluble polymer to be combined.

(6) Selection of soluble polymer or polymers having desired viscosity.

By selection of suitable conditions in regard to the above variables, there is obtained the pharmaceutical composition of the invention which releases one or more of active ingredients in the manner as contemplated. Since the surface of the composition of the invention is mainly composed of water soluble polymer, it does not give any uncomfortable feeling to patients.

The following examples are presented by way of illustration of specific embodiments of the pharmaceutical composition of the invention. In examples, part or parts are represented by weight basis.

Example 1

Poly(lactic acid) (10 parts) and tetracycline hydrochloride (2 parts) are dissolved in methylene chloride (100 parts). Flow casting of the resultant mixture yields a sheet, which is ground into particles having an average size of 50μm.

The particles (10 parts) and hydroxypropyl cellulose (10 parts) are uniformly admixed. The mixture is blended with water, extruded with pressure, and dried. The bar-like shaped product of 1.0 mm diameter is thus obtained.

Example 2

Methacrylic acid / methyl methacrylate copolymer (1:2 molar ratio) (80 parts) is dissolved in ethanol (1000 parts). In the solution are suspended or dissolved indomethacin (5 parts) and triacetin (20 parts), and the mixture is cast into a sheet, which is then pulverized into particles having an average size of 80μm.

Hydroxypropyl cellulose (10 parts) is dissolved in water (1000 parts), and tetracycline (25 parts) is added to the resultant solution, after adjusting to pH 6.0 by addition of hydrochloric acid. The resultant mixture (80 parts) is uniformly admixed with the particles obtained above (20 parts) to yield the product in a gel form.

Example 3

The particles produced in Example 2 (20 parts), methyl cellulose (80 parts) and tetracycline hydrochloride (5 parts) are uniformly admixed, and the resulting mixture is pressed to a sheet having a 500μm thickness.

Experiment 1

The controlled release of an active ingredient was evaluated for a pharmaceutical composition of the invention which contains two kinds of active ingredients.

Method and materials

(1) Preparation of Sample

Methacrylic acid / methyl methacrylate copolymer (1:2 molar ratio) (80 parts) was dissolved in ethanol (1000 parts). Triacetin (20 parts) and tetracycline hydrochloride (6 parts) were then mixed with the resultant solution. The mixture was cast on a Teflon tray and dried at 40°C. The resultant sheet was pulverized into particles of 105μm to 177μm in size.

On the other hand, hydroxypropyl cellulose (viscosity of 2% aqueous solution is 1000 to 4000 cp at 20°C) (one part) was dissolved in water (99 parts). In the solution was dissolved tetracaine hydrochloride (0.03 part).

The hydroxypropyl cellulose solution and the particles are uniformly admixed at a weight ratio of 100:0.5, and the mixture is deaerated, cast on a Teflon tray with care to ensure the constant thickness, and air-dried to yield a film having 300μm thickness.

In a solution of hydroxypropyl cellulose (1 part) dissolved in water (100 parts) were dissolved tetracycline hydrochloride (0.02 part) and tetracaine hydrochloride (0.02 parts), and the mixture was adjusted to pH 6, deaerated, cast on a Teflon tray, air-dried to obtain a film having 300μm thickness, which was employed as a reference.

(2) Evaluation of Dissolution Rate

The dissolution rates of the active ingredients released from the films obtained above were measured using a phosphate buffer (500ml), pH 7.2, at 37°C, in accordance with the Rotating Basket Method (100 rpm) of Japanese Pharmacopoeia (X).

Results

The dissolution profiles of the film of the invention and that of the reference are respectively shown in Fig. 1 and Fig. 2 of the accompanying drawing. The abscissa indicates immersion time and the ordinate indicates the dissolution rate. Fig. 1 shows that two active ingredients were released from the film with different release patterns while Fig. 2 shows the same and identical release pattern of the two active ingredients. Thus, this experiment illustrates that the composition of the invention permits separate control of the release patterns of two active ingredients. It also teaches that the composition of the invention in the form of a sustained release formulation may be obtained where a single active ingredient is employed rather than two active ingredients as employed in this experiment.

Claims

1. A controlled-released pharmaceutical composition in the form of gel, sheet, film, or bar to be inserted or placed into a periodontal pocket for treating a periodontal disease, said composition comprising a therapeutically effective amount of at least one active ingredient effective for the treatment or the periodontal disease, said active ingredient being dispersed in a two-phase carrier consisting of

   (a) a continuous phase consisting of a water-soluble polymer capable of dissolving in water at a concentration of more than 1% by weight irrespective of pH, and

   (b) a discontinuous phase consisting of solid particles composed of a polymer capable of dissolving in water at a concentration of at least about 0.1% and not more than about 1.0% by weight; or solid particles composed of a polymer capable of dissolving in water at a concentration of more than 1% by weight only at a pH higher than 4 or lower than 6.

   said particles having an average size ranging from 1 μm to 500 μm and being dispersed in said water-soluble polymer, with the weight ratio of said particles to said water-soluble polymer ranging from 1:99 to 99:1 on a dry weight basis, said water-soluble polymer being selected from the

   methyl cellulose, hydroxypropyl cellulose, sodium carboxymethyl cellulose, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, sodium alginate, propylene glycol al-

ginate, pullulan, tragacanth, xanthan gum, chitosan, polyethylene oxide, polyvinyl alcohol, polyacrylic acid, polymethacrylic acid, and salts thereof, and said solid particles being selected from

poly(glycolic acid), poly(lactic acid), polytetramethylglycolide, polydiethylglycolide, poly-ε-caprolactone, poly(DL-decalactone), poly(alkyleneadipate), methylacrylate/ methacrylic acid copolymer, methylacrylate/ methacrylic acid/ octylacrylate copolymer, ethylacrylate/ methacrylic acid copolymer, methylacrylate/ methacrylic acid/ methylmethacrylate copolymer, methylmethacrylate/ methacrylic acid copolymer, cellulose acetate phthalate, cellulose acetate succinate, cellulose acetate maleate, starch acetate phthalate, amylose acetate phthalate, methyl cellulose phthalate, hydroxypropylmethyl cellulose phthalate, hydroxyethyl ethylcellulose phthalate, hydroxypropylmethyl cellulose acetate succinate, carboxymethylethyl cellulose, polyvinylalcohol phthalate, polyvinyl acetate phthalate, polyvinylacetal phthalate, polyvinylbutylate phthalate, methylmethacrylate/ dimethylaminoethyl methacrylate copolymer, and polyvinylacetal/ dimethylamino acetate.

2. The composition of claim 1 wherein two active ingredients are dispersed in said carrier.

3. The composition of claim 1 having at least two active ingredients whereof one is in the continuous phase and one is in the discontinuous phase, whereby they have different release profiles.

4. Use of the two-phase carrier according to Claim 1 as a carrier for preparing a controlled-release pharmaceutical composition in the form of gel, sheet, film or bar to be inserted or placed into a periodontal pocket for treating a periodontal disease, a therapeutically effective amount of at least one active ingredient effective for tile treatment of the periodontal disease being dispersed in said two-phase carrier.

5. Use according to claim 4 wherein two active ingredients are dispearsed in said carrier.

6. Use according to claim 5 wherein one active ingredient is dispersed in the continuous phase and the other active ingredient is dispersed in the discontinuouse phase.

7. A process for preparing the controlled-released pharmaceutical composition of Claim 1, 2 or 3 which comprises the following steps:

(1) preparing polymer particles using a polymer capable of dissolving in water at a concentration of at least about 0.1% and not more than about 1.0% by weight or a polymer capable of dissolving in water only at a pH higher than 4 or a pH lower than 6 at a concentration of more than 1% by weight, said polymer being specified in Claim 1.

(2) uniformly admixing the particles and a polymer capable of dissolving in water at a concentration of more than 1% by weight irrespective of pH, said polymer being specified in Claim 1.

(3) processing the mixture to form a pharmaceutical composition in the form of gel, sheet, film or bar, wherein at least one active ingredient effective for the treatment of the periodontal disease is added in Step (1) and/or Step (2).

8. The process of Claim 7, wherein one active ingredient is added in Step (1) and another ingredient is added in Step (2).

Revendications

1. Composition pharmaceutique à libération contrôlée sous la forme de gel, feuille, pellicule ou barre à insérer ou placer dans une poche parodontale pour le traitement d'une parodontopathie, ladite composition comprenant une quantité thérapeutique efficace d'au moins un ingrédient actif efficace pour le traitement de la parodontopathie, ledit ingrédient actif étant dispersé dans un support à deux phases constitué de

(a) une phase continue formée d'un polymère hydrosoluble capable de se dissoudre dans l'eau à une concentration de plus de 1 % en poids quel que soit le pH, et

(b) une phase discontinue formée de particules solides constituées d'un polymère capable de se dissoudre dans l'eau à une concentration d'au moins environ 0,1 % et d'au plus environ 1,0 % en poids ; ou de particules solides constituées d'un polymère capable de se dissoudre dans l'eau à une concentration de plus de 1 % en poids uniquement à un pH supérieur à 4 ou inférieur à 6,

lesdites particules ayant une taille moyenne comprise entre 1 µm et 500 µm et étant dispersées dans ledit polymère hydrosoluble, le rapport en poids desdites particules audit polymère hydrosoluble étant compris entre 1:99 et 99:1 en poids sec, ledit polymère hydrosoluble étant choisi parmi ceux qui suivent : méthylcellulose, hydroxypropylcellulose, car-

boxyméthylcellulose sodique, hydroxypropylméthylcellulose, hydroxyéthylcellulose, alginate de sodium, alginate de propylène-glycol, pullulane, gomme adragante, gomme de xanthane, chitosane, poly(oxyde d'éthylène), alcool polyvinylique, acide polyacrylique, acide polyméthacrylique et leurs sels, et lesdites particules solides étant choisies parmi ceux qui suivent : poly(acide glycolique), poly(acide lactique), polytétraméthylglycolide, polydiéthylglycolide, poly-ε-caprolactone, poly(DL-décalactone), poly(adipate d'alkylène), copolymère acrylate de méthyle/acide méthacrylique, copolymère acrylate de méthyle/acide méthacrylique/acrylate d'octyle, copolymère acrylate d'éthyle/acide méthacrylique, copolymère acrylate de méthyle/acide méthacrylique/méthacrylate de méthyle, copolymère méthacrylate de méthyle/acide méthacrylique, acétophtalate de cellulose, acétosuccinate de cellulose, acétomaléate de cellulose, acétophtalate d'amidon, acétophtalate d'amylose, phtalate de méthylcellulose, phtalate d'hydroxypropylméthylcellulose, phtalate d'hydroxyéthyléthylcellulose, acétosuccinate d'hydroxypropylméthylcellulose, carboxyméthyléthylcellulose, phtalate d'alcool polyvinylique, acétophtalate de polyvinyle, phtalate de polyvinylacétal, butyrophtalate de polyvinyle, copolymère méthacrylate de méthyle/méthacrylate de diméthylaminoéthyle et polyvinylacétal/diméthylaminoacétate.

2. Composition selon la revendication 1, dans laquelle deux ingrédients actifs sont dispersés dans ledit support.

3. Composition selon la revendication 1, contenant au moins deux ingrédients actifs dont l'un se trouve dans la phase continue et l'autre dans la phase discontinue, de sorte qu'ils aient des profils de libération différents.

4. Utilisation du support à deux phases selon la revendication 1 comme support pour préparer une composition pharmaceutique à libération contrôlée sous la forme de gel, feuille, pellicule ou barre à insérer ou placer dans une poche parodontale pour le traitement de parodontopathies, une quantité thérapeutique efficace d'au moins un ingrédient actif, efficace pour le traitement de la parodontopathie, étant dispersée dans ledit support à deux phases.

5. Utilisation selon la revendication 4, dans laquelle deux ingrédients actifs sont dispersés dans ledit support.

6. Utilisation selon la revendication 5, dans laquelle un ingrédient actif est dispersé dans la phase continue et l'autre ingrédient actif est dispersé dans la phase discontinue.

7. Procédé pour préparer la composition pharmaceutique à libération contrôlée de la revendication 1, 2 ou 3, qui comprend les étapes suivantes :
   (1) préparer des particules de polymère en utilisant un polymère capable de se dissoudre dans l'eau à une concentration d'au moins environ 0,1 % et d'au plus environ 1,0 % en poids ou un polymère capable de se dissoudre dans l'eau a une concentration de plus de 1 % en poids uniquement à un pH supérieur à 4 ou un pH inférieur à 6 ledit polymère étant spécifié dans la revendication 1 ;
   (2) mélanger uniformément les particules et un polymère capable de se dissoudre dans l'eau à une concentration de plus de 1 % en poids quel que soit le pH, ledit polymère étant spécifié dans la revendication 1 ;
   (3) transformer le mélange pour former une composition pharmaceutique sous la forme de gel, feuille, pellicule ou barre,
   dans lequel au moins un ingrédient actif, efficace pour le traitement de parodontopathies, est ajouté dans l'Etape (1) et/ou l'Etape (2).

8. Procédé selon la revendication 7, dans lequel un ingrédient actif est ajouté dans l'Etape (1) et un autre ingrédient est ajouté dans l'Etape (2).

Patentansprüche

1. Pharmazeutisches Präparat mit kontrollierter, verzögerter Freigabe in Form eines Gels, einer Folie bzw. Platte, eines Films oder eines Stabes, das in eine periodontale Tasche eingesetzt oder eingesetzt wird, für die Behandlung einer periodontalen Krankheit, dadurch **gekennzeichnet,** daß das Präparat eine therapeutisch wirksame Menge von mindestens einem aktiven Bestandteil, der für die Behandlung der periodontalen Krankheit wirksam ist, enthält, wobei der aktive Bestandteil in einem Zweiphasen-Träger dispergiert ist, der aus
   (a) einer kontinuierlichen Phase, die aus einem wasserlöslichen Polymeren, welches sich in Wasser in einer Konzentration von über 1 Gew.-%, unabhängig vom pH-Wert, lösen kann, besteht, und
   (b) einer diskontinuierlichen Phase, die aus festen Teilchen, die aus einem Polymeren,

das sich in Wasser in einer Konzentration von mindestens etwa 0,1 Gew.-% und nicht mehr als etwa 1,0 Gew.-% lösen kann, bestehen, oder aus festen Teilchen, die aus einem Polymeren, das sich in Wasser in einer Konzentration von über 1 Gew.-% nur bei einem pH-Wert über 4 oder niedriger als 6 lösen kann, besteht,

besteht, wobei die Teilchen eine durchschnittliche Teilchengröße im Bereich von 1 µm bis 500 µm aufweisen und in dem genannten wasserlöslichen Polymeren dispergiert sind, das Gewichtsverhältnis der Teilchen zu dem wasserlöslichen Polymeren im Bereich von 1:99 bis 99:1 auf Trockengewichtsbasis liegt, das wasserlösliche Polymere ausgewählt wird aus der Gruppe:

Methylcellulose, Hydroxypropylcellulose, Natriumcarboxymethylcellulose, Hydroxypropylmethylcellulose, Hydroxyethylcellulose, Natriumalginat, Propylenglykolalginat, Pullulan, Traganthgummi, Xanthangummi, Chitosan, Polyethylenoxid, Polyvinylalkohol, Polyacrylsäure, Polymethacrylsäure und ihren Salzen, und daß die festen Teilchen ausgewählt werden aus:

Poly(glykolsäure), Poly(milchsäure), Polytetramethylglykolid, Polydiethylglykolid, Poly-ε-caprolacton, Poly-(DL-decalacton), Poly-(alkylenadipat), Methylacrylat/Methacrylsäure-Copolymeren, Methylacrylat/Methacrylsäure/Octylacrylat-Copolymeren, Ethylacrylat/Methacrylsäure-Copolymeren, Methylacrylat/Methacrylsäure/Methylmethacrylat-Copolymeren, Methylmethacrylat/Methacrylsäure-Copolymeren, Celluloseacetatphthalat, Celluloseacetatsuccinat, Celluloseacetatmaleat, Stärkeacetatphthalat, Amyloseacetatphthalat, Methyloellulosephthalat, Hydroxypropylmethylcellulosephthalat, Hydroxyethylethylcellulosephthalat, Hydroxypropylmethylcelluloseacetatsuccinat, Carboxymethylethylcellulose, Polyvinylalkoholphthalat, Polyvinylacetatphthalat, Polyvinylacetalphthalat, Polyvinylbutylatphthalat, Methylmethacrylat/Dimethylaminoethylmethacrylat-Copolymeren und Polyvinylacetal/Dimethylaminoacetat.

2. Präparat nach Anspruch 1, dadurch **gekennzeichnet,** daß zwei aktive Bestandteile in dem Träger dispergiert sind.

3. Präparat nach Anspruch 1, dadurch **gekennzeichnet,** daß es mindestens zwei aktive Bestandteile enthält, wovon einer in der kontinuierlichen Phase und einer in der diskontinuierlichen Phase vorliegt, wobei sie unterschiedliche Freigabeprofile aufweisen.

4. Verwendung eines Zweiphasen-Trägers nach Anspruch 1 als Träger für die Herstellung eines pharmazeutischen Präparats mit kontrollierter Freigabe in Form eines Gels, einer Folie bzw. Platte, eines Films oder eines Stabes, das in eine periodontale Tasche eingesetzt oder eingelegt wird, für die Behandlung einer periodontalen Krankheit, wobei das pharmazeutische Präpart eine therapeutisch wirksame Menge von mindestens einem aktiven Bestandteil, der für die Behandlung der periodontalen Krankheit wirksam ist und in dem Zweiphasen-Träger dispergiert ist, enthält.

5. Verwendung nach Anspruch 4, dadurch **gekennzeichnet,** daß zwei aktive Bestandteile in dem Träger dispergiert sind.

6. Verwendung nach Anspruch 5, dadurch **gekennzeichnet,** daß ein aktiver Bestandteil in der kontinuierlichen Phase dispergiert ist und der andere aktive Bestandteil in der diskontinuierlichen Phase dispergiert ist.

7. Verfahren zur Herstellung des pharmazeutischen Präparats mit kontrollierter Freigabe nach Anspruch 1, 2 oder 3, dadurch **gekennzeichnet,** daß die folgenden Stufen durchgeführt werden:

(1) Herstellung von Polymerteilchen unter Verwendung eines Polymeren, welches sich in Wasser in einer Konzentration von mindestens etwa 0,1 und nicht mehr als etwa 1,0 Gew.-% lösen kann, oder eines Polymeren, welches sich in Wasser nur bei einem pH-Wert über 4 oder einem pH-Wert unter 6 in einer Konzentration von nicht mehr als 1 Gew.-% lösen kann, wobei das Polymere das in Anspruch 1 definierte Polymere ist,

(2) einheitliches Vermischen der Teilchen und des Polymeren, welches sich in Wasser bei einer Konzentration von über 1 Gew.-%, unabhängig vom pH-Wert, lösen kann, wobei das Polymere in Anspruch 1 definiert wurde,

(3) Verarbeitung des Gemisches zu einem pharmazeutischen Präparat in Form eines Gels, einer Folie bzw. Platte, eines Films oder eines Stabes, wobei mindestens ein aktiver Bestandteil, der für die Behandlung der periodontalen Krankheit wirksam ist, bei der Stufe (1) und/oder der Stufe (2) zugegeben wird.

8. Verfahren nach Anspruch 7, dadurch **gekennzeichnet,** daß ein aktiver Bestandteil bei der

Stufe (1) und ein weiterer Bestandteil bei der Stufe (2) zugegeben werden.

Fig. 1

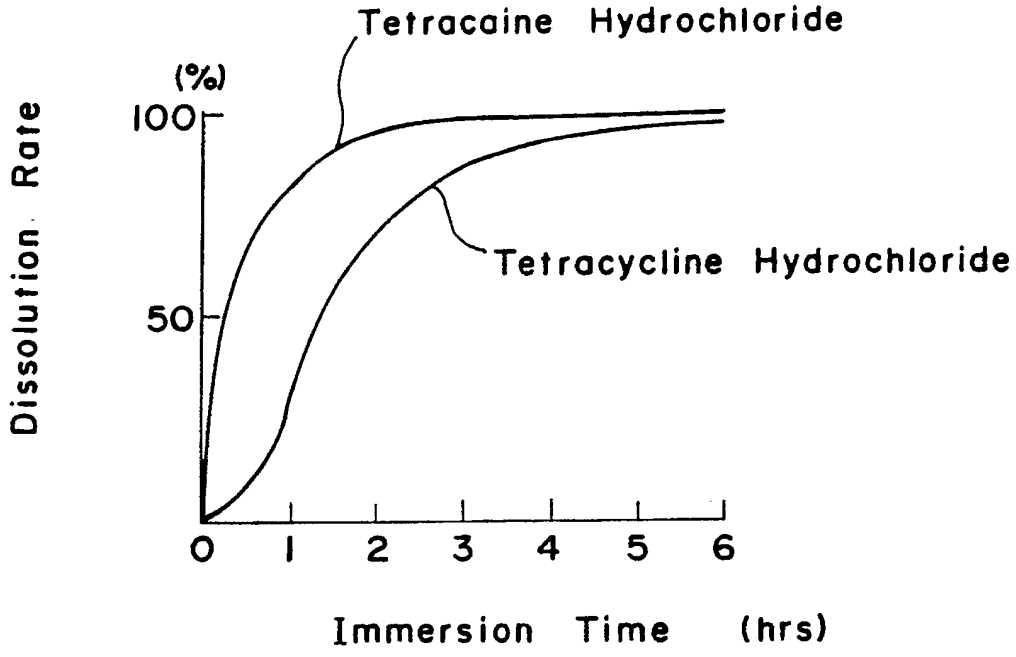
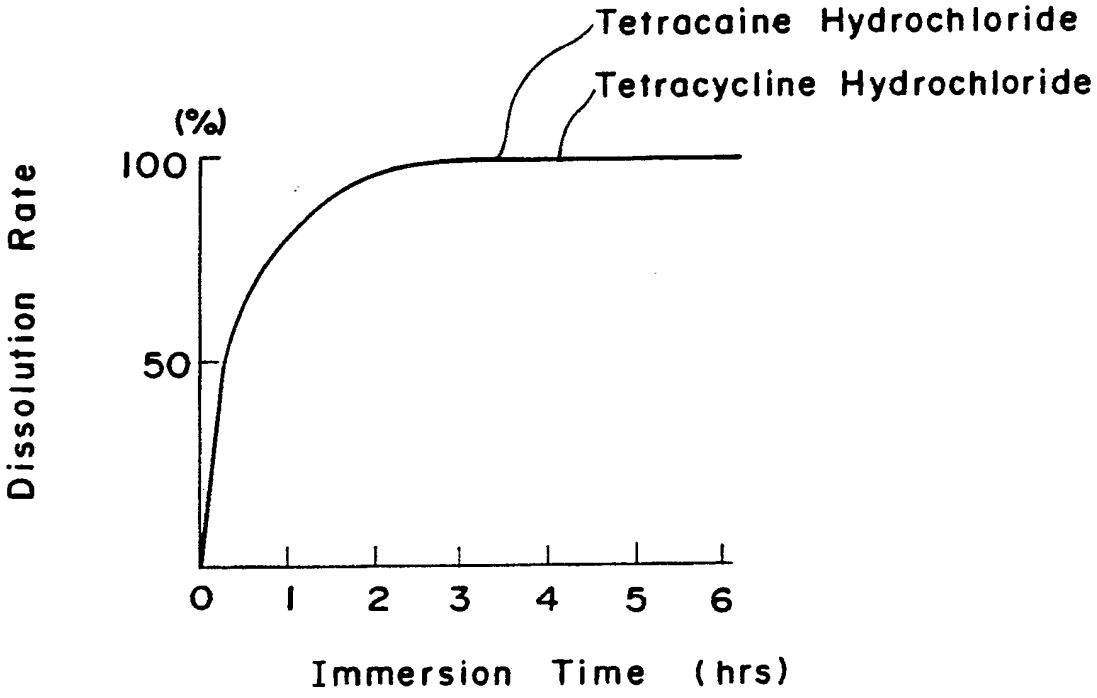


Fig. 2



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(54) **Bioadhesive extruded film for intra-oral drug delivery and process.**

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Description

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to a controlled-releasing medicament-containing preparation for intra-oral use. In particular it is more especially concerned with such a preparation (and the process of using it) in the form of a very thin extruded thermoplastic film (which can be in single layer or laminated multi-layer form) having at least one bioadhesive layer containing 22.4-68.3% by weight of a specified thermoplastic cellulose ether and 23.75-60% by weight of a specified homopolymer of ethylene oxide which can adhere to the mucosa of the oral cavity. The extruded film drug delivery system of the present invention, which has incorporated therein the medicament to be dispensed, is so thin and flexible when wet as to be unobtrusive to the patient after it has been properly positioned and placed in the mouth.

Description of the Prior Art

Several systems have previously been described which pertain to the delivery of drugs into the oral cavity. These include:

1. Treatment of periodontal disease with tetracycline. chlorhexidine or metronidazole loaded into hollow cellulose acetate fibers. These fibers are packed in the periodontal pockets and provide controlled release of the drug to the infected area.
2. Cast films containing ethyl cellulose/propylene glycol with chlorhexidine or metronidazole for treatment of periodontal disease.
3. An orthodontic appliance with a hydroxyethyl methacrylate/methyl methacrylate copolymer (HEMA/MMA) matrix. Sodium fluoride is incorporated into the HEMA/MMA matrix to provide sustained fluoride release and enhanced anticaries activity. HEMA/MMA with fluoride may also be attached to the tooth in the form of a wafer-like tablet.
4. Silicone/ethyl cellulose/polyethylene glycol films containing sodium fluoride are applied as coatings on orthodontic bands or in chewing gum. Controlled release of fluoride and anticaries activity is claimed.

The above systems are discussed in the "The Compendium of Continuing Education" Vol VI, No. 1, Jan.1985 p. 27-36 review article "Controlled Drug Delivery: A New Means of Treatment of Dental Disease", by J. Max Goodson, D.D.S., Ph.D. of the Forsyth Dental Center. Other systems, described in GB patent application 2,042,888 and U.S. Patents 4,292,299/4,226,848 (Teijin Ltd., Japan), use combinations of cellulosic and polyacrylate polymers. The preferred materials are hydroxypropyl cellulose ("Klucel") and a copolymer of acrylic acid ("Carbopol") that is administered in the form of thin tablets (discs), granules or powder. Other polymers that might be added are vinyl copolymers, polysaccharides, gelatin and collagen. U.S. patent 4,517,173 (Nippon Soda Co. Ltd, Japan) uses various celluloses in a multi-layered non-extruded cast film preparation.

Examples of prior art products currently on the market include ointments such as ORABASE* with Benzocaine (Squibb), Kenalog* (Triamcinolone Acetonide) in ORABASE* (Squibb) and Mycostatin* (Nystatin) ointment (Squibb).

The prior art products and delivery systems described above are useful but have the following disadvantages:

Tablets, appliances, hollow fibers are "bulky" in the mouth, are difficult to keep in place and inconvenient to apply.

Ethyl cellulose and/or silicone films do not adhere to mucosal tissue.

Ointments (i.e., ORABASE*) have an unpleasant feel and do not last very long.

Except for ORABASE*, all the foregoing systems require professional application to the tooth or periodontal pockets.

The bioadhesive film of the present invention alleviates many of the above problems. It may be applied easily by the consumer. It has very little or no mouthfeel, it has good adhesion to the mucosal tissues, and provides controlled release of the medicament.

Also EP-A-0 063 604 discloses a mucous membrane-adhering film preparation in which the one surface of water-soluble high polymer film containing pharmaceutical agents is treated to be made difficultly water-soluble. JP-A-5 890 507 discloses a film formed by an injection moulding machine or an extrusion moulding machine, the film comprising a mixture of a water-soluble polymer (water-soluble cellulose derivative), an active component (drug absorbable through the mucous membrane) arbitrary additives (diluent, taste or

scent improvers, colorants etc) and a plasticizer (polyethylene glycol).

Object of the Invention

It is an object of this invention to provide an extruded film that is an effective and convenient intra-oral drug delivery system and method for applying and delivering controlled dosages of therapeutic agents into the oral cavity. This technology may also be extended for controlled drug delivery in skin care, gynecological applications, wound care and like uses.

Summary of the Invention

The invention involves a pharmaceutically acceptable controlled-releasing medicament-containing extruded single or multi-layered thin film, capable of adhering to a wet mucous surface, comprising a water soluble or swellable polymer matrix bioadhesive layer which can adhere to a wet mucous surface and which bioadhesive layer consists essentially of 22.4-68.3% by weight of hydroxypropyl cellulose of molecular weight above 100,000 23.75-60% of a homopolymer of ethylene oxide of molecular weight above 100,000, 0-12.5%, of a water-insoluble polymer selected from ethyl cellulose, propyl cellulose, Carboxy methyl cellulose free acid, polyethylene and polypropylene, and 2.85-5% of a plasticizer, said film having incorporated therein a pharmaceutically effective amount of said medicament, the presence of medicament and optional components making the total 100%.

The present invention is directed to an extruded single or multi-layered laminated thin (1-10 mils or 0.025-0.25 mm) film, composed of selected water soluble and/or insoluble polymers. Various therapeutic agents are incorporated into the film during manufacture which are useful for treatment of oral disorders (i.e., denture discomfort, caries, periodontal disease, aphthous ulcers, etc.).

The extruded film of the present invention must have at least one bioadhesive layer, but may also have a reservoir layer and/or an outer protective barrier membrane layer. The therapeutic agent may be incorporated into any or all of the layers. When properly formulated and fabricated, these films will adhere to wet mucosal surfaces, provide a protective barrier for injured tissue and deliver controlled/sustained dosages of medication to the infected areas. The film may be designed for localized drug delivery (i.e., the periodontal pocket, an aphthous lesion), or may allow diffusion of the drug into the oral cavity.

An example of a non-localized system would be the delivery of sodium fluoride for caries prevention. A single or laminated film with good adhesion to the tooth or mucosal tissue may be employed in which the fluoride release rates may be controlled by varying film solubilities and/or concentration of fluoride in a multi-layered film.

An example of a localized application of medication would be in the treatment of aphthous lesions. A laminated two layer film with benzocaine incorporated into the adhesive layer would directly contact the injured mucosa. The outer layer would consist of non-soluble/non-adhesive polymers that provide durability, protection and directs the delivery of benzocaine toward the lesion.

The film forming polymers that are useful in this invention are selected from pharmaceutical grade materials, or those that are considered generally regarded as safe (GRAS) as food additives. They include, hydroxypropyl cellulose, and polyethylene oxide homopolymers. Small amounts of other polymers. e.g., polyvinyl ether-maleic acid copolymers and the like may be used in small amounts as well, replacing a small portion of the other polymers. The above materials are either water soluble or swellable and are most useful in the bioadhesive layer of the film. Various non-soluble polymers may also be incorporated for modification of the film's permeability properties, such as ethyl cellulose, propyl cellulose, polyethylene, polypropylene and carboxymethylcellulose (free acid) in an amount of up to 12.5% by weight. By varying the ratios of the above polymers both the solubility and the adhesive properties of each layer of film may be controlled. Therefore, depending on the desired delivery rate, the type of disorder to be treated, the area to be treated and the medication being administered it is possible to custom design the film by selecting and blending various polymers. The final film product may also be fabricated into flexible tapes of varied thickness and width, "spots" of different sizes and shapes or other pre-shaped forms.

The medicaments and pharmaceutical agents set forth in the prior art discussed above may generally be delivered by the drug delivery system of the present invention. Usable medicaments are those which are capable of withstanding the heats and pressures generated in the extrusion process involved in making the film of the present invention. Preferred medicaments include:

Anesthetics/Analgesics - benzocaine, dyclonine HCl, phenol, aspirin, phenacetin, acetaminophen, potassium nitrate, etc.

Anticaries Agents - sodium fluoride, sodium monofluorophosphate, stannous fluoride, etc.

Anti-inflammatories - hydrocortisone acetate, triamcinolone acetonide, dipotassium, glycyrrhizinate, etc.
Antihistamines - chlorpheniramine maleate, ephedrine HCL, diphenhydramine HCL, etc.
Antibiotics - i.e., tetracycline, doxycycline hyclate, meclocycline, minocycline, etc.
Antibacterials - chlorhexidine, cetyl pyridinium chloride, benzethonium chloride, dequalinium chloride, silver sulfadiazene, phenol, thymol, hexedine, hexetidine, alexidine, etc.
Fungistats - nystatin, miconazole, ketoconazole, etc.

The above are illustrative examples of therapeutic agents that are used to treat oral disorders. The present invention is not to be limited to these specific materials especially where it is intended to deliver drug outside of the oral cavity e.g. to skin where other drugs may be desirable.

The film of the present invention has the advantage of being an extruded film, rather than a cast film. When a multi-layered film is involved, the different layers can be coextruded and then laminated together, or else each layer can be separately extruded one on the other, and then laminated together, so that the final multi-layered film is still very thin. The films of the present invention can be made in thicknesses of only 1-10 mils or 0.025-0.25 mm. The films are so thin that when placed in the mouth after they become wet they soon become unobtrusive, and hardly noticeable by most patients.

The film must always have a bioadhesive layer, which enables it to adhere to wet mucosal surfaces. The bioadhesive layer has 22.4-68.3 wt % of hydroxpropyl cellulose, 23.75-60 wt % of a homopolymer of ethylene oxide and 2.85-5 wt % of a glycol plasticizer (all percents are % by weight).

The Hydroxypropyl cellulose (HPC), useful for purposes of the present invention is commercially available from Hercules, Inc. (Wilmington, DE) under the tradename KLUCEL*. Preferred grades include Klucel MF, with a molecular weight around 600,000 and having a viscosity of 4,000-6,000 cps (Brookfield) in 2 percent water solutions, or Klucel HP, having a molecular weight around 1,000,000 and viscosity of 1500-2500 cps in 1 percent water solution. Any HPC having a Molecular Weight above about 100,000 is useful for purposes of this invention.

The homopolymer of ethylene oxide useful for purposes of the present invention has a relatively high molecular weight, i.e., above 100,000 and preferably above 3,000,000. Such polymers are commercially available from various sources. The Union Carbide Corporation material, "Polyox WSR-301", which has a molecular weight of approximately 4,000,000 - 5,000,000 is most preferred for purposes of the present invention.

The "plasticizer" useful for purposes of the present invention are selected from glycols such as propylene glycol and polyethylene glycol; polyhydric alcohols such as glycerin and sorbitol; glycerol esters such as glycerol triacetate; fatty acid triglycerides such as NEOBEE* M-5 and MYVEROLS*; mineral oil; vegetable oils such as castor oil, etc.

For the uses for the present invention contemplated here, the plasticizer should be non-toxic. The purpose of the plasticizer is to improve polymer melt processing by reducing the polymer melt viscosity and to impart flexibility to the final product.

The preferred plasticizer for use in the present invention is either propylene glycol or polyethylene glycol (such as is available from Union Carbide Corporation as their series of Carbowaxes which runs from 200 to 600 molecular weight, of which we prefer to use Carbowax 400, which has a molecular weight of 400, average.

In addition to the polymers and plasticizer which are required ingredients of the films of the present invention, minor amounts of other non-essential but customary ingredients will often be used if desired, e.g., antioxidants, preservatives, flavors, colorants.

Detailed Description

The following examples will serve to illustrate the present invention in greater detail. The units shown in the examples are parts by weight. The thickness of the layers is expressed in either mils (.001 inches) or millimeters. For easy conversion, 4 mils is approximately equal to 0.1 mm.

EXAMPLE 1 - TRIPLE LAYERED LAMINATE CONTAINING SODIUM FLUORIDE FOR ANTICARIES PROTECTION:

This three layered film laminate is comprised of a "bioadhesive" layer, a sodium fluoride "reservoir" layer and, an "outer protective barrier membrane" layer, in which the composition and thickness of each layer are as shown below:

Ingredients	Bioadhesive Layer (4 mils) (0.1 mm)	% w/w Reservoir Layer (1 mil) (0.025 mm)	Outer Protective Barrier Membrane Layer (1 mil) (0.025 mm)
Polyethylene oxide homopolymer (Union Carbide-Polyox* WSR-301)	60.0	-	-
Hydroxypropyl Cellulose (Hercules, Inc.-Klucel* MF)	30.0	20.0	24.0
Polyethylene (Allied Chemical-6A) (Low Density)	5.0	-	-
Propylene Glycol, U.S.P.	3.0	-	-
Polyethylene Glycol 400 (Union Carbide)	2.0	-	-
Ethyl Cellulose (Hercules, Inc.-N100F)	-	59.0	69.6
Caprylic/Capric Triglyceride (PVO Incorporated-Neobee M-5)	-	5.0	6.0
Sodium Fluoride, U.S.P.	-	16.0	0.4
	100.0	100.0	100.0

The process used to make the above laminate was :

a) Powder Blending - Each layer is made separately and all ingredients used therein except propylene glycol and Neobee M-5 (liquid plasticizers) are placed in a Patterson Kelley (PK) V-blender equipped with liquid addition capabilities. The ingredients which are all powders are blended for approximately 10-15 minutes while the liquid plasticizer is slowly added to the mix. Three separate powder blends are made, one for each layer.

b) Extrusion Process - A standard Johnson 2-1/2 inch (0,0635 m) vinyl/polyolefin extruder equipped with a single three stage screw was used to extrude the "powder blend". The temperature conditions for the water soluble powders are however quite different from those used for vinyls and polyolefins. The

temperature (°C) profile for the "reservoir" and "membrane layers" of the triple laminate was as follows:

Barrel Zone 1	100
Barrel Zone 2	125
Barrel Zone 3	135
Barrel Zone 4	145
Barrel Zone 5	160
Barrel Zone 6	170
Adapter -	180
Die Zone 1	180
Die Zone 2	180
Die Zone 3	180

The films which had a width of 18 inches (0,45 m), were extruded at approximately 20 feet/minute (6 m/min) through a flat lipped die. The temperature profile for the "bioadhesive layer" was:

Barrel Zone 1	125
Barrel Zone 2	140
Barrel Zone 3	165
Barrel Zone 4	170
Barrel Zone 5	185
Barrel Zone 6	185
Adapter -	185
Die Zone 1	185
Die Zone 2	185
Die Zone 3	185

Each layer is extruded separately with the first layer extruded as a "free film". Successive layers are extruded onto each other and laminated by passing them through heated stainless steel rollers.

Test Results:

In vitro fluoride ion release studies were conducted on samples of the above described triple laminate film measuring 0.5 cm x 1.25cm (0.625 cm^2) according to the following procedures:
The test sample is adhered to a glass slide by prewetting the film and placing the bioadhesive layer on the glass surface. The slide is then immersed in a beaker containing 100 ml of distilled water with continuous stirring. Five milliliter aliquots are withdrawn from the solution, at prescribed time intervals, and analyzed for fluoride content with an Orion Ionanlyzer equipped with a fluoride specific electrode. Release rates are then calculated from the data.

The results obtained indicated fluoride release rates in the order of 0.05-0.2 mgs/cm^2/hr for 24 hours. This falls within the desirable range for maintaining constant low levels of fluoride in the mouth and enhanced anticaries activity. Release rates may be tailored to desired use levels by modification of the film composition and construction.

EXAMPLE 2 - SINGLE LAYER ADHESIVE FILM CONTAINING HYDROCORTISON ACETATE (0.5%) AS AN ANTI-INFLAMMATORY AGENT:

The composition of the film, which was 0.1 mm. thick, was as follows:

Ingredients	% w/w
Ethylene Oxide Homopolymer (Polyox* WSR-301)	59.4
Hydroxypropyl Cellulose (Klucel* MF)	30.0
Polyethylene (AC-6A)	5.0
Propylene Glycol	3.0
Polyethylene Glycol 400	2.0
Butylated Hydroxy Toluene (BHT) FCC (preservative)	0.1
Hydrocortisone Acetate	0.5
	100.0

The powder blending process and extruder conditions used were the same as those described in Example I for the "bioadhesive layer" of the sodium fluoride trilaminate. In vitro tests were performed on the above film and demonstrated a prolonged drug release pattern.

EXAMPLE 3 - SINGLE LAYER ADHESIVE FILM CONTAINING TRIAMCINOLONE ACETONIDE (0.1%) AS AN ANTI-INFLAMMATORY:

The composition of the film, which was 0.1 mm. thick, was as follows:

Ingredients	% w/w
Ethylene Oxide Homopolymer (Polyox WSR-301)	59.9
Hydroxypropyl Cellulose (Klucel MF)	29.9
Polyethylene (AC-6A)	5.0
Propylene Glycol	3.0
Polyethylene Glycol 400	2.0
BHT	0.1
Triamcinolone Acetonide	0.1
	100.0

The powder blending process and extruder conditions used to make the film of this Example 3 were the same as those of the "bioadhesive layer" of Example I.

Other desired active medicament ingredients may be incorporated into the adhesive films of any of Examples 1-3 in place of the particular medicament used in said examples. These include Benzocaine (analgesic), Potassium nitrate (analgesic), Silver sulfadiazene (antimicrobial).

Chlorhexidine (antimicrobial), miconazole nitrate (antifungal), Benzethonium chloride (antimicrobial), Tetracycline (antibiotic) and other similar therapeutic compounds.

EXAMPLE 4 - ANALGESIC FILMS WITH POTASSIUM NITRATE

This example shows 5 variations of the film having different solubilities, resulting in different release rates.

Ingredients	% w/w 1	2	3	4	5
Polyethylene oxide homopolymer (Polyox* WSR-301)	23.75	57.00	55.00	55.00	57.00
Hydroxypropyl Cellulose, N.F. (Klucel* HF)	68.30	-	-	-	-
Hydroxypropyl Cellulose, N.F. (Klucel* MF)	-	28.40	29.90	22.40	22.40
Ethyl Cellulose	-	4.75	5.00	12.50	12.50
Polyethylene Glycol 400	1.90	1.90	2.00	2.00	2.00
Polyethylene Glycol 8000	0.95	-	-	-	-
Propylene Glycol, U.S.P.	-	2.85	3.00	3.00	3.00
BHT, F.C.C.	0.10	0.10	0.10	0.10	0.10
Potassium Nitrate, F.C.C.	5.00	5.00	5.00	5.00	3.00

The above ingredients are blended in a Patterson-Kelly powder blender equipped with liquid addition capabilities. The resulting powder blend is then extruded into film on a Killion or Johnson vinyl extruder using processing procedures similar to those of the bioadhesive layer of Example I.

EXAMPLE 5 - ANESTHETIC FILMS WITH BENZOCAINE (LAMINATE)

This is an example of a two-layer laminate. The processing conditions used were similar to those of the bioadhesive layer and outer protective barrier membrane layer of Example I.

A.	Inner medicated bioadhesive layer	
	Polyoxyethylene Homopolymer (Polyox* WSR-301)	57.00
	Hydroxypropyl Cellulose, N.F. (Klucel* MF)	28.40
	Polyethylene (AC-6A)	4.75
	Propylene Glycol, U.S.P.	2.85
	Polyethylene Glycol 400	1.90
	BHT, F.C.C.	0.10
	Benzocaine, U.S.P.	5.00
		100.00
B.	Outer protective/barrier layer	
	Hydroxypropyl Cellulose (Klucel* MF)	78.00
	Ethyl Cellulose	20.00
	Polyethylene Glycol 400	2.00
		100.00

Part A was extruded on a Johnson extruder followed by subsequent extrusion and lamination of Part B to A.

Samples were applied to oral lesions, and provided profound anesthetic effects (lasting several hours) within minutes of application.

The identical two-layer laminate may also be made by coextruding the inner medicated bioadhesive layer (Part A) and the outer protective barrier layer (Part B) through separate die slots within a coextruder and laminating the two layers together.

EXAMPLE 6 - ANESTHETIC FILMS WITH PHENOL AND DYCLONINE HCl

Four variations of a single layer bioadhesive film were made as shown below:

Ingredients	1	2	3	4
Polyethylene oxide homo-polymer (Polyox* WSR-301)	59.10	54.00	59.70	58.20
Hydroxypropyl Cellulose (Klucel HF)	29.45	26.91	29.75	29.00
Ethyl Cellulose	4.93	4.50	4.98	4.85
Propylene Glycol, U.S.P.	2.96	2.70	2.99	2.91
Polyethylene Glycol 400	1.97	1.80	1.99	1.94
BHT, F.C.C.	0.09	0.09	0.09	0.10
Phenol, U.S.P.	1.50	-	-	-
Dyclonine HCl	-	10.00	0.50	3.00

Following the procedures for the bioadhesive layer of Example I, the powders were blended in P-K blender equipped with liquid addition capabilities. Resulting powders were extruded on a Killion laboratory-sized extruder.

EXAMPLE 7 - SILVER SULFADIAZENE FILMS - ANTIMICROBIAL

Three different single-layered bioadhesive films containing 1.0% 0.5% and 0.5% respectively of silver sulfadiazene (SSD) were prepared on a heated Carver laboratory press (designed to simulate extruded conditions) as shown below.

Ingredients	% w/w A	% w/w B
Polyethylene oxide homopolymer (Polyox* WSR-301)	60.00	60.00
Hydroxypropyl Cellulose (Klucel* HF)	28.9	29.4
Polyethylene (AC-6A)	5.0	5.0
Propylene Glycol, U.S.P.	3.0	3.0
Polyethylene Glycol 400	2.0	2.0
BHT, F.C.C.	0.1	0.1
Silver Sulfadiazine	1.0	0.5
	100.0	100.0

Effects on wound repair and activity against Staphylococcus aureus were evaluated in the guinea pig model. Full-thickness excisions were inoculated with 3.8 x 10^5 organisms, (Staph. aureus) and wound surface microbiology samples taken 10 minutes and 24 hours after treatment. Test films were placed on the wound and covered with BIOCLUSIVE* Transparent Dressings secured with elastic tape. Wound contraction was measured over an eight-day period using OPTOMAX* Computer-Assisted Image Analysis. The three films tested were the following:

A. 1.0% Silver Sulfadiazene, 125 ° C/2 minutes/4 tons
B. 0.5% Silver Sulfadiazene, 125 ° C/2 minutes/4 tons
C. 0.5% Silver Sulfadiazene, 150 ° C/3 minutes/4 tons

SILVADENE Cream and un untreated occluded control. The results indicated that:

1. SILVADENE* treated wounds significantly inhibited full-thickness wound contraction.
2. Film A, B and C inhibited wound contraction relative to that of BIOCLUSIVE* dressed wounds.
3. The three SSD films each permitted substantially faster wound contraction than that of wounds treated daily with SILVADENE* cream.
4. All films were very active against S. aureus 24 hours after inoculation.

The films may be scaled up by using an extruder. This example demonstrates the feasibility of such a film to perform its intended purpose. Use of a press for larger samples would result in a non-uniform and lower-quality film than an extruded film.

Based on the above findings, the films were very effective antibacterial agents, while mildly inhibiting wound contraction. They offer clinicians a convenient and more effective delivery system for antimicrobials which can be place in wounds beneath any dressing or can be laminated to any acceptable dressing face.

Claims

1. A pharmaceutically acceptable controlled-releasing medicament-containing extruded single or multilayered thin film, capable of adhering to a wet mucous surface, comprising a water soluble or swellable polymer matrix bioadhesive layer which can adhere to a wet mucous surface and which bioadhesive layer consists essentially of 22.4-68.3% by weight of a hydroxypropyl cellulose having a molecular weight above 100,000, 23.75-60% by weight of a homopolymer of ethylene oxide having a molecular weight above 100,000, 0-12.5% by weight of a water-insoluble polymer selected from ethyl cellulose, propyl cellulose, carboxymethyl cellulose free acid, polyethylene and polypropylene, and 2.85-5% of a plasticizer, said film having incorporated therein a pharmaceutically effective amount of said medicament, the presence of medicament and optional components making the total 100%.

2. The extruded film of claim 1, made in a form which is so thin and flexible when wet as to be unobtrusive to the patient when properly positioned and placed in the patient's mouth.

3. The extruded film of claim 2 having a thickness no greater than 0.25 millimeters.

4. The extruded film of claim 3 wherein, in the bioadhesive layer the homopolymer of ethylene oxide has a molecular weight from 3,000,000 to 5,000,000.

5. The extruded film of Claim 3, in multi-layer laminated form, which in addition to the bioadhesive layer also contains a reservoir layer in which at least a major portion of the medicament is contained.

6. The extruded multi-layer film of Claim 5 in which the reservoir layer consists essentially of a polymer matrix comprised of both a water soluble or swellable polymer and a non-water soluble polymer selected from ethyl cellulose, propyl cellulose, polyethylene and polypropylene, and also hydroxypropyl cellulose.

7. The extruded film of Claim 4 in multi-layer laminated form, which in addition to the bioadhesive layer also contains an outer protective-barrier membrane layer.

8. The extruded multi-layer film of Claim 7 in which the outer protective-barrier membrane layer is thinner than the bioadhesive layer, and said outer protective barrier layer consists essentially of a polymer matrix of a major proportion of a non-water-soluble polymer selected from ethyl cellulose, propyl cellulose, polyethylene and polypropylene, and a minor proportion of hydroxypropyl cellulose.

9. The extruded multi-layer film of Claim 1 in the form of a triple layered laminate containing sodium fluoride for anticaries protection having the following composition:

Ingredients	Bioadhesive Layer (0.1 mm)	% w/w Reservoir Layer (0.025 mm)	Outer Protective Barrier Membrane Layer (0.025 mm)
Polyethylene oxide homopolymer (MW 3,000,000 minimum)	60.0	-	-
Hydroxypropyl Cellulose (MW 1,000,000)	30.0	20.0	24.0
Polyethylene (Low Density)	5.0	-	-
Propylene Glycol, U.S.P.	3.0	-	-
Polyethylene Glycol (MW 400)	2.0	-	-
Ethyl Cellulose	-	59.0	69.6
Caprylic/Capric Triglyceride	-	5.0	6.0
Sodium Fluoride	-	16.0	0.4
	100.0	100.0	100.0

Patentansprüche

1. Ein pharmazeutisch verträglicher, dünner extrudierter Film, der ein Medikament enthält und kontrolliert freisetzt, mit einer einzigen oder mit mehreren Schichten, der die Fähigkeit aufweist, daß er auf der nassen Schleimhautoberfläche festkleben kann, umfassend eine wasserlösliche oder quellbare Polymermatrix einer bioadhäsiven Schicht, die auf der nassen Oberfläche der Schleimhaut kleben kann, wobei die bioadhäsive Schicht im wesentlichen aus 22,4 - 68,3 Gew.-% Hydroxypropyl-Cellulose mit einem Molekulargewicht von oberhalb 100 000, 23,75 - 60 Gew.-% eines Homopolymers von Ethylenoxid mit einem Molekulargewicht von oberhalb 100 000, 0 - 12,5 Gew.-% eines wasserunlöslichen Polymers, ausgewählt aus Ethyl-Cellulose, Propyl-Cellulose, Carboxymethyl-Cellulose in Form der freien Säure, Polyethylen und Polypropylen und 2,85 - 5 % eines Weichmachers besteht, wobei der Film eine pharmazeutisch wirksame Menge des Medikamentes inkorporiert enthält und das Medikament und die wahlweise enthaltenen Komponenten insgesamt 100 % ergeben.

2. Extrudierter Film nach Anspruch 1, der in einer Form hergestellt ist, die so dünn und flexibel ist, daß er, wenn er naß ist, den Patienten nicht stört, wenn er im Mund des Patienten an die richtige Stelle gelegt und eingebracht worden ist.

3. Extrudierter Film nach Anspruch 2 mit einer Dicke, die nicht größer als 0,25 mm ist.

4. Extrudierter Film nach Anspruch 3, bei dem die bioadhäsive Schicht des Homopolymers von Ethylenoxid ein Molekulargewicht von 3 000 000 bis 5 000 000 aufweist.

5. Extrudierter Film nach Anspruch 3 in einer mehrschichtigen laminierten Form, die zusätzlich zur bioadhäsiven Schicht noch eine Reservoir-Schicht enthält, in der zumindest ein Hauptanteil des Medikamentes enthalten ist.

6. Extrudierter mehrschichtiger Film nach Anspruch 5, in dem die Reservoir-Schicht im wesentlichen aus einer polymeren Matrix besteht, die sowohl aus einem wasserlöslichen und quellbaren Polymer und einem nichtwasserlöslichen Polymer besteht, das ausgewählt ist aus Ethyl-Cellulose, Propyl-Cellulose, Polyethylen und Polypropylen und auch Hydroxypropyl-Cellulose.

7. Extrudierter Film nach Anspruch 4 in Form eines mehrschichtigen Laminates, das zusätzlich zur bioadhäsiven Schicht auch eine äußere Schicht aus einer protektiven Membranbarriere enthält.

8. Extrudierter mehrschichtiger Film nach Anspruch 7, bei dem die äußere Schicht mit einer protektiven Membranbarriere dünner ist als die bioadhäsive Schicht und in dem die protektive Barriereschicht im wesentlichen aus einer Polymermatrix aus einem Hauptanteil eines nichtwasserlöslichen Polymers, das ausgewählt ist aus Ethyl-Cellulose, Propyl-Cellulose, Polyethylen und Polypropylen und einem geringeren Anteil von Hydroxypropyl-Cellulose, besteht.

9. Extrudierter mehrschichtiger Film nach Anspruch 1 in Form eines dreischichtigen Laminats, das Natriumfluorid zum Antikariesschutz enthält und das die folgende Zusammensetzung aufweist:

Bestandteile	bioadhäsive Schicht (0,1 mm)	% Gew./Gew. Reservoirschicht (0,025 mm)	äußere protektive Schicht der Membranbarriere (0,025 mm)
Homopolymer des Polyethylenoxids (MG mindestens 3 000 000)	60,0	-	-
Hydroxypropyl-Cellulose (MG 1 000 000)	30,0	20,0	24,0
Polyethylen (geringe Dichte)	5,0	-	-
Propylen-Glycol, U.S.P.	3,0	-	-
Polyethylen-Glycol (MG 400)	2,0	-	-
Ethyl-Cellulose	-	59,0	69,6
Capryl/Caprinsäure-Triglycerid	-	5,0	6,0
Natriumfluorid	-	16,0	0,4
	100,0	100,0	100,0

Revendications

1. Film mince extrudé mono- ou multicouche pharmaceutiquement acceptable contenant un médicament à libération contrôlée pouvant adhérer sur une surface de muqueuse humide, comprenant une couche bioadhésive de matrice de polymère gonflable ou soluble dans l'eau qui peut adhérer sur une surface de muqueuse humide et cette couche bioadhésive est constituée essentiellement de 22,4-68,3 % d'hydroxypropylcellulose ayant un poids moléculaire supérieur à 100 000, de 23,75-60% en poids d'un homopolymère d'oxyde d'éthylène ayant un poids moléculaire supérieur à 100 000, 0-12,5 % en poids d'un polymère insoluble dans l'eau choisi parmi l'éthylcellulose, la propylcellulose, la carboxyméthylcellulose exempte d'acide, le polyéthylène et le polypropylène, et 2,85-5 % d'un plastifiant, ledit film

contient une quantité pharmaceutiquement efficace du médicament qui y est incorporée, la présence du médicament et de composants éventuels faisant le complément du total de 100 %.

2. Film extrudé de la revendication 1, d'une forme suffisamment fine et souple quand il est humide de façon à ne pas gêner le patient quand il est placé et positionné correctement dans la bouche du patient.

3. Film extrudé de la revendication 2 ayant une épaisseur non supérieure à 0,25 millimètre.

4. Film extrudé de la revendication 3 dans lequel, dans la couche bioadhésive l'homopolymère d'oxyde d'éthylène a un poids moléculaire de 3 000 000 à 5 000 000.

5. Film extrudé de la revendication 3 sous forme feuilletée multicouche, qui contient aussi en plus de la couche bioadhésive une couche réservoir dans laquelle se trouve au moins une portion majeure du médicament.

6. Film multicouche extrudé de la revendication 5 dans lequel la couche réservoir est constituée essentiellement d'une matrice polymère contenant à la fois un polymère gonflable ou soluble dans l'eau et un polymère non soluble dans l'eau choisi parmi l'ethylcellulose, la propylcellulose, le polyéthylène et le polypropylène, et aussi de l'hydroxypropylcellulose.

7. Film extrudé de la revendication 4 sous forme feuilletée multicouche, qui contient en plus de la couche bioadhésive une couche membrane barrière de protection externe.

8. Film extrudé multicouche de la revendication 7 dans lequel la membrane barrière protectrice externe est plus mince que la couche bioadhésive, et ladite couche barrière protectrice externe est constituée essentiellement d'une matrice polymère composée en proportion majoritaire d'un polymère non soluble dans l'eau choisi dans le groupe de l'éthylcellulose, de la propylcellulose, du polyéthylène et du polypropylène, et d'une proportion mineure d'hydroxypropylcellulose.

9. Film multicouche extrudé de la revendication 1 sous forme d'un lamifié à triple couche contenant du fluorure de sodium pour la protection anticaries qui a la composition suivante :

Ingrédients	couche Bioadhésive 0,1 mm	% pds/pds Couche Réservoir (0,025 mm)	couche Membrane Barrière Protectrice Externe (0,025 mm)
Oxyde de Polyéthylène homopolymère (PM 3 000 000 minimum)	60,0	-	-
Hydroxypropylcellulose (PM 1 000 000)	30,0	20,0	24,0
Polyéthylène (basse densité)	5,0	-	-
Propylèneglycol, U.S.P.	3,0	-	-
Polyéthylèneglycol (PM 400)	2,0	-	-
Ethylcellulose	-	59,0	69,6
Triglycéride caprylique/caprique	-	5,0	6,0
Fluorure de sodium	-	16,0	0,4
	100,0	100,0	100,0

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(54) **Darreichungs- und Dosierungsform für Arzneimittelwirkstoffe, Reagentien oder dergleichen sowie Verfahren zu deren Herstellung.**

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Beschreibung

Arzneimittel können in Form von Pulvern, Tropflösungen oder Säften oral verabreicht werden. Da bei diesen Abgabeformen eine genaue Dosierung jedoch schwierig ist, werden vom Hersteller dosierte Applikationsformen wie Tabletten, Dragees oder Kapseln generell bevorzugt. Auch Reagentien und andere Wirkstoffe, z.B. Süßstoffe, werden für eine genaue dosierte Anwendung häufig tablettiert. Die Herstellungstechnik für Tabletten, Dragees, Kapseln und dergleichen ist zwar weitgehend ausgereift, doch sind eine Reihe von systembedingten Nachteilen nicht zu übersehen.

Für niedrig dosierte Wirkstoffe muß ein großer Anteil an Hilfsstoffen zugesetzt werden, um zu einer handhabbaren Größe der Einzeldosis zu gelangen. Weiterhin ist eine genaue Kennzeichnung einzelner Tabletten oder Dragees praktisch nicht möglich. Es haben sich deshalb Durchdrückpackungen durchgesetzt, welche eine Mehrzahl von Tabletten, Dragees oder auch Kapseln enthalten und welche mit den notwendigen Informationen, insbesondere dem Namen des Präparates bedruckt sind. Die Herstellung solcher Verpackungen erfordert naturgemäß einen zusätzlichen Arbeitsgang und es werden Umverpackungen in Form von Faltschachteln benötigt, welche ein beträchtliches Leervolumen aufweisen und dadurch zusätzlich Lagerraum beanspruchen. Ein besonders gravierender Nachteil von Dragees und Kapseln besteht darin, daß eine Zerteilung praktisch unmöglich ist, die kleinste Dosis somit vorgegeben ist. Auch bei Tabletten ist eine genaue Zerteilung schwierig, lediglich größere Tabletten mit einer Kerbe als Sollbruchstelle lassen sich allenfalls teilen, wobei häufig ungleichgroße Bruchstücke entstehen.

Es sind bereits Versuche zur Schaffung einer neuen Darreichungsform für die orale Verabreichung von Arzneimitteln bekannt geworden, welche aus wirkstoffhaltigen Folien bestehen. Gemäß der BE-PS 637 363 wird ein papierartiges Trägermaterial aus unlöslichen Zellulosefasern mit einer Wirkstofflösung getränkt bzw. beschichtet und eine Dosierung durch Perforation der Trägerfolie nach Art eines Briefmarkenbogens erreicht. Aus den DE-OS 24 32 925 und 24 49 865 ist es bekannt, Arzneimittelwirkstoffe in Folienbildner einzuarbeiten, bei denen es sich vorzugsweise um wasserlösliche Verbindungen wie Methyl- und Ethylzellulose, insbesondere aber Hydroxypropylzellulose, Hydroxyethylzellulose oder Methylhydroxypropylzellulose handelt. Auch die so erhaltenen wirkstoffhaltigen Folien lassen sich zur Dosierung durch Perforation in einzelne Abschnitte aufteilen. Aus DE-A-2746414 ist es ferner bekannt, derartige Dosierfolien mit weiteren Wirkstoffhaltigen oder- freien folien zu Dosierlaminaten zu vereinigen. Dadurch lassen sich inkompatible Wirkstoffe verarbeiten oder die Lösungsgeschwindigkeit bereinflussen. Diese Laminate insgesamt werden in form von Dosiereinheiten verwendet. Diese Vorschläge haben keinen Eingang in die Praxis gefunden und in dem neuesten Lehrbuch der "Arzneiformenlehre" von P.H. List, 4. Auflage, Stuttgart, 1985, finden sie keine Erwähnung. Dies beruht ersichtlich darauf, daß die bislang bekanntgewordenen Vorschläge es nicht ermöglichen, die geforderte Gewichtskonstanz und gleichmäßige Wirkstoffverteilung zu erreichen, welche heute gefordert werden. Die Ph. Eur. setzt zum Beispiel Maßstäbe für die Gleichförmigkeit des Gewichtes einzeldosierter Arzneiformen, wobei diese dem jeweiligen Durchschnittsgewicht entsprechend nach höchstzulässigen Abweichungen in % gestaffelt sind. Die Forderung liegt im allgemeinen bei +/- 5 bis max. 10%. Entsprechende Werte für feste Arzneiformen bestehen auch hinsichtlich anderer Parameter wie Zerfallzeit und Lösungsgeschwindigkeit.

Die oben erwähnten Vorschläge des Standes der Technik führen zu Produkten ungenügender Akzeptanz durch die Patienten (Papierabschnitte lassen sich nur schlecht einnehmen) und erlauben keine exakte Dosierung pro Flächeneinheit, wie sie unbedingt gefordert werden muß. Bei Inkorporieren des Wirkstoffes in eine Folie bereitet nicht nur die genaue Dosierung Schwierigkeiten, sondern ein wesentlicher weiterer Nachteil besteht darin, daß für jeden Wirkstoff eine entsprechende Folie gesondert hergestellt werden muß, so daß die Wirtschaftlichkeit des Herstellungsverfahrens nicht gegeben ist.

Der Erfindung liegt demgegenüber die Aufgabe zugrunde, eine "zweidimensionale" Darreichungs- und Dosierungsform zu schaffen, welche die genannten Nachteile nicht aufweist, sich leicht herstellen läßt und mit großer Flexibilität an die Anforderungen des Marktes und verschiedener Wirkstoffe angepaßt werden kann.

Gegenstand der Erfindung ist eine Darreichungs- und Dosierungsform für Arzneimittelwirkstoffe, Reagentien oder dergleichen in Form eines folienförmigen Trägermaterials mit einer wirkstoffhaltigen Beschichtung, wobei diese Darreichungsform dadurch gekennzeichnet ist, daß das Trägermaterial ein Release-Papier, ein Release-Film oder eine Release-Folie ist und daß das Trägermaterial einseitig mit der wirkstoffhaltigen Beschichtung versehen ist, welche nach Vorzerteilung in Dosiseinheiten von dem Trägermaterial dosisweise abziehbar ist.

Die erfindungsgemäße Darreichungsform weist mehrere wesentliche Vorteile auf:

- Da der Träger im Gegensatz zu den vorbekannten Ausführungsformen keinen Teil der Darreichungsform bildet, kann er die erforderliche Festigkeit aufweisen, ohne die Akzeptanz des Arzneimittels

durch Patienten zu beeinträchtigen,

- die wirkstoffhaltige Schicht kann bei hochwirksamen Arzneimitteln sehr dünn sein, da das Trägermaterial die mechanische Festigkeit gewährleistet,
- mit Hilfe moderner Auftragverfahren läßt sich die wirkstoffhaltige Beschichtung mit konstanter Schichtdicke aufbringen, so daß die erforderlichen Toleranzen eingehalten werden können,
- falls eine Sterilisierung erforderlich ist, kann diese wegen der geringen Schichtdicke problemlos mittels Strahlenbehandlung erreicht werden,
- der Träger läßt sich auf der Vorder- und insbesondere der Rückseite mit verschiedenen Informationen bedrucken,
- aufgrund der relativ großen Fläche von beispielsweise 4 bis 10 cm^2 lassen sich ausführliche Informationen für den Benutzer auf das unbeschichtete Trägermaterial oder auch nachträglich aufdrucken,
- die Dosiseinheiten lassen sich durch entsprechende Vorzerteilung flexibel gestalten, so daß für verschiedene Dosierungen (z.B. für Erwachsene und Kinder) nur ein Produkt hergestellt werden muß; die Vorzerteilung kann ggf. auch erst in der Apotheke oder im Krankenhaus nach ärztlichen Angaben vorgenommen werden.

Mit den vorbekannten Darreichungsformen in Folienform hat die erfindungsgemäße Darreichungsform darüberhinaus den Vorteil des äußerst geringen Platzbedarfes gemeinsam. Statt Faltschachteln können daher beispielsweise Taschen oder Beutel aus Kunststoffolie oder kunststoffbeschichtetem Papier verwendet werden, in welche das Produkt eingesiegelt wird, ähnlich wie feuchte Erfrischungstücher.

Als Trägermaterialien eignen sich die verschiedensten Materialien, beispielsweise Papiere mit einem Gewicht von etwa 80 bis 120, vorzugsweise 100 g/m^2, Kunststoffilme bzw. -folien auf Basis von Polyethylen, Polyvinylchlorid, Polyvinylidenchlorid, Polyester und anderen indifferenten Polymeren oder dünne Metallfolien, beispielsweise solche aus Aluminium. Bevorzugt werden siliconisierte Papiere, welche in unterschiedlichen Qualitäten im Handel erhältlich sind, und welche insbesondere zur Abdeckung von selbstklebenden Produkten wie Pflastern, Klebebändern oder Haftetiketten Verwendung finden. Die an sich auch geeigneten mit Wachs oder Paraffin beschichten Release-Papiere sind dagegen in der Praxis weitgehend durch die mit inerten Siliconen beschichteten Papiere ersetzt worden. Bei einem Auftrag der wirkstoffhaltigen Beschichtung auf nur eine Seite der Trägerfolie reicht es aus, wenn nur diese mit einer nicht haftenden Beschichtung versehen ist. Die Rückseite sollte dagegen vorzugsweise so beschaffen sein, daß sie mit Informationen unterschiedlicher Art gut und dauerhaft bedruckbar ist.

Die Möglichkeit der vorder- und rückseitigen Bedruckung ist ein besonderer Vorteil der erfindungsgemäßen Darreichungsform. Beispielsweise können die Kennzeichnung, Angaben über die Inhaltsstoffe sowie Dosierungsangaben aufgedruckt werden. Gegebenenfalls läßt sich sogar der ganze Inhalt eines Beipackzettels rückseitig aufdrucken mit der Folge, daß ein separater Beipackzettel, der auch häufig verlorengeht, überflüssig wird. Bei Arzneimitteln, welche regelmäßig genommen werden müssen, beispielsweise bei hormonalen Contrazeptiva, kann der gesamte Verabreichungsplan so angebracht werden, daß eine einfache Einnahmekontrolle gewährleistet ist. Da die einzelnen Dosiseinheiten von dem Träger abgezogen werden, bleibt dieser bis zum vollständigen Aufbrauch des Arzneimittels erhalten und es gehen keine der aufgedruckten Informationen verloren.

Für die wirkstoffhaltige Beschichtung findet vorzugsweise eine wässrige Beschichtungsmasse Verwendung, die physiologisch inert ist und deren Einzelkomponenten für Arzneimittel bzw. Lebensmittel geeignet sind. Dabei handelt es sich zum einen um wasserlösliche Quellstoffe in der Art polymerer Filmbildner, vorzugsweise Gelatine, Zellulosen oder Hemizellulosen, quellende oder lösliche Stärken. Vorzugsweise werden ferner Weichmacher zugesetzt, insbesondere mehrwertige Alkohole wie Glycerin oder Sorbitol. Zur Einstellung der erwünschten Viskosität der Beschichtungsmasse, welche etwa die Konsistenz eines Schleimes aufweist, finden polymere Quellstoffe Verwendung, vorzugsweise Alginate, Pectine, Chitine, Lecithine oder Polyethylenglykole. Diese letzteren Stoffe können gleichzeitig als Haftvermittler dienen. Andererseits können auch wasserlösliche Gumme oder Gummi arabicum zugesetzt werden, um die Haftung der Beschichtung auf dem Trägermaterial zu verbessern. Schließlich können noch Konservierungsmittel wie z.B. p-Hydroxybenzoesäureester, Farbstoffe (Lebensmittelfarbstoffe), Pigmente wie Titandioxid oder Aroma- und Süßstoffe zugesetzt werden.

Coatingmassen mit einem Wassergehalt von ungefähr 50% und einer Viskosität von etwa 30 bis zu 10000 cPs haben sich als besonders geeignet erwiesen. Die Rezeptur und Herstellung ähnelt derjenigen eines Arzneimittelsaftes, in welchem der Wirkstoff bzw. die Wirkstoffkombination gelöst oder gleichmäßig dispergiert wird. Die Beschichtungsmasse muß ausreichende Homogenität und galenische Stabilität aufweisen, damit ein gleichmäßiger Wirkstoffgehalt der fertigen Beschichtung sichergestellt ist.

Folgende Rahmenrezeptur hat sich bewährt:

Gelatine	8 bis 10 g
Stärke	3 bis 8 g
Glycerin	1 bis 2 g
Wasser	30 bis 50 g

In dieser Grundmasse wird der Wirkstoff gelöst bzw. dispergiert. Im Fall der Verwendung einer Dispersion muß der Wirkstoff für eine gleichmäßige Verteilung äußerst feinteilig sein. Vorzugsweise liegt die mittlere Teilchengröße im Bereich von etwa 1 bis 20 µm.

Die gewünschte Dosis des Wirkstoffes und die angestrebte Fläche der Dosiseinheiten bestimmen letztlich die Dicke der Schicht, wobei der Feuchtigkeitsgehalt der Beschichtungsmasse und der fertigen Beschichtung zu berücksichtigen sind.

Im Rahmen der Erfindung ist es auch möglich, die Beshichtungsmasse zu einer wirkstoffhaltigen Folie zu verarbeiten und diese anschließend, gegebenenfalls unter Verwendung eines physiologisch einsetzbaren inerten Klebstoffes, auf das Trägermaterial aufzukaschieren. Diese Ausführungsform kommt insbesondere dann in Betracht, wenn die wirkstoffhaltige Beschichtung eine größere Dicke aufweisen soll, so daß die Verarbeitung zu einer Folie möglich und sinnvoll ist.

Die erfindungsgemäße Darreichungsform ist besonders geeignet für Arzneimittel, welche niedrig dosiert verabreicht werden, d.h. bei welchen die Einzeldosis für die orale Applikation zwischen 0 mg (Placebo) und etwa 20 mg liegt. Geeignete Arzneimittelwirkstoffe finden sich in allen Bereichen der oralen Therapie; hervorzuheben sind u.a. Analeptika, Antibiotika, Antidiabetika, Antiemetika, Antiepileptika, Antihypertonika, Cortikoide, Geriatrika, Hypnotika, Cardiaka, Hypostatika und Biowirkstoffe.

Die Beschichtung kann einen oder mehrere Arzneimittelwirkstoffe enthalten. Falls bei Verwendung mehrerer Wirkstoffe diese nicht ohne weiteres miteinander verträglich sind, ist es bei der erfindungsgemäßen Darreichungsform möglich, die Beschichtung in mehreren Schichten unterschiedlicher Zusammensetzung aufzubringen und die Wirkstoffe dadurch voneinander zu trennen, wobei erforderlichenfalls eine wirkstofffreie Zwischenschicht vorgesehen werden kann. Weiterhin ist es möglich, über der wirkstoffhaltigen Schicht noch eine weitere Schutzschicht vorzusehen, welche den/die Wirkstoff(e) gegen eine Berührung mit der Atmosphäre und/oder gegen Licht schützt. In diesen Fällen muß die Schutzschicht demgemäß luft- und feuchtigkeitsundurchlässig und/oder durch Zusatz entsprechender Farbstoffe bzw. Pigmente lichtundurchlässig sein.

Weiterhin kann durch entsprechenden Aufbau der Beschichtung die Wirkstoffabgabe nach Verabreichung des Arzneimittels gesteuert werden. Beispielsweise ist es möglich, eine Wirkstoffschicht zwischen mindestens zwei weiteren Schichten anzuordnen, welche die Wirkstoffresorption im Magen/Darmtrakt in an sich bekannter Weise steuern. Dabei kann die Wirkstoffschicht z.B. zwischen zwei säureunlöslichen Schichten angeordnet werden, so daß bei Verabreichung der Magen passiert wird und die Resorption erst im Darmtrakt erfolgt. In ähnlicher Weise können unterschiedliche Wirkstoffe in verschiedenen Schichten übereinander auf die Trägerfolie aufgebracht werden, damit die Resorption nacheinander und/oder verzögert erfolgt. Ähnliche pharmakokinetische Effekte lassen sich durch das Einarbeiten (z.B. Suspendieren) von unterschiedlich vorbehandelten mikroverkapselten Wirkstoffen erzielen.

Die Aufbringung der wirkstoffhaltigen Beschichtungen auf den Träger, z.B. ein Release-Papier oder eine Release-Kunststoffolie, erfolgt vorzugsweise mit Hilfe eines Glattwalzen-Beschichtungsverfahrens. Die vorzugsweise auf ca. 60 bis 80 °C erwärmte Beschichtunsmasse wird dabei au einem geschlossenen Auftragsystem auf eine beheizte Walze in dünner Schicht übertragen. Mit verzögertem Gleichlauf in bestimmten wählbaren Verhältnissen wird die Masse auf eine parallel angeordnete Walze übertragen, wobei eine Reduzierung der Schichtdicke im Verhältnis 1:2 bis 1:10 erfolgen kann, wodurch gleichzeitig die Toleranzen bei der Auftragung um diese Faktoren verringert werden. Im Gleichlauf erfolgt dann über ein weiteres Walzensystem die Beschichtung des Trägermaterials. Bei einer Anpassung der Wirkstoffbeschichtungsmasse an den Release-Wert des Trägermaterials kann auf den Zusatz eines Klebemittels völlig verzichtet werden. Gegebenenfalls können jedoch auch geeignete Haftvermittler zugesetzt werden.

Bei Aufbringung mehrerer Schichten, wie dies oben bereits beschrieben wurde, werden diese nacheinander aufgebracht, wobei ggf. jede Beschichtung zuvor eine Trocknungsstation durchläuft. Diese kann beispielsweise aus einem temperierten Walzenpaar und einem in Sektionen steuerbaren Trockentunnel bestehen. Nach dem letzten Beschichtungsvorgang wird das beschichte Material auf Rollen aufgewickelt.

Die wirkstoffhaltige Beschichtung wird anschließend in Dosiseinheiten vorzerteilt, welche ähnlich wie Haftetiketten vom Trägermaterial abziehbar sind. Normalerweise wird diese Vorzerteilung beim Arzneimittelhersteller erfolgen, es ist jedoch auch denkbar, das beschichtete Material beispielsweise an Krankenhäuser oder Apotheken auszuliefern, wo dann die Vorzerteilung dosisabhängig oder auch individuell nach ärztlicher Vorgabe durchgeführt werden kann.

Die Vorzerteilung erfolgt in besonders einfacher Weise durch Stanzung, wobei es möglich ist, diesen

Schritt mit der Bedruckung des Trägermaterials zu kombinieren. In vielen Fällen wird es allerdings günstiger sein, die Bedruckung des Trägermaterials vor der Beschichtung vorzunehmen.

Vor oder besser nach Vorzerteilung der wirkstoffhaltigen Beschichtung in Dosiseinheiten wird das beschichtete Trägermaterial zu gebrauchsfertigen Abschnitten zerschnitten, welche eine bestimmte Anzahl von Dosiseinheiten enthalten. Es ist auch denkbar, das Material auf Rollen zu schmalen Bändern zu zerschneiden. Von einer solchen Einzelrolle können dann die einzelnen Dosiseinheiten ähnlich wie einzelne Haftetiketten abgezogen werden.

Vorstehend wurde die Erfindung im wesentlichen im Zusammenhang mit Arzneimitteln beschrieben, worauf sie jedoch keineswegs beschränkt ist. Beispielsweise lassen sich in derselben Weise auch Dosierungsformen für chemische Reagentien, Aromastoffe und dergleichen herstellen.

Zur näheren Erläuterung der Erfindung sollen die nachfolgenden Ausführungsbeispiele dienen.

Beispiel 1
Herstellung eines Cardiakum

Zum Naßauftrag auf ein Releasepapier (Silikonpapier mit einem Flächengewicht von 100 g/m^2) wurde eine Beschichtungsmasse gemäß folgender Rezeptur hergestellt:

Gelatine	10,0	Gew.-Teile	= 22,22%
Kartoffelstärke	3,0	-"- -"-	= 6,67%
Glycerin	1,5	-"- -"-	= 3,33%
Titandioxid	0,3	-"- -"-	= 0,67%
α-Acetyldigoxin	0,2	-"- -"-	= 0,44%
Wasser	30,0	-"- -"-	= 66,67%

Diese Beschichtungsmasse wurde in einer Schichtdicke von 90 g/m^2 mittels Walzen auf das Releasepapier aufgebracht. Nach dem Trocknen wies die Beschichtung einen Restwassergehalt von 11,76% auf. Das Beschichtungsgewicht lag bei 34 g/m^2, was einem Arzneimittelanteil von 0,4 g/m^{2}entspricht. Ein Abschnitt von 2 x 2,5 cm = 5 cm^2 (entsprechend den Abmessungen einer üblichen Briefmarke) enthält 0,2 mg α-Acetyldigoxin, was mit dem Gehalt der handelsüblichen Tabletten übereinstimmt.

Beispiel 2
Herstellung eines Contrazeptivum

Zum Naßauftrag auf ein Releasepapier (einseitig siliconisiertes Papier von 110 g/m^2) wurde eine Beschichtungsmasse von schleimartiger Konsistenz nach folgender Rezeptur hergestellt:

Gelatine	10,00	Gew.-Teile	= 22,222%
Maisstärke	3,17	-"- -"-	= 7,044%
Glycerin	1,50	-"- -"-	= 3,333%
Titandioxid	0,30	-"- -"-	= 0,667%
Levonorgestrel	0,03	-"- -"-	= 0,067%
Wasser	30,00	-"- -"-	= 66,663%

Die Beschichtungsmasse wurde mittels eines Walzenübertragungsverfahrens mit einem Beschichtungsgewicht von 45 g/m^2 auf das Releasepapier aufgebracht. Nach dem Trocknen wies die Beschichtung einen Restwassergehalt von 11,76% auf. Bei einem Beschichtungsgewicht von 17 g/m^2 betrug der Arzneimittelanteil 0,03 g/m^2.

Ein Abschnitt von 2,5 x 4 cm bzw. zwei Abschnitte von 2,5 x 2 cm = 10 cm^2 enthalten somit 0,03 mg Levonorgestrel, was dem Gehalt der handelsüblichen Dragees entspricht.

Patentansprüche

1. Darreichungs- und Dosierungsform für Arzneimittelwirkstoffe, Reagentien, Aromastoffe oder dergleichen in Form eines folienförmigen Trägermaterials mit einer wirkstoffhaltigen Beschichtung, dadurch gekennzeichnet, daß das Trägermaterial ein Releasepapier, ein Releasefilm oder eine Releasefolie ist und daß das Trägermaterial einseitig mit der wirkstoffhaltigen Beschichtung versehen ist, welche nach Vorzerteilung in Dosiseinheiten von dem Trägermaterial dosisweise abziehbar ist.

2. Darreichungsform nach Anspruch 1, dadurch gekennzeichnet, daß das Trägermaterial ein silicon- oder wachsbeschichtetes Releasepapier ist.

3. Darreichungsform nach Anspruch 1 oder 2, dadurch gekennzeichnet, daß die wirkstoffhaltige Beschichtung durch Stanzung in Dosiseinheiten vorzerteilt ist.

4. Darreichungsform nach einem der Ansprüche 1 bis 3, dadurch gekennzeichnet, daß die Beschichtung einen oder mehrere Arzneimittelwirkstoffe enthält.

5. Darreichungsform nach einem der Ansprüche 1 bis 4, dadurch gekennzeichnet, daß die Beschichtung wasserlösliche Quellstoffe als polymere Filmbildner und gegebenenfalls Weichmacher enthält.

6. Darreichungsform nach einem der Ansprüche 1 bis 5, dadurch gekennzeichnet, daß sie zur Viskositätseinstellung polymere Quellstoffe enthält, welche gleichzeitig als Haftvermittler dienen können.

7. Darreichungsform nach einem der Ansprüche 1 bis 6, dadurch gekennzeichnet, daß die Beschichtung in mehreren Schichten unterschiedlicher Zusammensetzung aufgebracht ist.

8. Darreichungsform nach Anspruch 7, dadurch gekennzeichnet, daß miteinander inkompatible Wirkstoffe in getrennten Schichten nacheinander auf das Trägermaterial aufgebracht sind.

9. Darreichungsform nach Anspruch 7, dadurch gekennzeichnet, daß eine Wirkstoffschicht zwischen mindestens zwei weiteren Schichten angeordnet ist, welche die Wirkstoff-Resorption im Magen/Darmtrakt in an sich bekannter Weise steuern.

10. Darreichungsform nach Anspruch 7, dadurch gekennzeichnet, daß über der Wirkstoffschicht eine weitere Schicht aufgebracht ist, die den Wirkstoff gegen Berührung mit der Atmosphäre und/oder gegen Licht schützt.

11. Darreichungsform nach einem der Ansprüche 1 bis 10, dadurch gekennzeichnet, daß die Rückseite des Trägermaterials mit die Wirkstoffzusammensetzung und/oder deren Einnahme betreffenden Informationen bedruckbar ist.

12. Verfahren zur Herstellung der Arzneimitteldarreichungsform der Ansprüche 1 bis 11, dadurch gekennzeichnet, daß man eine wirkstoffhaltige Zusammensetzung mit Hilfe von Walzen auf die nichthaftend ausgerüstete Seite eines Releasepapiers, eines Releasefilms oder einer Releasefolie aufbringt.

Claims

1. Presentation and dosage form for pharmaceutical active substances, reagents, aromas or the like in the form of a foil-like carrier material with an active-substance-containing coating, characterized in that the carrier material is a release paper, a release film or a release foil and that the carrier material is provided on one side with the active-substance-containing coating, which can be removed dosewise from the carrier material following prior division into dosage units.

2. Presentation form according to claim 1, characterized in that the carrier material is a silicone or wax-coated release paper.

3. Presentation form according to claims 1 or 2, characterized in that the active-substance-containing coating substance is pre-divided into dosage units by punching.

4. Presentation form according to one of claims 1 to 3, characterized in that the coating contains one or more pharmaceutical active substances.

5. Presentation form according to one of claims 1 to 4, characterized in that the coating contains water-soluble swelling substances as polymeric foil formers and optionally softeners.

6. Presentation form according to one of claims 1 to 5, characterized in that it contains, to set the viscosity, polymeric swelling substances, which can simultaneously serve as adhesion promoters.

7. Presentation form according to one of claims 1 to 6, characterized in that the coating is applied in the form of several layers having differing composition.

8. Presentation form according to claim 7, characterized in that incompatible active substances are applied one after the other as separate layers to the carrier material.

9. Presentation form according to claim 7, characterized in that an active substance layer is arranged between at least two other layers which control the absorption of the active substance in the gastro-intestinal tract in a manner known per se.

10. Presentation form according to claim 7, characterized in that a further layer is applied onto the active substance layer, said layer protecting the active substance against contact with the atmosphere and/or against light.

11. Presentation form according to one of claims 1 to 10, characterized in that the back of the carrier material can be printed with the active substance composition and/or information concerning the intake thereof.

12. Process for preparing the pharmaceutical presentation form according to claims 1 to 11, characterized in that an active-substance-containingcomposition is applied with the aid of rollers to the non-adhesively finished side of a release paper, a release film or a release foil.

Revendications

1. Forme de présentation ou de dosage de principes actifs médicamenteux, réactifs, substances aromatisantes ou similaires, sous la forme d'un matériau support en forme de feuille muni d'un revêtement contenant le principe actif, caractérisée en ce que le matériau support est un papier détachable, un film détachable ou une feuille détachable et, le matériau support est muni d'un côté du revêtement contenant le principe actif, que l'on peut détacher par doses du matériau support après l'avoir préalablement divisé en doses unitaires.

2. Forme de présentation selon la revendication 1, caractérisée en ce que le matériau support est un papier détachable revêtu de silicone ou de cire.

3. Forme de présentation selon la revendication 1 ou 2, caractérisée en ce que le revêtement contenant le principe actif est préalablement divisé en doses unitaires par poinçonnage.

4. Forme de présentation selon l'une quelconque des revendications 1 à 3, caractérisée en ce que le revêtement contient un ou plusieurs principe(s) actif(s) médicamenteux.

5. Forme de présentation selon l'une quelconque des revendications 1 à 4, caractérisée en ce que le revêtement contient des substances épaississantes, comme des agents filmogènes polymères et, le cas échéant, des plastifiants.

6. Forme de présentation selon l'une quelconque des revendications 1 à 5, caractérisée en ce qu'elle contient des substances épaississantes polymères pour ajustement de la viscosité, celles-ci pouvant servir en même temps d'agents adhésifs.

7. Forme de présentation selon l'une quelconque des revendications 1 à 6, caractérisée en ce que le

revêtement est constitué de plusieurs couches de compositions différentes.

8. Forme de présentation selon la revendication 7, caractérisée en ce que des principes actifs incompatibles entre eux sont appliqués successivement sur le matériau support, dans des couches séparées.

9. Forme de présentation selon la revendication 7, caractérisée en ce qu'une couche de principe actif est placée entre au moins deux autres couches qui règlent, par des moyens connus par eux-mêmes, la résorption du principe actif dans l'estomac/le tractus intestinal.

10. Forme de présentation selon la revendication 7, caractérisée en ce que l'on étale, sur la couche de principe actif, une couche supplémentaire qui préserve le principe actif, une couche supplémentaire qui préserve le lumière.

11. Forme de présentation selon l'une quelconque des revendications 1 à 10, caractérisée en ce que l'on peut imprimer au verso du matériau support la composition du principe actif et/ou des informations concernant sa prise.

12. Procédé pour préparer la forme de présentation de médicament des revendications 1 à 11, caractérisé en ce que l'on étale, à l'aide de cylindres, une composition contenant le principe actif sur le côté laissé non adhésif d'un papier détachable, d'un film détachable ou d'une feuille détachable.

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Description

BACKGROUND OF THE INVENTION

The present invention relates to a composition having a complex network structure that is formed by mixing glucomannan and optionally another natural polysaccharide with a polyhydric alcohol such as glycerin or a concentrated solution thereof in the presence of absence of an alkali. The present invention also relates to a film prepared from this composition.

The composition of the present invention can be dissolved in water to form a viscous solution. A film formed of this composition is water-resistant and may be given greater strengthand heat-resisting property. The film finds utility in various applications such as edible films, semipermeable membranes for separating low-molecular weight materials from those having high molecular weights ; wound dressings, and the shells of soft capsules.

The principal use of glucomannan has been to produce konjak by reacting it with an alkali in an aqueous solution, then heating the reaction product to form a gel. The gel formed bythis method has an inhomogeneous structure and finds no utility other than as konjak. Other natural polysaccharides have been used in an aqueous solution as thickeners, gelling agents, water retainers, stabilizers, dispersants, emulsifiers, binders, etc.

Compounds having multiple hydroxyl groups as exemplified by polyhydric alcohols, sugar alcohols, monosaccharides, dissaccharides and oligosaccharides have been used solely as additives such as sweeteners, humectants, softening agents and plasticizers. Moreover, these compounds have been used singly and no attempt has been made to allow the natural polysaccharidesto react directly with polyhydric alcohols in the presence of a small amount of water.

Edible films currently available include starch-based waters, gelatin-based collagen film, and pullulan films. All of these films except those based on gelatin lack resistance to water. Even gelatin films lack high resistance to acid, alkalies and heat. Films formed of cyclodextrins or special proteins obtained by extracting nucleic acids, cell membranes, etc. from yeasts are expensive and their high cost is not justified by corresponding improvements in water resistance, heat resistance and strength.

In the production of smoked meat products such as hams and sausages, semipermeable membranes such as those made of animal guts, regenerated cellulose or cellulose derivatives are used to allow the fragrant and seasoning components in the smoke to penetrate into the meat. However, the supply of animal guts is not abundant and, in addition, they lack strength and are not uniform in size. The supply of regenerated cellulose and cellulose derivatives is also limited because strict regulations against pollution has rendered the construction of new plants practically impossible.

Gelatin has heretofore been used as the shell matereal of soft capsules for cunfining drugs, flavors or seasonings but the user of gelatin is limited to applications where oily substances are employed.

Electrolytes or low-molecular weight materials have been separated from high-molecular weight materials by such means as electrodialysis, reverse osmosis, and ion-exchange membrane technology. However, these methods use a large number of electrodes or require high pressures so that the equipment for practicing these methods is becoming more and more complex. In order to desalt foods by these methods, large-sized equipmentis necessary and it often occurs that other seasoning componentsare eliminated as well as the sodium salt with the result that the taste of the food is impaired.

In the treatment of skin losses due to burns or other external injuries, the affected area is temporarily covered to prevent loss of water or body fluids from the wound, or any exudate from the wound is desplaced to prevent bacterial infection so that the formation of granulations and the epidermis is promoted. The films which have been used or attempted to be used for these purposes are formed of such materials as silicone rubber, poly -E -caprolactone, poly (vinyl alcohol) , polyamino acids,fibrin membranes, collagen, polyurethane and pigskin.

However, freeze-dried pigskin and other polyamino acid based wound dressings are all made of polypeptides which are subject to biochemical decomposition. In order to avoid the adverse effects of the degradation products which are liberated, these wound dressings have to be replaced at short intervals, typically every other day. However, replacement of the wound dressing involves much pain for the patient. Furthermore, the film itself has insufficient strength to attain satisfactory coverage. Wound dressings made of synthetic resins such as polyurethane and silicone rubber do not have sufficient affinity for the wound surface to achieve satisfactory permeation to oxygen and water. Nomal skin generally allows water to be evaporated in an approximate amount of 350g/m^2 per day, but it has been difficult to prepare synthetic resin films that exhibit this amount of water evaporation and which yet has sufficient strength.

It has been proposed to prepare a composite wound dressing by laminating a polyamino acid based

film with a synthetic resin film but this composite film still suffers from the defects of the respective film components.

SUMMARY OF THE INVENTION

The present inventors have found that if glucomannan, either independently or in combination with other natural polysaccharides, is mixed with a compound having multiple hydroxyl groups or with a concentrated solution thereof in the presence of absence ofan alkali, the respective components react with each other to form a composition having a dense three-dimensional structure. The present inventors have also found that a viscous solution formed by dissolving this composition in water has unique physicochemical properties that have been unattainable by glucomannan, other natural polysaccharides or polyhydric alcohols, and that various products having the characteristics shown below can be prepared from this composition. The present invention has been accomplished on the basis of these findings.

Firstly, edible films having desirable properties s such as water resistance, heat resistance and strength can be prepared from the above-described viscous aqueous solution either directly or after being mixed with other foods or food materials. The so prepared films may be eaten as such or used as edible food packages.

Secondly, the viscous aqueous solution may be dried into film form and the resulting film may be used in the production of processed meat products (e.g. hams and sausages) as semipermeable membranes having sufficient strength and heat resistance to withstand smoking condition.

Thirdly, the viscous aqueous solution may be processed to form a film that is suitable for use as the shell of a soft capsule, and using this film, soft capsules capable of confining non-oily drugs, health foods, seasonings or flavors can be prepared.

Fourthly, the film made from the viscous aqueous solution also serves as a high-performance filter medium that is capable of efficient separation of low-molecular weight substances from high-molecular weight substances at reasonably low pressures.

Fifthly, the membrane formed by drying the viscous aqueous solution into film form is a superior wound dressing that achieves close contact with the skin and exhibits superior vapor and oxygen permeation without undergoing any biodegradation during prolonged attachment to the skin.

Sixthly, the viscous aqueous solution cools to provide a gel-like or semifluid foodstuff having unique properties.

DETAILED DESCRIPTION OF THE INVENTION

The glucomannan used in the preparation of the composition of the present invention is the polysaccharide naturally occurring in Amorphophallus Koniac K. Koch which is the rhizome of a plane belonging to Colocasia antiquorum; it is composed of particles referred to as idioblasts which range from 0.5 to 1.05 mm in length and from 0.37 to 0.5 mm in breadth. The chemical structure of glucomannan is a chain of a 1 : 2 mixture of glucose and mannose with acetyl and phosphate groups forming pendant ester linkages.

Illustrative polyhydric alcohols that can be used in the present invention are polhydric alcohols in the narrow sense of the term such as propylene glycol and glycerin. These polyhydric alcohols are liquid and may be directly used; however, because of their high hygroscopicity they contain water and are in the form of concentrated aqueous solutions. Moreover they can be used as water solution of concentration in the range of 30 to 90 %. Illustrative sugar alcohols include sorbital, mannitol, maltitol, xylytol and saccharified products of reducing sugar. Illustrative monosaccharides include glucose, fructose, galactose and xylose. Illustrative disaccharides are saccharose, maltose and lactose. Starches such as sweet potato, potato and corn that have been decomposed with enzymes or acids are usable as oligosaccharides, and include di-, tri-, tetra-, penta- and hexasaccharides. The polyhydric alcohols listed above, both in the broad and narrow sense of the term, which are in a powder form at ordinary temperatures, are used as aqueous solutions having concentrations in the range of 30-90 wt %, preferably 50-80 wt %, more preferable 65-75wt%.

Other natural polysaccharides that may be used in the present invention include the following:

alginic acid which are intracellular polysaccharides in brown algae,

sodium alginate,

propylene glycol ester of alginic acid, and

agar;

carrageenan which is an intracellular polysaccharide in red algae and is hydrolyzed into D-galactose and D-galactose sulfate ester ;

locust bean gum which is a polysaccharide that is present in the seeds of leguminous locust bean and

carob and which is chiefly composed of glucomannan;

guar gum that is a polysaccharide present in the seed of leguminous guar and which is hydrolyzed into galactose and mannose ;

tamarind seed polysaccharide which is a polysaccharide present in the seed of leguminous Tamarindus indica and which is hydrolyzed into glucose, xylose and galactose ;

pectin which is a generic term for a group of polysaccarides that are the materials of construction of the cell walls of plants such as fruit and vegitables and which are hydrolyzed in to galacturonic acid;

xanthan gum is a polysaccharide produced by the microorganism Xanthomonas campestris during fermantation in the present of glucose and other appropriate essential elements;

chitin which is one kind of mucopolysaccharides;

pullulan which has a repeating unit of α -1,6 linkage derived from maltotriose ; and

cellulose,

cyclodextrin and

starches.

These natural polysaccharides are optionally used in amounts of 0.05 - 20 parts by weight, preferably from 0.1 to 10 parts by weight, per part by weight of glucomannan.

In the present invention, reaction is preferably carried out in the presence of an alkali. Ordinary inorganic or organic alkaline substances may be employed and suitable ones inclueded: sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, barium hydroxide, sodium carbonate, potassium carbonate, calcium carbonate, ammonium carbonate, magnesium carbonate, sodium bicarbonate, ammonium bicarbonate, basic amino acids and amines. The addition of these alkalis is generally effective in providing films with improved strength and heat resistance.

Part of the glucomannan and optionally used natural polysaccharides may be replaced by proteins to provide composition which generally have improved heat resistance. Solutions of these compositions in warm water have good mouth feel and can be readily eaten. Illustrative proteins are soybeen protein, wheat protein, milk protein, egg white, collagen, decomposed collagen and microbial proteins. Decomposition products of these proteins, such as polypeptides and amino acids, may also be used.

The present invention is characterized by reacting glucomannan directly with at least one compound selected from among the polyhydric alcohols, sugar alcohols, monosaccharides, disaccharides and oligosaccharides. The component made of at least one compound selected from polyhydric alcohols, sugar alcohols, monosaccharides, disaccharides and oligosaccharides is used in an amount which ranges from 0.05 to 10 parts by weight, preferably from 0.10 to 5.0 parts by weight, more preferably from 0.15 to 1.0 part by weight, per part by weight of the powder component made of glucomannan and optionally of other natural polysaccharides and proteins. Generally, a higher content of the polyhydric alcohol renders it difficult for a three-dimensional network to develop.

The reactants are mixed at a temperature ranging from 5 to 150 °C, preferably from 10 to 100 °C, more preferably from 20 to 80 °C. Mixing at low temperatures will cause no problem because the intended reaction can be allowed to proceed satisfactorily by heating the mixture in a subsequent step such as drying. Generally, mixing at high temperatures provides a composition having a dense structure whereas a brittle composition having a coarse network results if low mixing temperatures are used.

The composition formed by mixing the starting materials described above is a powder that is usually moist to some extent. A solution of this composition in water is viscous and will solidify irreversibly when left to stand at ordinary temperatures, frozen, refrigerated or heated. The properties, in particular the strength, heat resistance and the temperature for dissolution in water, of the solidified product can be altered by proper adjustment of the combination of the starting materials used. Therefore, the solidified product can be used as a base for semifluid or gel-like foods such as jelly and jam. Films may be formed from the viscous solution by shaping it into a soldified form of a suitable thickness between 1 and 1,000 μm by any of the known techniques such as wet casting, freeze-drying and extrusion molding. Some of the films formed by these methods are heat-resistant and heat-sealable. If desired, the viscous solution may be coated or sprayed onto a foodstuff and dried to form an edible film on the food.

Films having thicknesses in the range of 1-1,000 μm, preferably 2- 300 μm, are useful as semipermeable membranes. In a more preferable embodiment, a thin and reinforced semipermeable membrane can be formed by preparing a thin fibrous product from an appropriate material such as paper, nonwoven fabric, woven fabric or net, then filling the voids in the fibrous product with the filter film of the present invention. Filling of the voids in the thin fibrous product may also be achieved by coating the film with the viscous solution or submerging the film in the solution, followed by drying of the film.

Filtration may be achieved by any known technique such as simple filtering under gravity, ultrafiltration or reverse osmosis. The filter medium may be an assembly of hollow fibers or a module of a spirally wound

sheet.

In the simplest way, afoodstuff having high sodium chloride concentration is placed on top of the semipermeable membrane of the present invention which is in contact with an underlying water layer; in the absence of any applied pressure, sodium chloride and other low-molecular weight substances in the upper layer will permeate through the membrane to enter the underlying aqueous layer.

Soy sauce, miso and pickled products contain a large amount of sodium chloride in order to ensure that they can be transported long distances or to achieve various purposes such as storage, preservation or good manufacturing practice. The filter film of the present invention is capable of allowing the sodium chloride content of these food products to be lowered without impairing their taste.

In producing processed meat products such as hams and sausages, the meat wrapped in a semipermeable membrane must be smoked. Conventionally, the semipermeable membrane is formed of regenerated cellulose, cellulose derivatives, alginates, collagen, or sheep or bovine gut. However, as already mentioned, these materials have problems in terms of their physical strength and heat resistance, and in particular, sheep and bovine guts are not uniform in size and shape and suffer from instability in supply.

Fibrous products are usually porous and the films prepared by impregnating or coating them with the edible composition of the present invention serve as ideal casing materials wherein the semipermeable membrane formed of the edible material isreinforced with the fibrous product. Such casing materials may be prepared as follows: a fibrous product of a given width is shaped into a tubular base, which is continuously impregnated with an aqueous solution of the composition of the present invention and dried to form a strong fibrous casing.

The shell of conventional soft capsules is formed from an aqueous solution of gelatin and glycerin and is only capable of confining oily products. The soft capsules formed from an aqueous solution of the composition of the present invention are capable of confining not only oily products but also water-soluble substances and, hence, are applicable to enlarged areas of use, for instance: (1) water-soluble vitamins such as vitamins B_1, B_2, B_5, B_6, B_{12}, niacin folic acid and vitamin C; (2) nutrients such as liquid glycides, proteins and minerals; (3) diets formed of soft capsules that incorporate liquid seasonings or flavors and which are readily edible after cooking ; and (4) cosmetics in soft capsules that are to be punctured with a needle to allow the contents to be used.

Soft capsules may be prepared from the composition of the present invention as follows : the composition is dissolved in water and the solution is allowed to flow out of a spreader box to form a gel which is subsequently shaped into a film form, two sheets of the film thus obtained are passed through a pair of die rolls to adhere to each other ; a predetermined amount of the content (ie, fill) is forced with a pump to obtain a caplule form, which is subsequently dried to form a soft capsule.

The film prepared in accordance with the present invention is also useful as an ideal wound dressing. It swells readily upon absorbing body fluids from a wounded site of the human body but its three-dimensional network will remain intact. The film increases in thickness but its area remains the same so as to allow the absorbed moisture to be evaporated from its furface. The film supplies the wound surface not only with moisture but also with the drug applied onto the outer surface of the film ; at the same time, the film allows the unwanted exudate to be liberated on its surface. Therefore, the film does not have to be peeled off until after the wound has healed. The thickness of the film used as a wound dressing generally ranges from 1 to 1,000μm, preferably form 5 to 200 μm, more preferably from 7 to 50 μm.

When the composition of the present invention is dissolved in water, a vicous solution or slurry with a solids content of 2-10 % will form and this can be incorporated in a large amount in suitable food materials. The incorporated composition will solidify irreversibly be being left to stand at ordinary temperatures, frozen, refrigerated or heated. The properties, in particular the strength, heat resistance and the temperature for dissolution in water of the solidified product can be altered by properly adjusting the combination of starting materials used. Furthermore, the solidifed product retains the tast flavor of the food material present.

The food materials that can be mixed with the viscous solution or paste of the composition of the present invention are diverse and include: seaweeds ; marine products such as shrimp, cuttlefish, fish (e.g. bonito, tuna and salmon) , and fish roe; vegitables such as spinach, cabbage, carrot and pumpkin; fruits such as orange, grape, apple and pineapple ; meats such as beef, pork, chicken, and corned beef ; processed foods such as cheese, jam, mayonnaise and miso ; seasonings such as soy sauce and sodium glutamate ; as well as spices and flavors such as peanut, almond, mustard, pepper, curry, cocoa, coffee an chocolate.

These food materials may be mixed with the viscous solution or slurry of the composition of the present invention either directly, or after being conditioned for a given particle size or shape, or after being formed into a paste. The mixing ratio of these food material to the glucomannan /polyhydric alcohol composition of

the present invention is not limited to any particular value because it largely depends on the type of food material used or the specific formulation of the composition. It should however be noted that a preferable mixing ratio is such that the mixture can be readily formed into a film, and that the shaped food is easy to handle and does not reveal the mouth feel of the composition.

The aqueous solution of the composition of the present invention is viscous and its properties, in particular its strength, heat resistance and temperature for dissolution in water, can be altered by allowing it to stand at ordinary temperatures, freezing, refrigerating or heating the same. Therefore, the aqueous solution, after being shaped into a gelled block of an appropriate hardness, may be mixed with a non-alcoholic beverage such as juice or yogurt or foods, and the resulting mixture can be safely heated without melting to thereby provide a composite dietary product that shows a desirable combination having the sort of mouth feed that is possessed by dissimilar components. There is no particular limitation on the size of the gel block and its hardness varies with the type of base used: if the base is a liquid material such as juice, the moisture content of the block is preferably increased to provide a soft texture, whereas if the base is jelly or any other material that has a certain amount of self-retaining property, its moisture content is decreased to provide a hardness slightly lower than that of the jelly. In either case, the resulting product is composed to two dissimilar materials and yet displays good palatability.

Glucomannan has a complex structure containing various side chains and reactive groups and, because of the presence of many hydroxyl groups at high concentrations, glucomannan enters into reaction to form a complex matrix even under a substantially water-free condition. The matrix forming reaction will be enhanced by the presence of an alkali and an even more complex compound will form. In the presence of both an alkali and water, the development of a three-dimensional network is further promoted to form an irreversibly solidified product, which can be processed to provide a characteristic gel-like base or a coating.

The present invention is hereinafter described in greater detail with reference to the following examples to which the scope of the invention is by no means limited and wherein all parts are on a weight basis.

EXAMPLE 1

Eight parts of glucomannan was mixed with 2 parts of glycerin for 15 minuites an 70 °C to form a sample of the composition of the present invention which was a somewhat moist powder. Two parts and a half of this composition were mixed with 97.5 parts of water to form a viscous aqueous solution. This solution was coated onto the peel of orange and dried at 50 °C for 1 hour to provide orange having an edible film coating on its peel. This orange and uncoated orange were stored at 25 °C for 10 days. Thereafter, the appearance of the two oranges and the mouth feel of their pulp were compared. Compared with the uncoated orange, the one having an edible film coat had undergone a smaller degree of water evaporation and oxidation, retained more luster and experienced less surface discoloration. The pulp of the coated orange was fresher and more palatable.

EXAMPLE 2

Three parts of the composition prepared in Example 1 was mixed with 0.04 parts of a vitamin E powder (70% natural vitamin E and 30 % emulsifier) and 97 parts of water to form an aqueous solution. An orange whose peel was coated with the resulting aqueous solution as in Example 1 was stored at 25 °C for 15 days together with an uncoated orange. The results of comparison of the two oranges were the same as in Example 1.

EXAMPLES 3 - 10

The components listed in Table 1 were mixed for 10 minutes at 80 °C in the amounts also shown in Table 1, so as to prepare eight additional samples of the composition of the present invention. Three parts of each of the samples was mixed with 97 parts of water and the resulting aqueous solutions were cast by the wet process to form translucent edible films having thicknesses ranging from 10 to 20 μm. The films prepared in Examples 3 to 6 were water-resistant and stable in the following solutions: aqueous solutions with NaCl concentrations of 5% or more ; acidic aqueous solutions with pH of 2.5 - 4.5; alkaline aqueous sloutions with pH of 9.0 - 12.0 ; aqueous solutions with ethanol concentrations of 10 % or more. The films prepared in Examples 7 - 10 were not only water-resistant; they were resistant to hot water and stable in aqueous solutions heated to 80 - 100 °C.

Table 1

(unit in parts by weight)

Example No.		3	4	5	6	7	8	9	10
natural polysaccharide	glucomannan	5	5	5	5	5	5	5	5
	carrageenan	3			2		4		3
	agar		2					1	
	locust bean gum			2					1
	xanthan gum				1		0.5		
alkali	calcium carbonate							0.3	0.1
	calcium hydroxide					0.05			
	sodium bicarbonate						0.5		0.3
glycerin			1.5		1.5	1		1	
sorbitol (70% aq.sol.)		1.5					1		
saccharose (80% aq. sol.)				1.5					1

EXAMPLE 11

An edible package film 15 μm thick was formed from a composition having the same formulation as used in Example 3. Stripped lobster (150g) was wrapped with this film and stored at-25°C for 3 months. The frozen lobster as wrapped in the film was thawed in a microwave oven and cooked. The cooked lobster had the edible film on it but one did not sense any peculiar feel as a result of the presence of the film.

EXAMPLE 12

An edible film 15μm thick was formed from a composition having the same formulation as used in Example 8. Vegitable salad with dressing was sandwiched between two slices of bread. During subsequent storage, the dressing did not permeate into the bread at all. After the strage, the bread was eaten ; it tasted good and the taste of the edible film was not sensed.

EXAMPLE 13

Components	Amount (in parts)
Glucomannan	5
Sodium bicarbonate	0.1
Calcium Carbonate	0.02
Glycerin	1

These components were mixed at 75 °C for 20 minutes. Three parts of the resulting composition were dissolved in 97 parts of water. The aqueous solution was applied continuously to form a uniform coating on the inner surface a fluoroethylen resin-coated cylindrical pipe having a diameter of 120 mm. The applied coat was dried to form a tubular casing.

Processed meat was packed into the casing at a pressure of up to 2 kg/cm^2 without causing its disruption. The packed meat was smoked and sterilized by heating in hot water (80 °C) for 2 hours to produce a satisfactory ham.

EXAMPLE 14

Components	Amount (in parts)
Glucomannan	5
Agar	0.5
Calcium carbonate	0.5
Sodium citrate	0.3
Sorbitol (70% aq. sol.)	1

These components were mixed at 80 °C for 10 minuites. Three parts and a half of the resulting composition were dissolved in 96.5 parts of water to form a viscous aqueous solution. A sheet of porous paper having a thickness of 100 μm was prepared, with wood pulp and cotton linter being used as chief components. The two side edges of the sheet were adhered together to form a tubular base. The wall of this base was impregnated with the previously prepared viscous aqueous solution and dried to form a casing that was formed of a sample of the film of the present invention that had a thickness of 120 -130 μm and which was reinforced with a fibrous product.

Processed meat was packed into the casing at a pressure of up to 6 kg/cm^2 without causing its disruption. The packed meat was smoked and sterilized by heating in hot water (80 °C) for 2 hours to produce a satisfactory sausage.

EXAMPLE 16

A mixture of gelatin (100 parts) and glycerin (30 parts) was dissolved in 60 parts of water at 75 °C with stirring and defoamed with a vacuum pump. The solution was shaped into a 450 μm thick film on an automatic rotary continuous soft capsule filling machine. A film 25 μm thick that was prepared asin Example 6 was stacked on the inside surface of the 450 μm thick film to form a double-layered film. Two units of this double-layered film were passed between a pair of die rolls to be adhered to each other and an aqueous solution of 30% L-ascorbic acid was forced in with a filling pump to form capsules each containing 500 mg of the fill. The capsules were dried to produce soft capsules.

EXAMPLE 16

Components	Amount (in parts)
Glucomannan	5
Carrageenan	0.5
Calcium carbonate	0.12
Glycerin	1

These components were mixed at 70 °C for 30 minutes. Three parts of the resulting composition was dissolved in 97 parts of water to form a viscous aqueous solution. the solution was formed into an edible film 15 μm thick by the wet casting method. As in Example 15, a dual-layered capsule shell was formed by staking this film over a gelatin film. Using this shell, soft capsules each containing 5 g of seasonings for instant chicken soup were produced. On of these capsules was mixed well with 150 ml of hot water (90 °C) under agitation ; the capsule was disintegrated in the water to provide chicken soup.

EXAMPLE 17

A mixture of gelain (100 parts) and glycerin (30 parts) was dissolved in 10 parts of water at 75 °C with stirring. Thesolution was defoamed with a vacuum pump and designated A. In a separate step, 5 parts of glucomannan, 3.5 parts of carrageenan and 1.5 parts of glycerin were mixed at 70 °C to form a sample of the composition of the presnet invention ; 3 parts of the composition was dissolved in 97 parts of water to form an aqueous solution which was designated B. An intimate blend of solution A (60 parts) and solution B (40 parts) was fed into an automatic rotary continuous soft capsule filling machine to form soft No. 5 oval capsules by the known rotary die method, with each capsule having confined therein 290 mg of an astringent lotion. Just prior to use, each soft capsule was punctured with a needle to recover to lotion in an amount sufficient for single use.

EXAMPLE 18

Components	Amount (in parts)
Glucomannan	5
Carrageenan	3
Cellulose	1
Glycerin	2

These components were mixed at 80 °C for 10 minutes and 2.5 parts of the resulting composition was dissolved in 97 parts of water. The solution was formed into a circular film (thickness, 15 μm ; diameter, 29 mm) by the wet casting method. The film was set in a filtration vessel which was filled with 450 ml of tap water in its lower compartment and with 150 ml of soy sauce (18% NaCl) in its upper compartment. The vessel was left to stand at 20 °C for a given period and the contents of NaCl and amino acid nitrogen in the soy sauce were measured at predetermined intervals. The results are shown in Table 2.

Table 2

(effective surface area of film: 960.6 m㎡)

Time (min)	NaCl (%)	Amino acid N_2	Increase in water content (%)
0	16.4	0.91	0
30	15.7	0.86	0.7
60	16.5	0.82	1.6
90	15.0	0.86	2.7
120	14.1	0.79	4.1
150	13.3	0.78	5.7

As Table 2 shows, the NaCl content of the soy sauce decreased with time and this was accompanied by gradual depletion of amino acids and increase in the moisture content. However, most of the amino acids that flowed out were those having low molecular weights such as glycin and alanine and their depletion did not cause any substantial deterioration of the taste of the soy sauce. The soy sauce prepared in accordance with the present invention had a generally mellow taste and its sodium chloride content was low.

EXAMPLE 19

An aqueous solution of the composition used in Example 18 was heated to 70 °C with stirring and applied to a thin sheet of paper (basis weight: 16g / m^2) to form a film having a thickness of 35μm. This fiber-reinforced film was tested as in Example 18. The results were substantially the same as those obtained in Example 18. The film prepared in this example was superior to that prepared in Example 18 in terms of self-retaining property and tensile strength.

EXAMPLE 20

Components	Amount (in parts)
Glucomannan	5
Xanthan gum	0.5
Calcium hydroxide	0.06
Glycerin	1

These components were mixed at 60 °C for 20 minuites to obtain a sample of the composition of the present invention. Three parts of this composition were dissolved in 97 parts of water and a thin layer of the solution was spread onto a fluoroethylen resin-coated sheet. The coating was freeze-dried by a conventional method to prepared a wound dressing in a film form having a thickness of 12 μm. The film was sterilized, coated with a drug layer and attached to the surface of a wound produced by a third-degree burn. The treatment that ensured consisted of delivering the drug daily onto the surface of the film. Formation of granulations continued steadily without suppuration and in 10 days normal skin tissue was restored,

whereupon the film separated from the skin spontaneously.

EXAMPLE 21

An aqueous solution of the composition used in Example 20 was coated onto a nonwoven polyester fabric (basis weight : 10g / m^2) and freeze-dried by a known method so as to make a film having a thickness of 30μm. This film was used as a wound dressing to cure a burn in accordance with the same regimen as employed Example 20. The results were substantially the same as those obtained in Example 20.

EXAMPLE 22

Components	Amount (in parts)
Glucomannan	5
Alginic acid	1
Guar gum	0.5
Glycerin	1

These components were mixed at 65°C for 20 minutes to form a sample of the composition of the present invention. Three partsof this composition were dissolved in 97 parts of water. Seventyfive parts of the solution were mixed with 25 parts of a beef fillet and the blend was shaped into an edible film (thickness : 25μm) by the wet casting method. The film was laid down on a slice of bread ; the product had a characteristic flavor originating from the blending of the taste of beef with the bread.

EXAMPLE 23

Components	Amount (in parts)
Glucomannan	5
Tamarind seed polysaccharide	1
Gelatin	1
Glucose (80% aq. sol.)	1

These components were mixed at 60°C for 40 minuites to form a sample of the composition of the present invention. Three parts of this composition were dissolved in 97 parts of water to form a viscous aqueous solution. Eighty parts of this solution were blended with 20 parts of a dried spinach powder (particle size : 100-Tylermesh pass) and the blend was shaped into an edible film (15μm thick) by a known freeze-drying technique. This film was rolled around a bar of cooked rice so as to provide a low-calorie dietary product.

EXAMPLE 24

Components	Amount (in parts)
Glucomannan	5
Carrageenan	5
Calcium carbonate	0.2
Glycerin	1.5

These components were mixed at 70 °C for 30 minutes to form a sample of the composition of the present invention. Five parts of this composition were mixed and kneaded with 95 parts of cocoa paste and the necessary seasonings to make a chocolate mass, which was refined and molded into a sheet. Although conventional chocolate products are soften at 35 °C or higher, the chocolate sheet of the Example 24 did not soften until it was heated to 50 °C.

Claims

1. A glucomannan/polyhydric alcohol composition prepared by uniformly mixing at 5 to 150 °C 1 part by weight of a glucomannan powder with 0,05 to 10 parts by weight of an aqueous solution of 30-100 wt.-% of at least one polyhydric alcohol selected from the group consisting of propylene glycol, glycerin, sugar alcohols, monosaccharides, disaccharides and oligosaccharides.

2. A composition according to claim 1, characterized in that the components are mixed in the presence of an alkali.

3. A composition according to claim 1 or 2 wherein part of the glucomannan is replaced by another natural polysaccharide.

4. A composition according to claim 3, wherein the other natural polysaccharide is carrageenan.

5. A film prepared by a process comprising the steps of: dissolving a glucomannan/polyhydric alcohol composition according to anyone of the claims 1 to 4 in water, forming the solution into a film by shaping it into a solidified form of a suitable thickness between 1 and 1000 µm by any of the known techniques, and drying the film.

6. A film according to claim 5, characterized in that it is edible.

7. A film according to claim 5 or 6 which is reinforced with a thin fibrous product.

8. The use of a film according to anyone of the claims 5 to 7 as a food packaging.

9. The use of a film according to anyone of the claims 5 to 7 as a casing in the manufacture of smoked food products.

10. The use of a film according to anyone of the claims 5 to 7 as a shell of a soft capsule.

11. The use of a film according to anyone of the claims 5 to 7 as a semipermeable membrane for separating a high-molecular weight substance from a low-molecular weight substance.

12. The use of a film according to anyone of the claims 5 to 7 as a wound dressing.

Patentansprüche

1. Glucomannan/mehrwertiger Alkohol-Zusammensetzung, erhalten durch gleichförmiges Vermischen bei

5 bis 150 °C von 1 Gew.-Teil eines Glucomannanpulvers mit 0,05 bis 10 Gew.-Teilen einer wäßrigen Lösung von 30 bis 100 Gew.-% mindestens eines mehrwertigen Alkohols, ausgewählt aus der aus Propylenglykol, Glycerin, Zuckeralkoholen, Monosacchariden, Disacchariden und Oligosacchariden bestehenden Gruppe.

2. Zusammensetzung nach Anspruch 1, dadurch gekennzeichnet, daß die Komponenten in Gegenwart von Alkali vermischt werden.

3. Zusammensetzung nach Anspruch 1 oder 2, bei der ein Teil des Glucomannans durch ein anderes, natürliches Polysaccharid ersetzt ist.

4. Zusammensetzung nach Anspruch 3, bei der das andere natürliche Polysaccharid Carrageen ist.

5. Film bzw. Folie, erhalten durch ein Verfahren, das die Schritte umfaßt:
Auflösen einer Glucomannan/mehrwertiger Alkohol-Zusammensetzung gemäß einem beliebigen der Ansprüche 1 bis 4 in Wasser,
Überführung der Lösung in einen Film bzw. eine Folie durch Überführen derselben in eine verfestigte Form mit einer geeigneten Dicke zwischen 1 und 1000 µm durch eine beliebige, bekannte Arbeitsweise,
und
Trocknen des Films bzw. der Folie.

6. Film bzw. Folie nach Anspruch 5, dadurch gekennzeichnet, daß er bzw. sie eßbar ist.

7. Film bzw. Folie nach Anspruch 5 oder 6, der bzw. die mit einem dünnen, faserförmigen Produkt verstärkt ist.

8. Verwendung eines Films bzw. einer Folie gemäß einem beliebigen der Ansprüche 5 bis 7 als Verpackung für Lebensmittel.

9. Verwendung eines Films bzw. einer Folie gemäß einem beliebigen der Ansprüche 5 bis 7 als Umhüllung bei der Herstellung von geräucherten Lebensmitteln.

10. Verwendung eines Films bzw. einer Folie gemäß einem beliebigen der Ansprüche 5 bis 7 als Hülle einer Weichkapsel.

11. Verwendung eines Films bzw. einer Folie gemäß einem beliebigen der Ansprüche 5 bis 7 als semipermeable Membran zur Abtrennung einer Substanz mit hohem Molekulargewicht von einer Substanz mit niedrigem Molekulargewicht.

12. Verwendung eines Films bzw. einer Folie gemäß einem beliebigen der Ansprüche 5 bis 7 als Wundverband bzw. Wundabdeckung.

Revendications

1. Composition à base de glucomannan et d'alcool polyhydrique, préparée en mélangeant uniformément à la température de 5 à 150 °C, une partie en poids de poudre de glucomannan avec 0,05 à 10 parties en poids d'une solution aqueuse de 30-100% en poids d'au moins un alcool polyhydrique, choisi parmi le groupe comportant propylène glycol, glycérine, alcools de sucres, monosaccharides, disaccharides et oligosaccharides.

2. Composition selon la revendication 1, caractérisée en ce que les composants sont mélangés en présence d'un alcali.

3. Composition selon la revendication 1 ou 2, dans laquelle une partie du glucomannan est remplacée par un autre polysaccharide naturel.

4. Composition selon la revendication 3, dans laquelle l'autre polysaccharide naturel est le carrageenan.

5. Film préparé par un procédé comprenant les étapes de :
dissoudre une composition à base de glucomannan et d'alcool polyhydrique selon l'une quelconque des revendications 1 à 4, dans l'eau, former avec solution un film en la traitant dans une forme solidifiée, d'une épaisseur convenable, entre 1 et 1000 µm par n'importe quelle technique connue, et sécher le film.

6. Film selon la revendication 5, caractérisé en ce qu'il est comestible.

7. Film selon la revendication 5 ou 6, qui est renforcé avec un produit fibreux mince.

8. Utilisation d'un film selon l'une quelconque des revendications 5 à 7, comme emballage de nourriture.

9. Utilisation d'un film selon l'une quelconque des revendications 5 à 7, comme emballage dans la fabrication des produits alimentaires fumés.

10. Utilisation d'un film selon l'une quelconque des revendications 5 à 7, comme enveloppe d'une capsule molle.

11. Utilisation d'un film selon l'une quelconque des revendications 5 à 7, comme membrane semiperméable pour séparer une substance de poids moléculaire élevé d'une substance de faible poids moléculaire.

12. Utilisation d'un film selon l'une quelconque des revendications 5 à 7, comme pansement d'une plaie.

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Description

This invention relates to a drug preparation applicable to the oral mucosa to maintain a long-term administration of a systemic drug.

Known dosage forms for intraoral administration of drugs include solutions, ointments, troches, buccal tablets, and sublingual tablets. Recently, slow-releasing intraoral tablets of the track-field type which are less causative of a feeling of foreign matter (as described in JP-A-55-59109, JP-A-58-154547, and JP-A-58-154548, the term "JP-A" as used herein means an "unexamined published Japanese patent application") and slow-releasing Nifedipine tablets of the track-field type applied to the oral mucosa (as described in JP-A-61-15829 and JP-A-61-17510) have been proposed. For the purpose of further reducing an adverse feeling in the oral cavity, a medical bandage using, as a base, a water-soluble high polymer which exhibits adhesion when dissolved or gelled with water (as described in JP-A-60-142927), preparations applicable to the oral mucosa comprising a water-soluble film having incorporated thereinto a steroid or non-steroid agent (as described in JP-A-61-280423), and sheet preparations comprising a support sheet having thereon a drug, gelatin, agar, gluten, a carboxyvinyl polymer, a polyhydric alcohol, a gum, and a wax as essential components (as described in JP-A-61-85315) have also been proposed.

More recently, there have been proposed bases for application to the oral mucosa which comprise a mixture of a water-soluble substance and a water-insoluble substance; for example, an intraoral bandage composed by a soft film in which at least one of a polycarboxylic acid and a polycarboxylic acid anhydride, and a vinyl acetate polymer are mixed in a compatible state as disclosed in JP-A-61-249472 and JP-A-61-249473; a base comprising a water-insoluble or sparingly water-soluble support having thereon an adhesive layer containing an acrylic acid polymer which exhibits adhesion when dissolved in or swollen with water and a water-insoluble cellulose derivative as disclosed in JP-A-63-160649; a composite for application to the oral mucosa comprising a surface layer containing ethyl cellulose and a vinylpyrrolidone polymer or copolymer having thereon an adhesive layer as disclosed in JP-A-63-171564 and JP-A-63-171565; and an adhesive composition containing a vinylpyrrolidone polymer or copolymer, at least one of hydroxyethyl cellulose and hydroxypropyl cellulose, and a water-retaining softener as disclosed in JP-A-63-174660.

However, none of these known intraoral preparations or bases satisfies both duration of adhesion and freedom from an adverse feeling in the oral cavity on use. For example, since solutions, ointments or the like preparations easily run away with saliva or water , it is difficult to maintain efficacy for a long time with these preparations. Troches, which are large tablets prepared by punching a mixture of a drug and a base, e.g., sacchardides, cause a considerable adverse feeling. Buccal tablets and sublingual tablets are generally designed for rapid mucosal absorption of drugs and are, therefore, of short duration. The track-field type tablets, though slowly releasing a drug, have a thickness as large as 1.3 to 3 mm and lack softness, still involving the problem of an adverse feeling on use. The preparations for application to the oral mucosa comprise a water-soluble film containing a drug have softness and thereby cause a reduced adverse feeling in the oral cavity. However, since the film base is water-soluble, it is easily dissolved in saliva or water in the oral cavity and is, therefore, poor in duration of efficacy. The bases comprising a mixture of a water-soluble substance and a water-insoluble substance are soft and less causative of an adverse feeling upon use. Also, they take time to disappear in the oral cavity and are thus expected to have a longer duration of pharmaceutical effects as compared with bases comprising a water-soluble substance alone. These bases nevertheless exhibit adhesion only for 2 to 10 hours at the longest.

Hence, an intraoral preparation satisfying all three requirements, i.e., freedom from a feeling of foreign matter on use, excellent shape retention on water absorption, and long-term adhesion to the wet oral mucosa, has not yet been developed.

EP-A-0106107 discloses a drug preparation applicable to the oral mucosa comprising an adhesive sheet containing prostaglandin, said sheet comprising a homogeneous mixture comprising one or more high molecular weight compounds. The high molecular Weight compounds may be, for example, a vinyl acetate resin, polyacrylic acid salts and cellulose derivatives.

EP-A-0241179 discloses a pharmaceutical composition comprising a mixture of an active ingredient and a polymer capable of dissolving in an aqueous medium of pH 4.0 or higher.

SUMMARY OF THE INVENTION

It is the object of this invention to provide a drug preparation applicable to the oral mucosa for administering a systemic drug, which is less causative of an adverse feeling in the oral cavity on use, excellent in shape retention on water absorption, and adhesive to the oral mucosa for an extended time.

Said object is achieved by a drug preparation applicable to the oral mucosa comprising a soft

adhesive film containing a systemic drug, the adhesive film comprising a homogeneous mixture comprising a vinyl acetate homopolymer, an acrylic acid polymer, and a cellulose derivative capable of being dissolved in or swollen with water and a lower alcohol, wherein said mixture contains maximum 0.2 equivalent based on said acrylic acid polymer, of a salt or base.

Figure 1 illustrates the relationship of the rate of Propranolol Hydrochloride release to the time.

Figure 2 illustrates the relationship of the rate of Sodium Indometacin release to the time.

When the drug preparation applicable to the oral mucosa according to the present invention is applied to, for example, the fore gingiva of the upper jaw, the adhesive film base absorbs saliva and water in the oral cavity to exhibit adhesion to the oral mucosa. The adhesiveness in retained for a long period of time because of the excellent shape retention. Since the film base is homogeneous and soft, it is tightly adhered to the oral mucosa without causing an adverse feeling during application. The terminology "homogeneous" as used herein means that the vinyl acetate homopolymer, acrylic acid polymer and cellulose derivative in the mixture are homogeneously mixed under optical microscopic observation and that each of these components does not exist solely in parts.

The adhesive film of the drug preparation according to the present invention is obtained using a homogeneous mixture of a vinyl acetate homopolymer, an acrylic acid polymer, and a cellulose derivative. A two-component mixture comprising only the vinyl acetate homopolymer and the acrylic acid polymer forms a homogenous and soft film but is swollen with saliva or water in the oral cavity and is inferior in shape retention on application to the oral mucosa. Further, a two-component mixture comprising only the acrylic acid polymer and the cellulose derivative forms a homogeneous and soft film but does not withstand long-term use in the oral cavity because of water-solubility of these components. Furthermore, a two-component mixture comprising only the vinyl acetate homopolymer and the cellulose derivative hardly forms a homogeneous and soft film.

The vinyl acetate homopolymer which can be used in the present invention is not particularly limited, and any known vinyl acetate homopolymer (as disclosed, e.g., in S.Imoto, Plastic Zairyo Koza - (Lectures on Plastic Materials) vol.14 Vinyl Acetate Resins, published by Nikkan Kogyo Press, Japan, on May 15, 1970) can be used as such either alone or in combination thereof. The weight average molecular weight of the vinyl acetate homopolymer is preferably from 40,000 to 200,000.

Examples of the acrylic acid polymer which can be used in the present invention includes an acrylic acid homopolymer; copolymers of acrylic acid and vinyl monomers, such as acrylic esters (e.g., butyl acrylate and 2-ethylhexyl acrylate), methacrylic esters (e.g., methyl methacrylate), and vinyl acetate; and other polymers, e.g., a carboxyvinyl polymer. Among these, an acrylic acid polymer having a carboxyl group content of 20% by weight or more is preferred. These polymers may be used either alone or in combinations thereof.

The cellulose derivative which can be used in the present invention must be capable of being dissolved in or swollen with water and a lower alcohol. Examples of the cellulose derivatives include methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, and hydroxypropylmethyl cellulose. The degree of substitution of the cellulose derivative is preferably from 0.1 to 4.5, and more preferably from 1.0 to 2.5. Hydroxypropyl cellulose having a degree of substitution of from 1.3 to 2.0 is most preferred. These cellulose derivatives may be used either alone or as a mixture of two or more thereof.

The weight ratio of acrylic acid polymer (B) to cellulose derivative (C) (B/C) preferably ranges from 1/9 to 9/1. To ensure long-term adhesion to the oral mucosa, the weight ratio B/C suitably ranges from 3/7 to 6/4. The weight ratio of vinyl acetate homopolymer (A) to the sum of acrylic acid polymer (B) and cellulose derivative (C) (A/(B + C)) preferably ranges from 2/8 to 8/2. To further ensure long-term adhesion to the oral mucosa, the weight ratio B/C more preferably ranges from 4/6 to 6/4.

Thus, the working time of the preparation in the oral cavity, which partly depends on the duration of adhesion, can be appropriately controlled by varying the ratio of vinyl acetate homopolymer (A), acrylic acid polymer (B), and cellulose derivative (C).

If desired, the drug preparation of the present invention may further contain a salt or a base. Since the drug preparation comprising only the above-described components assumes acidicity attributed to the acrylic acid polymer, it sometimes give a slight irritation to excitable parts, such as an injured part. Where such an irritation due to acidicity gives rise to troubles, incorporation of a salt or base having a neutralizing effect substantially removes the irritation to the injured part.

Examples of suitable salts and bases are salts of metals and weak acids, e.g., a salt of an alkali metal (e.g., sodium and potassium) and a carboxylic acid (e.g., acetic acid, lactic acid, and citric acid); metal hydroxides, e.g., sodium hydroxide and potassium hydroxide; amines, e.g., triethanolamine and diisopropanol amine; and mixtures thereof. A salt of an alkali metal (e.g., sodium and potassium) and a carboxylic acid (e.g., acetic acid, lactic' acid, and citric acid) is preferably used.

The amount of the salt or base to be incorporated is maximum 0.2 equivalent based on the acrylic acid polymer. For example, a monovalent metal salt is preferably used in an amount of from 0.03 to 0.2 equivalent based on the acrylic acid polymer. Amounts less than 0.03 equivalent produce insufficient effects to reduce the irritation of an injured part. If the amount exceeds 0.2 equivalent, water resistance of the adhesive film is reduced, failing to attain sufficient adhesion to the oral mucosa.

The drug preparation applicable to the oral mucosa according to the present invention can be obtained as follows. A vinyl acetate homopolymer, an acrylic acid polymer, and a cellulose derivative are dissolved in a solvent commonly compatible to them, and a systemic drug is added to the solution to form a film-forming composition. The systemic drug in the composition may be either in a dissolved state or in a dispersed state so that the mode of addition is arbitrarily chosen. The film-forming composition is cast on a releasable liner and dried to form a film.

Examples of the solvent commonly compatible to the film-forming components include an alcohol and a water-alcohol mixed solvent. Taking the solubility of the cellulose derivative into consideration, lower alcohols, e.g., methanol and ethanol are exemplified as the alcohol. The water content in the mixed solvent is preferably not more than 30% by weight. If it exceeds 30% by weight, the vinyl acetate homopolymer tends to be hardly dissolved.

Examples of the releasable liner on which the film-forming composition is cast include a release-treated polyethylene laminated paper, a polyethylene film, and a silicon-treated polyethylene terephthalate film.

Drying of the cast film is carried out in a high-temperature air bath using a drying oven or a drying tower, and a vacuum drier.

The thickness of the drug preparation of the present invention can be adjusted by controlling the amount of the composition cast and is preferably in the range of from 5 to 500 μm. From the standpoint of film strength and feeling on use, a thickness of from 10 to 100 μm is more preferred.

The drug preparation applicable to the oral mucosa according to the present invention basically comprises a homogeneous and soft adhesive film which is obtained from a vinyl acetate homopolymer, an acrylic acid polymer, and a cellulose derivative as described above. If desired, a water-insoluble support may be provided on the adhesive film to endew the preparation with improved shape retention on water absorption.

Examples of the water-insoluble support includes a film of a synthetic resin, e.g., polyethylene, a vinyl acetate homopolymer, an ethylene-vinyl acetate copolymer, polyvinyl chloride, and polyurethane; a metal foil, e.g., an aluminum foil and a tin foil; and a laminate film comprising cloth or paper and a synthetic resin film. From the viewpoint of safety and feeling on use, it is preferable to use a film of a synthetic resin, e.g., polyethylene, a vinyl acetate homopolymer, and an ethylene-vinyl acetate copolymer as a support. In order to assure ease in handling and to avoid to give an adverse feeling on use, the water-insoluble support preferably has a thickness of from 10 to 100 μm.

The above-described drug preparation of a laminate type can be prepared by, for example, hot pressing the adhesive film and the water-insoluble support film. Alternatively, the laminate type drug preparation can be obtained by casting the film-forming composition on the water-insoluble support followed by drying.

The thus obtained drug preparation according to the present invention, when applied to the wet oral mucosa, absorbs water and is swollen with the water to exhibit excellent adhesion and shape retention for an extended time without causing an adverse feeling, thereby liberating a systemic drug present in the preparation for a prolonged time while protecting the site. During the application, the drug can be prevented from running off due to saliva, etc., and the administration of the drug can be maintained in a stable manner.

The drug preparation of the present invention contains a systemic drug and administers it through the oral mucosa. Some drugs, when orally administered, are difficult in manifestation of efficacy commensurate with dosages because they undergo primary metabolism in the liver. Moreover, some drugs produce undesired side effects to organs, such as stomach. In order to eliminate these disadvantages associated with oral administration of drugs, preparations applicable to the skin which deliver the active ingredient by cutaneous absorption have recently called attention. However, the skin essentially functions to prevent entrance of a foreign substance into the body and does not easily absorb drugs. This is the reason why studies have been directed to the administration route through the oral mucosa which is considered to have a higher absorption of a drug than the skin. By the route through the oral mucosa, the drug preparation according to the present invention makes it possible to effectively deliver a systemic drug present in the preparation into the body.

The systemic drug which can be incorporated into the drug preparation of the invention may be either solid or liquid at room temperature, and any systemic drug which can be dissolved or dispersed in the soft adhesive film can be employed. The method for dissolving or dispersing the systemic drug in the soft adhesive film is not particularly

limited. For example, the vinyl acetate homopolymer, the acrylic acid polyer and the cellulose derivative are dissolved in a solvent which is compatible With these components, and the systemic drug is separately dissolved or dispersed in the same solvent. The resulting solutions (or solution and dispersion) are mixed with each other to form a film-forming composition, and the film-forming composition is then cast on a releasable liner followed by drying so as to form the preparation.

Examples of the systemic drugs include general anesthetic agents, hypnotics, sedatives, antiepileptics, analeptics, awakening agents, anti-dizziness agents, psychoneurotropic agents, neuromuscular blocking agents, autonomic neutrotropic agents, antispasmodics, anti-Perkinson's disease, antihistaminics, stimulation therapeutics, antiallergic agents, cardiotonics, antiarrhythmics, diuretics, hypotensives, vasopressors, coronary vasopressors, peripheral vasopressors, anti-arteriosclerotic agents, agents for other circulatory organs, respiration accelerating agents, antitussive expectorants, treating agents of peptic ulcers, pituitary hormone, thyroid hormone, parathormone, androkinin, female sex hormone (i.e., vesicular ovarian follicle hormone and corpus luteum hormone), other hormones, oxytocics, agents for the urogenital system, oxygen preparations, anti-diabetic agents, other metabolic drugs, anti-tumor agents, antibiotics, chemotherapeutics, and narcotics.

The amount of the systemic drug to be incorporated into the drug preparation depends on the kind of the drug and is usually selected from 0.001 to 40% by weight, preferably from 0.002 to 20% by weight, based on the adhesive film in view of the pharmacological effects and adhesion to the oral mucosa.

The drug preparation applicable to the oral mucosa according to the present invention is less causative of an adverse feeling on use, excellent in shape retention on water absorption, and adhesive to the oral mucosa for an extended period of time. Accordingly, the present invention makes it possible to maintain a stable administration of a systemic drug.

As described above, the drug preparation applicable to the oral mucosa of the present invention which comprises a soft adhesive film prepared from a homogeneous mixture of a vinyl acetate homopolymer, an acrylic acid polymer, and a specific cellulose derivative is soft, less causative of an adverse feeling in the oral cavity on use and excellent in shape retention on water absorption. Further, since the drug preparation can be adhered to the oral mucosa for a long period of time, a systemic drug present in the preparation can be stably administered for a long time. Furthermore, because of the homogeneity and softness of the film base, the drug preparation can be deformed in perfect accordance with the shape of the oral mucosa simply by lightly pressing and adhered close to the mucosa.

The present invention is now illustrated in greater detail by way of the following examples. In these examples, all parts, percents and ratios are by weight unless otherwise specified.

Prior to conducting the examples, an agar gel as a substitution for the oral mucosa was prepared as follows.

Preparation of Agar Gel:

Distilled water was added to 2 g of an agar powder (Japanese Pharmacopeia) to make 100 g, and the mixture was boiled to completely dissolve the agar. The solution was poured into a dish and allowed to cool to prepare an agar gel.

EXAMPLE 1

Five parts of a vinyl acetate homopolymer (weight average molecular weight: 129,000), 2 parts of a carboxyvinyl polymer (carboxyl group content: 58-63% by weight) (as the acrylic acid polymer), 3 parts of hydroxypropylmethyl cellulose (degree of substitution: 1.86-1.90) (as the cellulose derivative), 0.2 part of diisopropanolamine (as the base for neutralizing the acrylic acid polymer), and 2 parts of Propranolol Hydrochloride (as the systemic drug) were added to 90 parts of a 2/8 water-methanol mixture as a common solvent to prepare a film-forming composition containing the systemic drug. The composition was cast on a silicon-release paper, dried, and stripped off to obtain a 30 μm thick adhesive film. A 20 μm thick soft alumina foil as a water-insoluble support was hot-pressed on the resulting adhesive film to obtain a drug preparation applicable to the oral mucosa.

EXAMPLE 2

Five parts of a vinyl acetate homopolymer (weight average molecular weight: 129,000), 2 parts of a carboxyvinyl polymer (carboxyl group content: 58-63% by weight) (as the acrylic acid polymer), 3 parts of hydroxypropylmethyl cellulose (degree of substitution: 1.86-1.90) (as the cellulose derivative), and 0.5 parts of Sodium Indometacin (as the systemic drug) were added to 90 parts of a 1/9 water-methanol mixture as a common solvent to prepare a film-forming composition. The composition was cast on a silicon-release paper, dried, and stripped off to obtain a 60 μm thick adhesive film. A 20 μm thick soft vinyl acetate film as a water-insoluble support was hot-pressed on the resulting adhesive film to obtain a preparation applicable to the oral

mucosa.

Evaluation:

Specimens having a size of 1 cm x 2 cm were cut out of each of the drug preparations obtained in Examples 1 and 2 and adhered to the surface of the above-prepared agar gel. After a prescribed period of time, the specimen was peeled off the agar gel and extracted from 50 mℓ of methanol. The drug in the extract was determined by high performance liquid chromatography. The resulting data of Examples 1 and 2 were plotted in Figs. 1 and 2, respectively, with rate of drug release as ordinate and time as abscissa.

It can be seen from Figs. 1 and 2 that the drug preparation according to the present invention keeps adhered to the agar gel, a substitution for the oral mucosa, for a long time so that the active ingredient in the preparation is stably and steadily released with time.

Further, the specimens were adhered to the oral mucosa of panel members to conduct organoleptic tests of the feeling. As a result, the specimens were judged to have little adverse feeling.

Claims

1. A drug preparation applicable to the oral mucosa comprising a soft adhesive film containing a systemic drug, said adhesive film comprising a homogeneous mixture comprising a vinyl acetate homopolymer, an acrylic acid polymer, and a cellulose derivative capable of being dissolved in or swollen with water and a lower alcohol, wherein said mixture contains maximum 0,2 equivalent based on said acrylic acid polymer of a salt or base.

2. The drug preparation of claim 1, wherein said cellulose derivative is selected from the group consisting of methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, and hydroxypropylmethyl cellulose.

3. The drug preparation of claim 1, wherein said acrylic acid polymer and cellulose derivative are present in a weight ratio of from 1/9 to 9/1.

4. The drug preparation of claim 3, wherein said acrylic acid polymer and cellulose derivative are present in a weight ratio of from 3/7 to 6/4.

5. The drug preparation of claim 1, wherein the weight ratio of said vinyl acetate homopolymer to the sum of said acrylic acid polymer and cellulose derivative is from 2/8 to 8/2.

6. The drug preparation of claim 5, wherein said acrylic acid polymer and cellulose derivative are present in a weight ratio of from 4/6 to 6/4.

7. The drug preparation of claim 1, wherein said adhesive film has a thickness of from 5 to 500 μm.

8. The drug preparation of claim 1, wherein said preparation further comprises a water-insoluble soft film support laminated on said adhesive film.

9. The drug preparation of claim 8, wherein said support has a thickness of from 10 to 100 μm.

10. The drug preparation of claim 8, wherein said support is a polyethylene film, a vinyl acetate homopolymer film or an ethylene-vinyl acetate copolymer film.

Patentansprüche

1. Auf die Mundschleimhaut aufbringbare Arzneimittelzubereitung umfassend einen weichen Klebefilm, der ein systemisches Arzneimittel enthält, wobei der Klebefilm ein homogenes Gemisch, umfassend ein Vinylacetathomopolymer, ein Acrylsäurepolymer und ein Cellulosederivat, das in Wasser und einem niederen Alkohol aufgelöst oder damit gequollen werden kann, umfaßt, worin das Gemisch maximal 0,2 Äquivalente, bezogen auf das Acrylsäurepolymer, eines Salzes oder einer Base enthält.

2. Arzneimittelzubereitung nach Anspruch 1, worin das Cellulosederivat ausgewählt ist aus der Gruppe bestehend aus Methylcellulose, Ethylcellulose, Hydroxyethylcellulose, Hydroxypropylcellulose und Hydroxypropylmethylcellulose.

3. Arzneimittelzubereitung nach Anspruch 1, worin das Acrylsäurepolymer und das Cellulosederivat in einem Gewichtsverhältnis von 1/9 bis 9/1 vorhanden sind.

4. Arzneimittelzubereitung nach Anspruch 3, worin das Acrylsäurepolymer und das Cellulosederivat in einem Gewichtsverhältnis von 3/7 bis 6/4 vorhanden sind.

5. Arzneimittelzubereitung nach Anspruch 1, worin das Gewichtsverhältnis des Vinylacetathomopolymers zu der Summe des Acrylsäurepolymers und des Cellulosederivats 2/8 bis 8/2 beträgt.

6. Arzneimittelzubereitung nach Anspruch 5, worin das Acrylsäurepolymer und das Cellulosederivat in einem Gewichtsverhältnis von 4/6 bis 6/4 vorhanden sind.

7. Arzneimittelzubereitung nach Anspruch 1, worin der Klebefilm eine Dicke von 5 bis 500 µm hat.

8. Arzneimittelzubereitung nach Anspruch 1, worin die Zubereitung ferner einen wasserunlöslichen weichen Filmträger auf dem Klebefilm laminiert umfaßt.

9. Arzneimittelzubereitung nach Anspruch 8, worin der Träger eine Dicke von 10 bis 100 µm hat.

10. Arzneimittelzubereitung nach Anspruch 8, worin der Träger ein Polyethylenfilm, ein Vinylacetathomopolymerfilm oder ein Ethylen-Vinylacetat-Copolymerfilm ist.

Revendications

1. Préparation pharmaceutique applicable sur la muqueuse buccale, comprenant un film adhésif souple contenant un médicament systémique, ledit film adhésif comprenant un mélange homogène qui comprend un homopolymère d'acétate de vinyle, un polymère d'acide acrylique et un dérivé de cellulose capable de se dissoudre ou de gonfler dans l'eau et un alcool inférieur, ledit mélange contenant au maximum 0,2 équivalent, par rapport audit polymère d'acide acrylique, d'un sel ou d'une base.

2. Préparation pharmaceutique selon la revendication 1, dans laquelle ledit dérivé de cellulose est choisi dans le groupe constitué par la méthylcellulose, l'éthylcellulose, l'hydroxyéthylcellulose, l'hydroxypropylcellulose et l'hydroxypropylméthylcellulose.

3. Préparation pharmaceutique selon la revendication 1, dans laquelle ledit polymère d'acide acrylique et ledit dérivé de cellulose sont présents en un rapport en masse compris entre 1/9 et 9/1.

4. Préparation pharmaceutique selon la revendication 3, dans laquelle ledit polymère d'acide acrylique et ledit dérivé de cellulose sont présents en un rapport en masse compris entre 3/7 et 6/4.

5. Préparation pharmaceutique selon la revendication 1, dans laquelle le rapport en masse dudit homopolymère d'acétate de vinyle à la somme dudit polymère d'acide acrylique et dudit dérivé de cellulose est compris entre 2/8 et 8/2.

6. Préparation pharmaceutique selon la revendication 5, dans laquelle ledit polymère d'acide acrylique et ledit dérivé de cellulose sont présents en un rapport en masse compris entre 4/6 et 6/4.

7. Préparation pharmaceutique selon la revendication 1, dans laquelle ledit film adhésif a une épaisseur de 5 à 500 µm.

8. Préparation pharmaceutique selon la revendication 1, dans laquelle ladite préparation comprend en outre un support formé d'un film souple insoluble dans l'eau laminé sur ledit film adhésif.

9. Préparation pharmaceutique selon la revendication 8, dans laquelle ledit support a une épaisseur de 10 à 100 µm.

10. Préparation pharmaceutique selon la revendication 8, dans laquelle ledit support est un film de polyéthylène, un film d'un homopolymère d'acétate de vinyle ou un film de copolymère éthylène-acétate de vinyle.

Figure 1

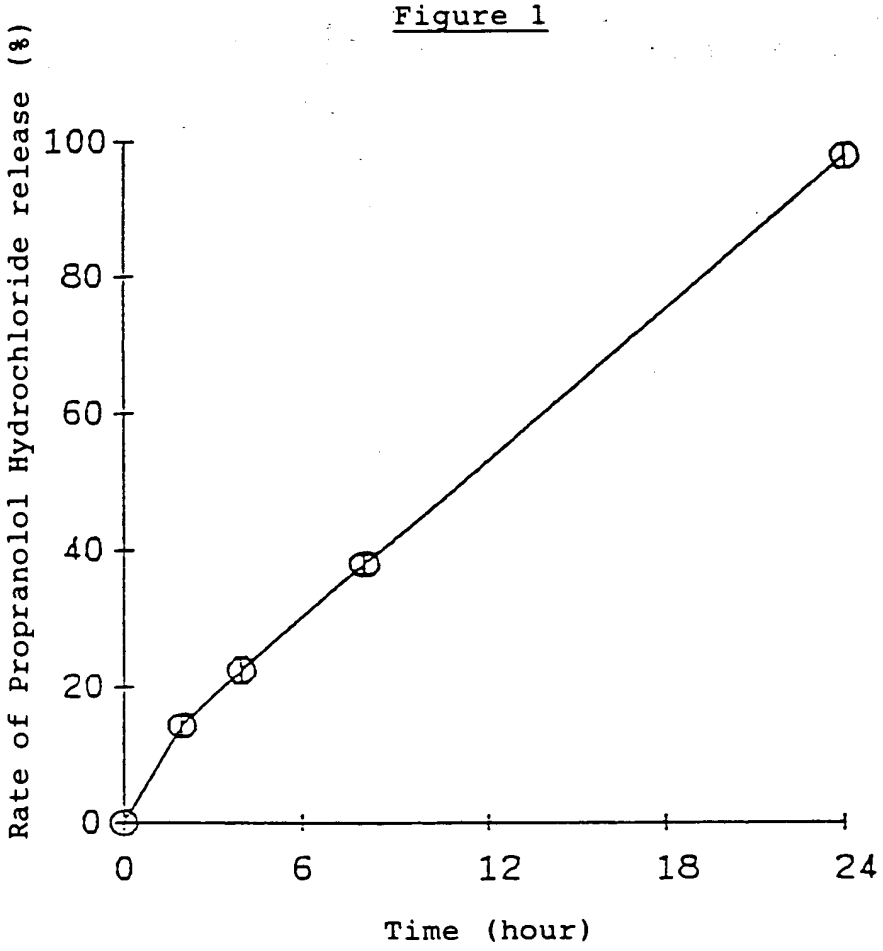
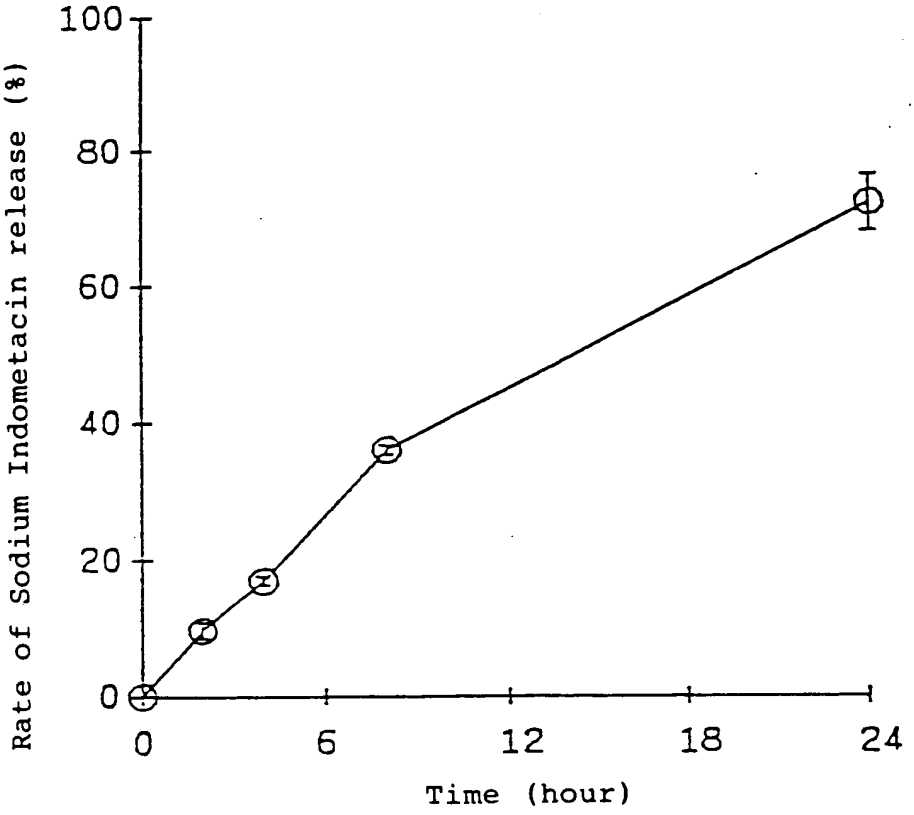


Figure 2



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Beschreibung

Zahnpflegemittel werden seit vielen Jahren als Pasten, sogenannte Zahnpasten hergestellt. Dabei ist der wesentliche Ausgangsstoff eine Schlämmkreide, die mit Wasser, Glycerin, waschaktiven Stoffen und Verdickungsmitteln zu einer Paste verarbeitet und in Tuben oder Spendern abgefüllt wird. Die Zahnpasta hat den Markt erobert, während andere Zahnpflegemittel wie Tropfen, Zahnseifen und - pulver oder Granulate kaum noch eine Rolle spielen. Mit den Mitteln soll der bakterielle Zahnbelag entfernt, Kariesprophylaxe betrieben sowie die Reinigung der Zähne schonend und durch die Bürstenbehandlung wesentlich unterstützt durchgeführt und der Mundraum gründlich gereinigt und angenehm erfrischt werden.

In neuerer Zeit hat sich das Bild der Zahnpasten nicht wesentlich verändert, obwohl die Rezepturen in vielerlei Hinsicht abgewandelt wurden. Die Verwendung einer recht groben Kreideform zum mechanischen Reinigen der Zähne wich mehr und mehr modernen, feineren Poliermitteln auf Basis von Aluminiumoxid oder Siliciumdioxid (Kieselgele). Neben Tensiden finden strukturbildende Komponenten und ausgefeilte Geschmackskorrigentien Verwendung. Oft werden Wirkstoffe wie insbesondere verschiedene Fluorderivate oder Mineralsalze zugefügt. Das Volumen konnte teilweise reduziert werden; sicherlich hat die Einführung und allgemeine Verwendung elektrischer Zahnbürsten hierbei einen starken Einfluß gehabt.

Die Handhabung von Zahnpasten ist jedoch mit einer Reihe von Nachteilen verbunden. Weil die Dosierung aus einfachen Tuben Schwierigkeiten bereitet, hat man in neuerer Zeit Zahnpastaspender entwickelt, welche jeweils eine vorbestimmte Menge Zahnpasta abgeben. Diese Spender sind jedoch verhältnismäßig groß und daher keinesfalls zur Mitnahme auf Reisen geeignet. Tuben sind druckempfindlich und daher auf Reisen ebenfalls nicht ideal. Sowohl in Spendern als auch in Tuben kann Zahnpasta austrocknen, so daß die angebrauchten Behälter dann weggeworfen werden müssen. Ferner lassen sich sowohl Tuben als auch Spender nicht vollständig entleeren. Nach Verbrauch bleiben die aus Metall oder Plastik hergestellten Behälter zurück und verursachen Umweltprobleme.

Aus der GB-A-21 63 348 sind Zahnreinigungstabletten bekannt, welche durch Zerbeißen und längeres Kauen im Munde eine pastenartige Konsistenz annehmen und dann zur Zahnreinigung dienen können. Eine Anwendung in der üblichen Weise durch Aufbringung auf eine Zahnbürste und anschließendes Einführen in den Mund ist nicht möglich. Verbrauchern mit schadhaften Zähnen oder Zahnersatz ist ein Zerbeißen spröder, harter Tabletten nicht möglich. Ferner können Kautabletten dieser Art auch nicht zur Reinigung künstlicher Zähne bzw. Gebisse verwendet werden.

Der Erfindung liegt demgegenüber die Aufgabe zugrunde, eine neue Verabreichungs- und Dosierungsform für Mund- und Zahnpflegemittel zu entwickeln, welche die vorstehend genannten Nachteile nicht aufweist, sich jedoch ähnlich wie Zahnpasta mit Hilfe einer Zahnbürste anwenden läßt.

Insbesondere soll eine genaue Dosierung für eine Zahnreinigung ermöglicht und sichergestellt werden, daß das Mittel vollständig aufgebraucht werden kann, ohne daß Reste in der Packung zurückbleiben.

Das erfindungsgemäße Mund- und Zahnpflegemittel auf Basis von Tensiden, Poliermitteln, Aromastoffen sowie weiteren üblichen Zusätzen ist dadurch gekennzeichnet, daß die Wirk- und Zusatzstoffe in ein Bindemittel oder eine Bindemittelmischung eingearbeitet sind, welche aus wasserlöslichen oder -quellbaren, physiologisch unbedenklichen Folienbildnern bestehen, wobei die gebildete Folie in Dosiseinheiten vorzerteilt ist.

Als Bestandteile des Mund- und Zahnpflegemittels kommen die Komponenten in Frage, welche üblicherweise zur Herstellung von Zahnpasten Verwendung finden, wobei natürliche Rohstoffe besonders bevorzugt sind. Wichtig ist darüber hinaus, daß alle Bestandteile völlig ungiftig und physiologisch unbedenklich sind, was selbstverständlich auch für die verwendeten Folienbildner gilt. Als wesentliche Bestandteile von Zahnpflegemitteln sind zu nennen:

- Schleifmittel wie Kreide (Calciumcarbonat), Calcium- und Natriumphosphate, Aluminiumoxid oder Siliciumdioxid, insbesondere Kieselgele
- Tenside (Schaummittel) wie Natriumlaurylsulfat, Natriumlaurylsulfoacetat, Sarcoside, Monoglyceridsulfate und andere
- Aromastoffe wie Pfefferminzöl, Krauseminzöl, Anisöl, Zimtöl, Nelkenöl, Menthol und ähnliche
- Süßstoffe wie Saccharin, Cyclamat, Aspartam und ähnliche.

Die in Zahnpasten üblicherweise enthaltenen flüssigen Komponenten wie Glycerin, Propylenglykol oder Sorbitsirup müssen den erfindungsgemäßen Mitteln in Folienform nicht in den üblichen Mengen zugesetzt werden, da hier die für Tuben oder Spender erforderliche Plastizität keine Rolle spielt. Weitere übliche Zusätze wie Fluorverbindungen, Mittel gegen Zahnsteinbildung, antibakterielle Wirkstoffe und ähnliche, wie sie in Mund- und Zahnpflegemitteln üblicherweise Verwendung finden, können auch erfindungsgemäß eingesetzt werden.

Als wasserlösliche bzw. -quellbare Folienbildner eignen sich vor allem Stärken, Gelatinen, Glycerin und/oder Sorbit sowie ferner natürliche oder synthetische Harze und Gumme. Folgende Rahmenrezeptur hat sich

bewährt:

Gelatine	8 - 10 g
Stärke	3 - 8 g
Glycerin	1 - 2 g
Wasser	30 - 50 g.

In dieser Grundmasse werden die Bestandteile des Mund- und Zahnpflegemittels gelöst bzw. dispergiert, um eine gleichmäßige Verteilung der Stoffe zu erreichen. Die so erhaltene Mischung kann erfindungsgemäß in verschiedener Weise zu einem folienförmigen Mund- und Zahnpflegemittel verarbeitet werden:

a) Es ist einmal möglich, die Masse direkt zu einer Folie zu verarbeiten, welche im allgemeinen eine Dicke zwischen 0,1 und etwa 3 mm aufweist. Durch Sollbruchstellen mittels Stanzung oder Perforierung kann diese Folie in Dosiseinheiten vorzerteilt werden, wobei die Streifenbreite und -länge vorzugsweise etwa der Zahnbürstengröße, d.h. der von den freien Borstenenden gebildeten Fläche des Borstenblocks oder der Längsquerschnittfläche des Borstenblocks in der Borstenebene entsprechen sollte.

b) Alternativ kann die Masse auf eine Trägerfolie aufgebracht werden, deren Zusammensetzung derjenigen des Bindemittels der Masse entspricht, wie dies in der EP-A-219,762 im einzelnen offenbart ist. Auch die auf diese Weise erhaltenen Folien können wie oben angegeben vorzerteilt werden.

c) Es ist ferner möglich, die Masse auf eine Releasefolie oder ein Releasepapier aufzubringen, wie dies aus der EP-A-259 749 bekannt ist. In diesem Fall wird die Beschichtung in einzelne Abschnitte der oben angegebenen Größe vorzerteilt, welche sich ähnlich wie Haftetiketten von der Trägerfolie vor Gebrauch abziehen lassen.

In allen Fällen erhält man eine Darreichungs- und Dosierungsform, deren Anwendung besonders leicht ist, da die jeweils zu verwendende Menge gleichmäßig vorgegeben ist. Eine Dosis wird in Form eines Folienabschnittes abgetrennt bzw. abgezogen und auf die angefeuchtete Zahnbürste bzw. zwischen die Borsten gelegt, wo sie durch die Feuchtigkeitsberührung haftet und anquillt. Durch das Einführen in die Mundhöhle und in Verbindung mit dem Speichel und der intensiven Zahnbürstenbewegung wird der Streifen an- und aufgelöst, so daß die Inhaltsstoffe zur vollen Wirkung gelangen. Nach der Anwendung und der anschließenden Mundspülung mit Wasser verbleiben keinerlei Rückstände im Mund.

Gewünschtenfalls können die Folien in unterschiedlicher Weise bedruckt, geprägt oder gestanzt werden, wobei beispielsweise für Kinder auch bildliche Darstellungen möglich sind. Es entfällt das Öffnen und Schließen von Tubenverschlüssen, es wird keine Zahnpasta vergeudet und die erfindungsgemäße Darreichungsform läßt sich auch besondes gut auf Reisen einsetzen, da sie leicht ist, ein Auslaufen nicht befürchtet werden muß und sie äußerst wenig Platz beansprucht. Die Verpackung ist umweltfreundlich in Pappschachteln ohne Verwendung von Metallen oder Kunststoff möglich.

Die Mittel der Erfindung eignen sich nicht nur zur Zahnpflege im Mund, sondern bei geeigneter Zusammensetzung auch zur Reinigung und Pflege von künstlichen Zähnen und Gebissen. Für diesen letzteren Einsatzzweck ist eine Mehrfachbeschichtung besonders günstig, bei der sich in einer Schicht die reinigenden, desinfizierenden und sauren Komponenten befinden, während sich, ggf. getrennt durch eine ebenfalls wasserlösliche Sperrschicht, in einer zweiten Schicht die CO_2 bzw. O_2 abgebenden Substanzen enthalten sind.

Beispiel

Ein erfindungsgemäßes Zahnpflegemittel hat folgende Zusammensetzung:

Amylogum	57,0 g
Honig	25,0 g
Zitronensäure	2,0 g
Titandioxid	1,0 g
Aroma	1,0 g
Siliciumdioxid	3,0 g
Ca-Hydrog-phos.	10,0 g
Na-Laurylsulfat	1,0 g

Mit der erforderlichen Menge Wasser wird ein Brei hergestellt, der zu einer Folie verarbeitet wird, die ca. 0,5 mm dick ist. Durch Perforation wird die Folie in Abschnitte von 8 x 35 mm unterteilt.

Gegebenenfalls kann die Masse auch als Beschichtung auf ein Releasepapier als Träger aufgebracht und durch Stanzung in Abschnitte der angegebenen Größe vorzerteilt werden.

Patentansprüche

1. Mund- und Zahnpflegemittel auf Basis von Tensiden, Poliermitteln, Aromastoffen sowie weiteren üblichen Zusatzstoffen, dadurch gekennzeichnet, daß die Wirk- und Zusatzstoffe in ein Bindemittel oder eine Bindemittel-Mischung eingearbeitet sind, welche aus wasserlöslichen oder -quellbaren, physiologisch unbedenklichen Folienbildnern bestehen, und daß diese Mischung zu einer Folie verarbeitet ist, wobei die so gebildete Folie in Dosiseinheiten vorzerteilt ist.

2. Mund- und Zahnpflegemittel gemäß Anspruch 1, dadurch gekennzeichnet, daß es als Folienbildner Stärken, Gelatinen, Glycerin und/oder Sorbitol oder natürliche und/oder synthetische Harze und Gumme enthält.

3. Mund- und Zahnpflegemittel gemäß Anspruch 1, dadurch gekennzeichnet, daß es als Folienbildner Amylogum enthält.

4. Mund- und Zahnpflegemittel nach den Ansprüchen 1 bis 3, dadurch gekennzeichnet, daß es als Folienbildner eine Mischung aus 8 bis 10 Gewichtsteilen Gelatine, 4 bis 8 Gewichtsteilen Stärke und 1 bis 2 Gewichtsteilen Glycerin enthält.

5. Mund- und Zahnpflegemittel nach den Ansprüchen 1 bis 4, dadurch gekennzeichnet, daß es aus einer Trägerfolie aus dem Bindemittel oder der Bindemittel-Mischung besteht, auf welche eine Schicht aufgebracht ist, welche die Bestandteile des Pflegemittels zusammen mit Bindemittel oder der Bindemittel-Mischung enthält, wobei das Bindemittel oder die Bindemittel-Mischung in der Trägerfolie und in der Beschichtung im wesentlichen die gleiche qualitative Zusammensetzung aufweisen.

6. Mund- und Zahnpflegemittel nach den Ansprüchen 1 bis 4, dadurch gekennzeichnet, daß eine Beschichtung aus den Bestandteilen des Pflegemittels und dem Bindemittel oder der Bindemittel-Mischung auf eine Trägerfolie in Form eines Trennpapiers, eines Trennfilms oder einer Trennfolie aufgebracht ist, wobei die Beschichtung nach Vorzerteilung in Dosiseinheiten von dem Trägermaterial dosisweise abziehbar ist.

Claims

1. Oral and dental hygiene preparation based on surfactants, polishing agents, flavours, and other conventional additives, characterised in that the active ingredients and additives are incorporated in a binder or a binder mixture comprising water-soluble or water-swellable, physiologically harmless film formers, and in that said mixture is processed to a film, the film thus formed being predivided into dose units.

2. Oral and dental hygiene preparation according to claim 1, characterised in that it contains as film formers starches, gelatins, glycerol and/or sorbitol or natural and/or synthetic resins and gums.

3. Oral and dental hygiene preparation according to claim 1, characterised in that it contains starch gum as film former.

4. Oral and dental hygiene preparation according to claims 1 to 3, characterised in that it contains as film former a mixture of 8 to 10 parts by weight of gelatin, 4 to 8 parts by weight of starch and 1 to 2 parts by weight of glycerol.

5. Oral and dental hygiene preparation according to claims 1 to 4, characterised in that it comprises a carrier film made of the binder or the binder mixture, onto which is deposited a layer which contains the constituents of the hygiene preparation together with binder or the binder mixture, whereby the binder or the binder mixture in the carrier film and in the coating have essentially the same qualitative composition.

6. Oral and dental hygiene preparation according to claims 1 to 4, characterised in that a coating consisting of the constituents of the hygiene preparation and the binder or the binder mixture is deposited on a carrier film in the form of a release paper, a release film or a release sheet, whereby the coating can be removed in doses from the carrier material after predivision into dose units.

Revendications

1. Préparation d'hygiène bucco-dentaire à base d'agents tensio-actifs, d'agents de polissage, de substances aromatiques ainsi que d'autres ingrédients habituels, caractérisée en ce que les principes actifs et les ingrédients additionnels sont incorporés à un agent liant ou à un mélange d'agents liants, qui sont constitués d'agents filmogènes solubles ou gonflables dans l'eau, physiologiquement sans danger, le film formé étant prédivisé en unités de dosage.

2. Préparation d'hygiène bucco-dentaire selon la revendication 1, caractérisée en ce qu'elle contient à titre d'agents filmogènes des amidons, des gélatines, de la glycérine et/ou du sorbitol ou des résines et des gommes naturelles et/ou synthétiques.

3. Préparation d'hygiène bucco-dentaire selon la revendication 1, caractérisée en ce qu'elle contient à titre d'agent filmogène de l'amylogum.

4. Préparation d'hygiène bucco-dentaire selon les revendications 1 à 3, caractérisée en ce qu'elle contient à titre d'agent filmogène un mélange de 8 à 10 parties en poids de gélatine, de 4 à 8 parties en poids d'amidon et de 1 à 2 parties en poids de glycérine.

5. Préparation d'hygiène bucco-dentaire selon les revendications 1 à 4, caractérisée en ce qu'elle est constituée d'une feuille de support formée de l'agent liant ou du mélange d'agents liants, feuille de support sur laquelle est appliquée une couche qui contient les composants de la préparation d'hygiène conjointement avec l'agent liant ou le mélange d'agents liants, l'agent liant ou le mélange d'agents liants de la feuille de support et du revêtement ayant essentiellement la même composition qualitative.

6. Préparation d'hygiène bucco-dentaire selon les revendications 1 à 4, caractérisée en ce que l'on applique un revêtement formé des composants de la préparation d'hygiène et de l'agent liant ou du mélange d'agents liants sur une feuille de support sous la forme d'un papier de séparation, d'un film de séparation ou d'une feuille de séparation, le revêtement pouvant être séparé de la matière de support par doses individuelles après prédivision en unités de dosage.

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(54) Non-porous collagen sheet for therapeutic use, and the method and apparatus for preparing it

Nichtporöse Kollagenfolie zur therapeutischen Verwendung, und Verfahren und Vorrichtung zu ihrer Herstellung

Feuille non poreuse de collagène à usage thérapeutique, et procédé et appareil pour sa préperation

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Description

Collagen is a scleroprotein widespread in nature. It represents about one third of the total proteins of the human body.

Medical practice has recently seen the introduction of the use of collagen as a stimulating agent in the cicatrization process involving an interaction effect with various growth factors, because of its capturing action on fibronectin, a glycoprotein which promotes cell attachment and the migration and replication of the resultant cells (see "I1 collageno nella cicatrizzazione" by B. Palmieri, publ. Artestampa, January 1990, pp. 40-42) and other actions which are still not totally clear. The known collagen product, using a particular non-denaturing process, is prepared in stable form by a process of extraction from animal organs rich in this scleroprotein, purification and subsequent lyophilization. The final product is in the form of mats of greater or lesser thickness, characterised by high absorbent power (exudates and liquids in general) because of its structure in the form of fibres which are spaced apart and branched in such a manner as to make a large specific surface available for absorption (up to 50 times its weight). The hydrophilic nature of collagen also greatly favours this absorbent power.

In addition to the aforesaid function, the role of collagen in cicatrization is characterised by collagen/platelet interaction and the formation of a bond between the collagen, the fibronectin and the growth factors, molecules which are known to be implicated in regulating the cicatrization process (see pages 45-46 of the aforesaid text).

There are however cases in which the absorbent formation of the collagen sponge and its hydrophilic nature lead to an excessive loss of physiological liquids. It is well known that an evaporation process normally occurs through the undamaged skin, and this increases considerably in the case of skin lesion, resulting in dehydration of the underlying layers. The phenomenon is accentuated for example in burn cases, when large skin portions are damaged traumatically. In this case the absorbent effect of lyophilized collagen further increases the process of evaporation, with consequent damage to the underlying structure.

Another kind of known collagen-based medicament useful for wound healing is represented by the collagen membranous material disclosed by EP-A-0376931, which is prepared by disrupting and centrifuging a collagen gel matrix so to precipitate collagen, homogenizing the precipitated material in the form of a paste, casting and drying the paste.

The present invention provides a product which while maintaining the rapid cicatrization characteristics of collagen, at the same time prevents excessive evaporation, allows constant inspection of the bed of the wound without having to be removed (transparency), is simple and practical to use, adheres satisfactorily to the injured surface, does not require frequent replacement, can transpire to allow oxygenation of the bed of the wound while preventing its contamination by bacteria, is absorbable but not soluble in the biological liquids with which it comes into contact, unless by specific enzymatic action, and is structurally homogeneous.

Another important characteristic of the collagen according to the invention is that of being suitable as interposition material for preventing accretions in the internal surgery operations.

To obtain a product with these characteristics, type I collagen was used as defined in Table 1 on page 3 of the aforestated text, that is having molecular structure $[\alpha 1(I)_2]\alpha 2(I)$, this having the characteristic of being insoluble in the various types of biological liquids. Type I collagen present in the skin represents about 80% of the total located in the deep dermis, 90-95% in the tendons and 100% in the bones. Type I collagen is therefore the most biologically similar to that present in the human skin.

Because of its insolubility, in order to obtain a product of homogeneous structure, use was made of the known method of dispersing fibrous collagen in a dilute acetic acid solution of about pH 2.5 and maintaining agitation until a good dispersion of the collagen fibres in the liquid is obtained. At this pH value the fibres swell to form a gel. The gel obtained, still comprising fibre fractions which have not completely gelled and possibly corpuscles of extraneous substances, is further diluted with an acetic acid solution of pH 2.5-3.5 until a sufficiently fluid mass is obtained, which is then filtered.

The filtering, which is done under vacuum, uses a special filter, indicative (but not limitative) characteristics of which are given hereinafter, and allows practically total elimination of the inevitable air bubbles which form during gelling and are difficult to eliminate given the viscosity of collagen gel.

By the effect of the vacuum, which has to be of the order of 3999 Pa residual pressure, these bubbles increase their volume, the passage through the mesh then breaks down and eliminates them. It has been found experimentally that the best filtration conditions to achieve the described phenomenon are a gel temperature of 10-30°C, preferably 25-28°C, and a residual vacuum of 2666-7998 Pa (20-60 mmHg), preferably about 3999 Pa (30 mmHg).

These data are indicative and have been found experimentally to be the most effective, although not representing a limitation on the operating conditions of this process.

The filtered gel is collected in a closed vessel maintained under vacuum and constructed in such a manner that the filtered gel runs along vessel partition walls located below the filter mesh and structured to produce a continuous liquid film which does not allow further air absorption after filtration, following inclusion of air bubbles.

The filtered gel is further maintained under vacuum

at 2666-3332.5 Pa (20-25 mmHg) for a further hour to allow total elimination of any air bubbles which may still be present in the gel.

FILTER APPARATUS

The filter required for filtering the collagen gel, which besides eliminating the solid particles, which are retained on the mesh, also eliminates the air bubbles contained in it, consists of an upper cylindrical stainless steel shell provided with a scraping stirrer to keep the collagen gel mixed and to remove solid particles from the mesh so that they do not clog it. The bottom of the cylindrical shell houses a stainless steel mesh with a mesh size of less than 0.1 mm (Taurail meshes have been found to be particularly effective).

The lower part (below the mesh) consists of a cylindrical shell in which vacuum can be generated by a suitable pump. The air bubbles contained in the gel which filters through the mesh increase considerably in volume because of the vacuum.

At about 3 mm below the filter mesh there is a device consisting of a series of stainless steel plates which are vertically or raking placed and parallel between them. The filtered gel descends along these plates in the form of a continuous liquid film and runs by gravity towards the bottom of the vessel.

Those air bubbles which do not break down by the effect of the reduced pressure remain mainly in the upper part of the device whereas the gel, now free or almost free of air, runs to the bottom of the vessel. Any very small bubbles still present in the filtered gel decrease considerably in volume when returned to atmospheric pressure, so that they become practically absent.

In this respect, during filtration because of the difference between the pressure of the gel environment before filtration and the residual pressure below the mesh (about 3999 Pa), the bubble volume increases more than 25 times. Likewise, on passing from vacuum to the environmental pressure the bubble volume decreases 25 times. Hence the air bubbles of diameter less than 0.100 mm (advisable mesh passage size) have a diameter of less than 0.034 mm when returned to atmospheric pressure, ie are practically invisible. During drying, these residual bubbles are eliminated without leaving appreciable craters in the structure of the obtained sheet.

This means that extremely uniform thicknesses can be obtained over the entire sheet surface, so avoiding any porosity which could represent a point of preferential attack by enzymatic action, which would annul the protective effect against invasion by micro-organisms.

DRYING

The filtered gel obtained as described, free from extraneous particles and air bubbles and perfectly clear and transparent, can then be used for preparing films of desired thickness and diameter. For this, after analysis to exactly determine the concentration of the filtered gel, exactly measured quantities for obtaining films with the desired collagen thickness must be metered into suitable containers. This metering is generally effected by a suitable peristaltic pump which prevents incorporating air into the gel while at the same time preventing heating or friction which could damage the structure of the collagen protein. The containers are of tray shape and are formed of antiadherent material.

The described trays loaded with the gel in a controlled environment (relative humidity 60-80%, temperature 20-22°C, environment class 10,000 or less) are placed in a suitable controlled drying oven where they are left to stand for at least two hours to obtain perfect gel thickness uniformity. The oven is purged with a nitrogen stream for about 30 minutes to totally eliminate air and remove oxygen, in order to ensure constant operating conditions and prevent possible oxidation.

This operation has also been shown to practically totally block the growth of micro-organism colonies, which sometimes occurs if the procedure is carried out with air present in the environment. Drying is effected in a nitrogen stream under closed cycle.

The drying, being the critical stage for obtaining films with the desired characteristics, is conducted under particular conditions in an appropriate oven shown schematically in Figure 1.

In this, the reference numeral 1 indicates the drying trays resting on perforated side walls, V indicates the fan for circulating nitrogen through the apparatus, N_2 indicates the nitrogen feed valve, GF indicates the refrigeration unit with coil, S represents a parallel plate device for separating condensate droplets, T_1 indicates a first thermometer, SC indicates the condensed water discharge, R indicates the heating device, T_2 indicates a second thermometer, I_1 indicates a first hygrometer, MO indicates an oxygen meter (analyzer), Sg indicates the gas discharge, Tr indicates an overpressure trap and I_2 indicates a second hygrometer.

The oven is arranged in this manner to satisfy the following requirements:

1) the facility for eliminating air by purging with nitrogen to a residual oxygen content of less than 2%;

2) the facility for varying the nitrogen cooling and heating temperature to a maximum of 30°C, to control the relative humidity in the drying chamber and the water evaporation rate;

3) the facility for regulating the rate of nitrogen circulation through the chamber so as not to create high flow points and hence maintain a uniform drying rate over the entire surface and prevent the formation of creases which, besides being undesirable from the appearance aspect, are an indication of different collagen concentrations and poor homogeneity of drying (localized drying).

The H_2O content of the product must not be higher than 20% by weight. It is preferable to achieve a higher level of drying (down to 2% or 3% of H_2O), in particular to ensure proper elimination of the acetic acid present in the initial gel. The dried product obtained easily reabsorbs moisture from the environment, while being maintained within the maximum limit of 20%.

EXAMPLE

The conditions found experimentally to be most appropriate for conducting a drying cycle are given below by way of non-limiting example.

1st stage:

Nitrogen purging until the oxygen content is less than 1%, standing for two hours to come to equilibrium, loaded gel level 10 mm, gel collagen concentration 0.5%.

2nd stage:

Starting of nitrogen circulation by fan.
Nitrogen temperature after cooling -5°C (T_1).
Nitrogen temperature after heating 26-28°C (T_2).
Time about 12 hours.
Relative humidity entry to drying region (point I_1) 12-14%.
Relative humidity exit of drying region (point I_2) 70-80%.

3rd stage:

Nitrogen temperature after cooling -15°C (T_1).
Nitrogen temperature after heating 26-28°C (T_2).
Time about 12 hours.
Relative humidity entry to drying region (point I_1) 6-7%.
Relative humidity exit of drying region (point I_2) 45-50%.

4th stage:

Final drying

Nitrogen temperature after cooling -40°C (T_1).
Nitrogen temperature after heating 26-28°C (T_2).
Time about 12 hours.

5th stage:

Product discharge, preparation of a new load. Complete removal of water from the cooling coil and purging the oven by nitrogen circulation at 70-80°C for two hours, cooling to 20°C and loading new product.

The nitrogen flow rate through the drier is adjusted on the basis of the required degree of drying.

A semi-transparent film with a thickness of about 200 micron is obtained. The thickness can vary in general between 0.02 and 2 mm. This represents a non-specific item for the purposes of the therapeutic application as it determines only the product absorption time but not its specific characteristics. The degree of drying can also vary as stated.

The characteristics of the film obtained are:

- maintaining of the "native" structure of collagen fibre (the classical triple spiral structure of collagen has been demonstrated by the electron microscope)
- absence of degradation products such as monomers or dimers of collagen not organized into fibrils, or gelatin, an indication of potential allergenicity
- high protein nitrogen content (exceeding 90%)
- high hydroxyproline content (exceeding 12%)
- low absorbent power (about 10-15 times its weight against 50 times for the lyophilized product of the known art)
- high resistance to enzymatic attack
- good product transparency
- excellent plasticity after immersion in physiological solution.

The product obtained in this manner is sterilized by irradiation with gamma rays and used in the treatment of burns and generally all cases of skin removal or damage.

The result is excellent both in terms of tolerance (no case of allergenicity or hypersensitivity to the medicament has been recorded, the native characteristic of the product remaining unaltered during the process) and in terms of pain attenuation. The cicatrization time is very rapid and product absorption considerably longer compared with equivalent treatment using lyophilized collagen (sponge) and consequently there is lesser need to replace it. Exudate loss is very low, and much lower than that when using lyophilized collagen.

The transparency of the product means that the progress of the injury can be viewed without the need to remove the collagen sheet (generally a painful procedure).

The product can be presented in the form of sheets of different dimensions (square, rectangular, round, elliptical or others) supported or not supported by adhesives (such as plasters) or by sheets of inert substances such as nylon, polyurethane, polyethylene etc., or associated during the drying process, or subsequently, with pharmacologically active substances.

Claims

1. A sheet of type I collagen gel, having molecular structure $[\alpha 1(I)]_2\alpha 2(I)$, suitable for the therapeutic cicatrizing treatment of wounds and burns, said sheet being free from native collagen degradation products, having an H_2O content not exceeding 20% by weight, a uniform thickness, comprised between 0.02 and 2 mm, said sheet being characterized in that it is of transparent structure, it has an homogeneous structure, it has the classical triple-helical structure of native collagen, it comprises gas bubbles with a diameter of less than 0.034 mm under atmospheric pressure, it has a capacity for absorbing aqueous biological liquids limited to a maximum of 15 times its weight and a high resistance to enzymatic attack.

2. A method of preparing a sheet of type I collagen as claimed in claim 1 from aqueous diluted collagen gel of pH 2.5-3.5, comprising filtering the gel through a filter surface with a passage size of less than 0.1 mm, the lower part of filtering apparatus being under a vacuum of 2666-7998 Pa and provided in the region immediately below the filter mesh with a device consisting of a series of plates vertically or raking placed and parallel between them, then drying the liquid gel contained in trays by purging with nitrogen to a residual oxygen content of less than 2%, at a temperature of 20-22°C and with a relative humidity of 60-80%.

3. A device suitable for filtering under vacuum the collagen gel in accordance with claim 2, comprising an upper shell provided with a scraping stirrer, a metal mesh with a mesh size of less than 0.1 mm placed at the bottom of the upper shell, a lower shell connected with a vacuum pump, and provided in the region immediately below the filter mesh with a pack of plates vertically or raking placed and parallel between them for the purpose of conveying the filtrate constitued by the said collagen gel as a continuous liquid film.

4. Use of the sheet of type I collagen as claimed in claim 1, for the preparation of a medicament useful for the treatment of wounds and burns and as interposition material for preventing accretions in the internal surgery operations.

Patentansprüche

1. Folie aus Typ I-Kollagengel, das die Molekularstruktur $[\alpha 1(I)]_2\alpha 2(I)$ hat und für die therapeutische Narbenbildungsbehandlung geeignet ist, wobei die Folie von Abbauprodukten natürlichen Kollagens frei ist, einen Wassergehalt hat, der 20 Gew.-% nicht übersteigt; eine gleichmäßige Dicke zwischen 0,02 und 2 mm hat,
dadurch gekennzeichnet, daß
die Folie eine transparente Struktur aufweist, eine homogene Struktur hat, daß sie die klassische Dreifachhelix-Struktur von natürlichem Kollagen hat, bei atmosphärischem Druck Gasblasen mit einem Durchmesser von weniger als 0,034 mm enthält, ihre Kapazität zur Absorption wäßriger biologischer Flüssigkeit auf ein Maximum des 15-fachen ihres Gewichts limitiert ist, und sie eine hohe Beständigkeit gegenüber einem enzymatischen Angriff hat.

2. Verfahren zur Herstellung einer Folie aus Typ I-Kollagengel nach Anspruch 1 aus wäßrigem verdünntem Kollagengel mit einem pH von 2,5 bis 3,5, umfassend

   - Filtrieren des Gels durch eine Filteroberfläche mit einer Durchgangsgröße von weniger als 0,1 mm, wobei der untere Teil der Filtrierapparatur unter einem Vakuum von 2666 bis 7998 Pa steht und in dem Bereich unmittelbar unter dem Filtersieb bereitgestellt ist, mit einer Vorrichtung, die aus Reihen von Platten besteht, welche senkrecht oder schräg und zueinander parallel angeordnet sind;

   - Trocknen des flüssigen Gels, das in Schalen enthalten ist, durch Spülen mit Stickstoff bis zu einem Restsauerstoffgehalt von weniger als 2%, bei einer Temperatur von 20 bis 22°C und einer relativen Feuchtigkeit von 60 bis 80%.

3. Vorrichtung, die zum Filtrieren des Kollagengels nach Anspruch 2 geeignet ist, und die aus einem oberen Mantel, der mit einem Shabrührer ausgestattet ist; einem Metallsieb mit einer Maschengröße von weniger als 0,1 mm, das am Boden des oberen Mantels angeordnet ist; einem unteren Mantel, der mit einer Vakuumpumpe verbunden ist, besteht, und die im Bereich unmittelbar unter dem Filtersieb mit einer Reihe von Platten, die vertikal oder schräg und zueinander parallel angeordnet sind, zum Zwecke eines Beförderns des Filtrats, das aus dem Kollagengel besteht, als kontinuierliche flüssige Folie, versehen ist.

4. Verwendung der Folie aus Typ I-Kollagengel nach Anspruch 1 zur Herstellung eines Medikaments, das zur Behandlung von Wunden und Verbrennungen sowie als Interpositionsmaterial zur Verhinderung von Verwachsungen bei inneren Operationen verwendbar ist.

Revendications

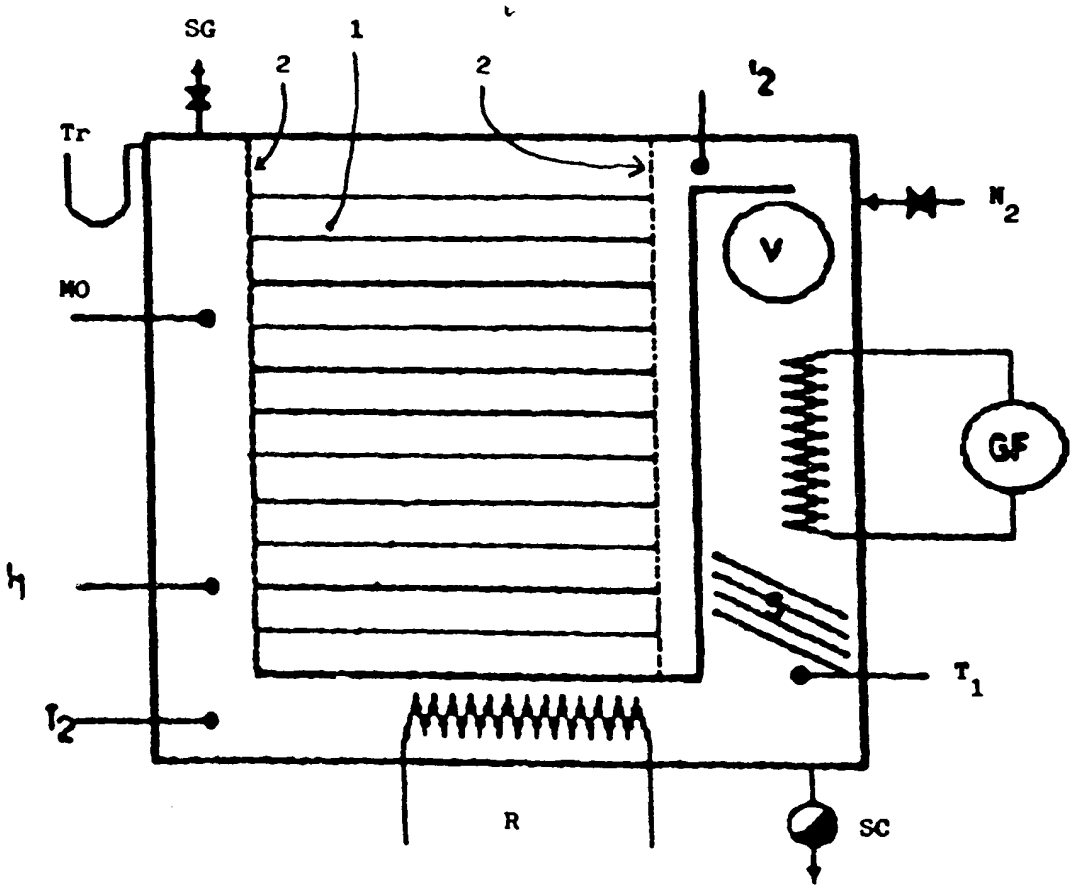
1. Feuille de gel collagène du genre I ayant une structure moléculaire $[\alpha 1(I)]_2\alpha 2(I)$, apte au traitement thérapeutique cicatrisant de blessures et brûlures, la susdite feuille étant sans produits de dégradation du collagène naturel, ayant un contenu de H_2O qui n'est pas supérieur à 20% en poids et une épaisseur uniforme de 0,02-2 mm, la susdite feuille étant characterisée en ce qu'elle a une structure transparente et homogène, la structure typique à triple-hélice de collagène naturel, en ce qu'elle comprend des bulles de gaz ayant un diamètre de moins de 0,034 mm à pression atmosphérique, et en ce qu'elle est capable d'absorber des liquides biologiques aqueux pour un maximum de 15 fois son poids et est très resistante à l'attaque enzymatique.

2. Méthode pour préparer une feuille de collagène du genre I selon la revendication 1 à partir de gel collagène aqueux dilué avec un pH 2,5-3,5, comprenant la filtration du gel à travers une surface filtrante avec un passage inférieur à 0,1 mm, la partie inférieure de l'appareil filtrant étant sous un vide de 2666-7998 Pa et étant pourvue dans la région directement au-dessous du filet de filtration d'un appareil composé par une série de plaques arrangées verticalement ou inclinées et parallèles entre elles, la susdite méthode comprenant ensuite le séchage du gel liquide contenu dans des plateaux en le purgeant avec azote jusqu'à obtenir un contenu en oxygène inférieur à 2% à une température de 20-22°C et avec une humidité relative de 60-80%.

3. Appareil apte à la filtration sous vide du gel collagène selon la revendication 2, comprenant une coque supérieure avec un agitateur raclant, un filet métallique avec une maille inférieure à 0,1 mm placé au fond de la coque supérieure, une coque inférieure liée avec une pompe à vide et pourvu dans la région directement au-dessous du filet de filtration d'une pile de plaques arrangées verticalement ou inclinées et parallèles entre elles pour acheminer le filtrat constitué par le susdit gel collagène comme une pellicule liquide continue.

4. Emploi de la feuille de collagène du genre I selon la revendication 1 pour la préparation d'un médicament utilisé dans le traitement de blessures et brûlures et comme matériel d'interposition pour éviter des excroissances dans les opérations de chirurgie interne.

FIG. 1



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(54) Method of preparing a water soluble film

(57) The present invention provides a method of preparing a water soluble film. The method comprises (a) preparing a solution comprising a film former, a water soluble plasticizer, a pharmaceutically active agent, and a solvent; (b) drying the solution at a temperature of from about 50 to about 100° C to form a film; and (c) curing the film at a temperature of from about 15 to about 60° C and at a relative humidity of at least about 30%. The film former is a polyacrylic acid, cellulose derivatives, polyethylene oxide, polyvinyl alcohol, or any combination of any of the foregoing. The water soluble plasticizer contains at least one of a hydroxyl, amido, or amino group and has a boiling point greater than about 150° C. The water soluble film of the present invention may be incorporated into vaginal devices, such as tampons and applicators. This method produces a uniform and homogeneous film which is more flexible and drips less than prior water soluble films, especially those incorporated into vaginal dosage forms. As a result, the film is less irritating. Furthermore, unlike most prior art water soluble films, the film may be shaped to provide a larger contact area within a body cavity, such as the vagina, in order to increase drug delivery. The film is also non-messy.

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Description

[0001] This application claims priority from U.S. Serial No. 60/172,085, filed December 23, 1999, which is incorporated herein by reference.

FIELD OF THE INVENTION

[0002] The present invention relates to a method of preparing a water soluble film for use in dosage unit forms, such as tampons and applicators.

BACKGROUND OF THE INVENTION

[0003] Current vaginal dosage forms, except the sponge and film, are messy to use and readily drip out of the vagina. Furthermore, the sponge requires removal after use and is believed to cause infection. Films often cause irritation due to their rigidity and sharp edges.

[0004] U.S. Patent Nos. 5,393,528 and 5,529,782 disclose a device having a dissolvable element for administration of an agent material in an internal body area. The dissolvable element is a film made of polyvinyl alcohol, polyethylene oxide, and/or a complex carbohydrate material.

SUMMARY OF THE INVENTION

[0005] The present invention provides a method of preparing a water soluble film. The method comprises the steps of (a) preparing a solution comprising a film former, a water soluble plasticizer, a pharmaceutically active agent, and a solvent; (b) drying the solution at a temperature of from about 50 to about 100° C to form a film; and (c) curing the film at a temperature of from about 15 to about 60° C and a relative humidity of at least about 30%. The film former is a polyacrylic acid, cellulose derivative, polyethylene oxide, polyvinyl alcohol, or any combination of any of the foregoing. The water soluble plasticizer contains at least one of a hydroxyl, amido, or amino group and has a boiling point greater than about 150° C. The water soluble film of the present invention may be incorporated into vaginal devices, such as tampons and applicators. The formulation of the film may be optimized as known in the art to provide controlled release of the pharmaceutically active agent.

[0006] This method produces a uniform and homogeneous film which is more flexible and drips less than prior water soluble films, especially those incorporated into vaginal dosage forms. As a result, the film is less irritating. Furthermore, unlike most prior art water soluble films, the film may be shaped to provide a larger contact area within a body cavity, such as the vagina, in order to increase drug delivery. The film is also non-messy.

[0007] Another embodiment of the present invention is a dosage unit form, such as a tampon or applicator, comprising a water soluble film prepared by the aforementioned method.

DETAILED DESCRIPTION OF THE INVENTION

[0008] The method of the present invention comprises the steps of (a) preparing a solution comprising a film former, a water soluble plasticizer, a pharmaceutically active agent, and a solvent; (b) drying the solution at a temperature of from about 50 to about 100° C to form a film; and (c) curing the film at a temperature of from about 15 to about 60° C and at a relative humidity of at least about 30%. The inventors have discovered that curing the film under the aforementioned conditions produces a significantly more flexible film which drips less when administered into the vagina and other body cavities than the same film prepared without curing. The film is also non-messy, uniform, and homogeneous.

[0009] The solution may be prepared by mixing the ingredients, if the pharmaceutically active agent is water soluble.

[0010] Water insoluble pharmaceutically active agents may be dispersed, preferably uniformly, in the solvent by any method known in the art. The other ingredients may be added before or after dispersing the pharmaceutically active agent.

[0011] The film former is a polyacrylic acid, cellulose derivative, polyethylene oxide, polyvinyl alcohol, or any combination of any of the foregoing. Suitable cellulose derivatives include, but are not limited to, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, and any combination of any of the foregoing. The film former is preferably polyvinyl alcohol. More preferably, the film former is a partially hydrogenated polyvinyl alcohol, such as Elvanol™ grade 51-05, 52-22, and 50-42 available from DuPont Co. of Wilmington, DE, and Airvol™ grade 205S and 523S available from Air Products & Chemicals, Inc., of Allentown, PA. The viscosity of the polyvinyl alcohol generally ranges from about 3 to about 1000 cps and preferably ranges from about 3 to about 50 cps. The solution typically comprises from about 5 to about 40% by weight and preferably from about 15 to about 35% by

weight of film former, based upon 100% total weight of solution.

[0012] The water soluble plasticizer contains at least one of a hydroxyl, amido, or amino group and has a boiling point greater than about 150° C. Preferably, the boiling point of the plasticizer is greater than about 180° C. Suitable plasticizers include, but are not limited to, polyhydroxy compounds, such as propylene glycol, polyethylene glycol, glycerin, and any combination of any of the foregoing. Other suitable plasticizers include, but are not limited to, fatty acid derivatives having a melting point less than about 45 ° C, such as ehydrogenated vegetable oil available as Wecobee™ from Stepan Company of Northfield, IL, and hydrogenated coco-glycerides available as Witepsol H15™ from Hüls America of Somerset, N.J.; and fatty alcohol derivatives having a hydroxy value of greater than about 30. The solution typically comprises from about 0.1 to about 10% by weight and preferably from about 0.5 to about 5% by weight of water soluble plasticizer, based upon 100% total weight of solution.

[0013] The pharmaceutically active agent may be water-insoluble or water soluble. Suitable pharmaceutically active agents include, but are not limited to, imidazole antifungal agents, such as imidazole antifungal agents include, but are not limited to, miconazole, econazole, terconazole, ketoconazole, saperconazole, itraconazole, clotrimazole, tioconazole, and butaconazole; antibacterial agents, such as nystatin, neomycin, polymycin, tetracycline, clindamycin, and metronidazole; antiseptic agents, such as oxyquinoline benzoate and aminacrine; hormones, such as estrogens, testolactone, androgens, progestins, megestrol acetate, medroxyprogesterone acetate, esterified estrogens, conjugated estrogens, estradiol, polyestradiol, ethinyl estradiol, estropipate, diethylstilbestrol diphosphate, polyestradiol phosphate, and leuprolide acetate; anti-inflammatory agents, hydrocortisone, triamcinolone, betamethasone, flucinonide, and halcinonide; anesthetics, such as lidocaine and benzocaine; spermicides, such as nonoxynol-9 and octoxynol-9; and any combination of any of the foregoing. A preferred imidazole antifungal agent is miconazole nitrate. A preferred antibacterial agent is metronidazole. A preferred spermicide is nonoxynol-9.

[0014] Generally, the amount of pharmaceutically active agent in the solution is an amount effective to accomplish the purpose for which it is being used. The amount of pharmaceutically active agent is typically a pharmaceutically effective amount. However, the amount can be less than a pharmaceutically effective amount when the film is used in a dosage unit form, because the dosage unit form may contain a multiplicity of films or may contain a divided pharmaceutically effective amount. The total effective amount can then be determined in cumulative units containing, in total, a pharmaceutically effective amount of pharmaceutically active agent. The total amount of pharmaceutically active agent may be determined by those skilled in the art. Generally, the solution comprises from about 1 to about 30% by weight and preferably from about 5 to about 20% by weight of pharmaceutically active agent, based upon 100% total weight of solution.

[0015] The solvent may be water, ethanol, glycerin, ethylene glycol, amides, amines, or any combination of any of the foregoing. The solvent is preferably water or a mixture of water and ethanol. Preferably, the mixture comprises less than about 30% by weight of ethanol, based upon 100% total weight of mixture. The solution typically comprises from about 20 to about 90% by weight and preferably from about 40 to about 80% by weight of solvent, based upon 100% total weight of solution.

[0016] According to a preferred embodiment of the present invention, the solution comprises about 26.4% by weight of polyvinyl alcohol, about 2.4% by weight of glycerin, about 11.2% by weight of nonoxynol 9, and about 60% by weight of water, based upon 100% total weight of solution.

[0017] The solution may include other adjuvants, such as surfactants, preservatives, viscosity enhancers, colorants, fragrances, flavorants, lubricants, fillers, binders, wetting agents, penetration agents, pH adjusters, disintegrants, excipients, or any combination of any of the foregoing. Suitable surfactants include, but are not limited to, polyethylene glycol ether of cetearyl alcohol, such as ceteareth-20; hydrogenated coco-glycerides; and any combination of any of the foregoing.

[0018] The solution typically has a viscosity of from about 15,000 to about 30,000 cps at room temperature prior to drying. Generally, the water soluble film prepared by the method of the present invention has a thickness of from about 0.03 to about 0.50 mm. Preferably, the thickness of the film is from about 0.05 to about 0.10 mm.

[0019] The drying step is generally performed at a temperature of from about 50 to about 100° C. Preferably, the drying step is performed in two stages. In the first stage, the solution is heated to from about 50 to about 70° C. The solution in the first stage is typically heated for less than about 5 minutes. The solution is then heated to from about 70 to about 100° C during the second stage. The solution in the second stage is typically heated for less than about 25 minutes.

[0020] The curing step is preferably performed immediately after the drying step. Curing is generally performed at a temperature of from about 15 to about 60° C and at a relative humidity of at least about 30%. Preferably, the curing step is performed at a temperature of from about 25 to about 60° C. The curing step is preferably performed at a relative humidity of at least about 50% and more preferably at a relative humidity of from about 60 to about 90%. The solution may be dried and cured with a drying tunnel having multiple zones or chambers, such as a 5, 6, or 7 zone drying tunnel.

[0021] A preferred water soluble film prepared by the method of the present invention comprises about 66% by weight of polyvinyl alcohol, about 6% by weight of glycerin, and about 28% by weight of nonoxynol 9, based upon 100% total

weight of water soluble film.

[0022] The water soluble film may be coated or laminated onto a substrate, such as non-woven fiber or cotton, by pouring or casting the solution onto the substrate and then drying and curing the solution as described above. Casting may be performed by any method known in the art, such as with a weigh boat, stainless steel tray, teflon rod, cone shape rod, and reverse roller.

[0023] The water soluble film alone or coated or laminated on a substrate may be incorporated into a dosage unit form for administration into a body cavity, such as the vagina, rectum, and mouth. The dosage unit form may be a tampon or an applicator. For example, the film coated on a substrate may be utilized as a liner for a tampon. The dosage unit form is preferably flexible. The dosage unit form may be any shape, such as a flat sheet or thimble shape. Preferably, the film is contoured to maximize its contact area with the body cavity for which it is intended to be administered.

[0024] According to one embodiment, the outer wrap of the tampon is comprised of non-woven fiber laminiated with the water soluble film. According to another embodiment, the water soluble film is positioned between the inside material of a tampon, such as cotton, and an outer wrap, such as a non-woven fiber material.

[0025] A dosage unit form of the present invention containing an antifungal agent, such as miconazole, may be administered to treat yeast infections. It is possible to treat a yeast infection in 3 days, instead of the common 5 day period, with a dosage unit form of the present invention, since a film prepared by the present method has very little drip and may have controlled release of the antifungal agent.

[0026] The film may be formulated to be puncture resistant and tear resistant. Also, the film may be formulated to achieve desired release rates of the pharmaceutically active agent as known in the art.

[0027] The following examples are intended to describe the present invention without limitation.

Examples 1-32

[0028] Water soluble films having the formulations of Table 1 were prepared as follows. Water was heated to 50-80° C. The film former, *i.e.,* polyvinyl alcohol, is added to the water with constant mixing. The active ingredient, *i.e.,* nonoxynol-9, was added to the solution with constant mixing. The solution was mixed, deaerated, and cooled to room temperature. The solution was coated onto a substrate in the casting device indicated in Table 1 below. The substrate for Examples 1-8 was polypropylene. The substrate for Examples 9-18 and 32 was stainless steel. The substrate for Examples 19-25 was polyester. The substrate for Examples 26-28 was teflon. The substrate for Example 29 was a polyester liner. The substrate for Example 30 was aclar with foil liner. The substrate for Example 31 was a polyethylene and paper liner.

[0029] The solution was dried in a multi-zone drying tunnel to form a film. In Examples 1-28 and 31, the solution was dried at a temperature of about 60-90° C for less than about 30 minutes. In Examples 29 and 30, the solution was first dried at a temperature of about 60-75° C for less than about 8 minutes and then dried at a temperature of about 75-90° C for less than about 15 minutes. In Example 32, the solution was first dried at a temperature of about 60-80° C for less than about 5 minutes and then dried at a temperature of about 70-90° C for less than about 25 minutes.

[0030] After drying, the film was cured with moisture at a relative humidity of about 30-60% and at about room temperature. For examples 29 and 32, the film was cured with moisture at a relative humidity of about 60-90% and at a temperature of about 40-60° C.

[0031] The thickness of the film was measured. The results are shown in Table 1 below.

Table 1

Example	Casting Device	Nonoxynol-9 (% by weight)	Polyvinyl alcohol (<60 cps) (% by weight)	Polyvinyl alcohol (<30 cps) (% by weight)	Polyvinyl alcohol (<10 cps) (% by weight)	Plasticizer (% by weight)	Dry Film Thickness (mm)
1	Weigh Boat	33.33	33.33	-	-	33.33% PG	0.3
2	Weigh Boat	33.33	33.33	-	-	33.33% PEG 300	0.3
3	Weigh Boat	33.33	50.00	-	-	16.67% PEG 300	0.45
4	Weigh Boat	33.33	58.33	-	-	8.33% Glycerin	0.3
5	Weigh Boat	33.33	41.67	-	-	25.00% Glycerin	0.1
6	Weigh Boat	33.33	50.00	-	-	16.67% Glycerin	0.1
7	Weigh Boat	33.33	50.00	-	-	16.67% PG	0.2
8	Weigh Boat	33.33	41.67	-	-	25.00% PG	0.1
9	Stainless Steel Tray	33.00	58.67	-	-	8.33% Glycerin	0.07
10	Stainless Steel Tray	33.33	63.33	-	-	3.33% Glycerin	0.05

Example	Casting Device	Nonoxynol-9 (% by weight)	Polyvinyl alcohol (<60 cps) (% by weight)	Polyvinyl alcohol (<30 cps) (% by weight)	Polyvinyl alcohol (<10 cps) (% by weight)	Plasticizer (% by weight)	Dry Film Thickness (mm)
11	Stainless Steel Tray	33.33	58.33	-	-	8.33% PEG 300	-
12	Stainless Steel Tray	33.33	58.67	-	-	8.33% PG	0.06
13	Stainless Steel Tray	27.78	69.44	-	-	2.78% Glycerin	-
14	Stainless Steel Tray	33.33	-	-	58.33	8.33% Glycerin	0.06
15	Stainless Steel Tray	32.79	-	-	49.18	18.03% Glycerin	0.07
16	Stainless Steel Tray	33.33	-	-	41.67	25.00% Glycerin	-
17	Stainless Steel Tray	33.33	-	-	63.33	3.33% Glycerin	0.07

Example	Casting Device	Nonoxynol-9 (% by weight)	Polyvinyl alcohol (<60 cps) (% by weight)	Polyvinyl alcohol (<30 cps) (% by weight)	Polyvinyl alcohol (<10 cps) (% by weight)	Plasticizer (% by weight)	Dry Film Thickness (mm)
18	Stainless Steel Tray	28.33	-	-	68.00	3.67% Glycerin	-
19	Resource I®	33.33	-	58.33	-	8.33% Glycerin	-
20	Resource I®	33.11	-	62.913	-	3.97% Glycerin	-
21	Resource I®	33.33	-	49.50	-	17.16% Glycerin	-
22	Resource I®	33.33	-	-	63.35	3.33% Glycerin	-
23	Resource I®	33.33	50.00	-	-	16.33% PEG 300	-
24	Resource I®	33.33	58.33	-	-	8.33% PEG 300	-
25	Resource I®	33.33	63.33	-	-	3.33% PEG 300	-
26	Teflon Rod, Thimble	33.33	-	-	63.35	3.33% Glycerin	-
27	Cone Shape Rod, Thimble	31.58	-	-	60.00	3.16% Glycerin & 5.26% H-15	-

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Example	Casting Device	Nonoxynol-9 (% by weight)	Polyvinyl alcohol (<60 cps) (% by weight)	Polyvinyl alcohol (<30 cps) (% by weight)	Polyvinyl alcohol (<10 cps) (% by weight)	Plasticizer (% by weight)	Dry Film Thickness (mm)
28	Cone Shape Rod, Thimble	30.51	-	-	57.97	3.05% Glycerin & 8.47% H-15	-
29	Reverse Roller, Scale-up Run, with Polyester Liner	33.33	-	-	63.33	3.33% Glycerin	-
30	Reverse Roller, Scale-up Run, with Aclar and Foil Liner	33.33	-	-	63.36	3.30% Glycerin	-

Example	Casting Device	Nonoxynol-9 (% by weight)	Polyvinyl alcohol (<60 cps) (% by weight)	Polyvinyl alcohol (<30 cps) (% by weight)	Polyvinyl alcohol (<10 cps) (% by weight)	Plasticizer (% by weight)	Dry Film Thickness (mm)
31	Knife Over Roller, Scale-up Run, with Polyethylene and Paper Liner	28.00	-	-	67.00	5.00% Glycerin	-
32	Extrusion, Scale-up Run, with Stainless Steel Surface Carrier	28.00	-	-	67.00	5.00% Glycerin	-

* - Resource I is a casting device for solutions available from Byk-Gardner Instruments of Silver Spring, MD.

The polyvinyl alcohol is a water soluble polyvinyl alcohol, such as Elvanol™ available from DuPont Co. of Wilmington, DE, or Airvol™ available from Air Products & Chemicals, Inc., of Allentown, PA.

PG is propylene glycol.

PEG 300 is polyethylene glycol having an average of 300 ethylene oxide repeating units.

H-15 is Witepsol H-15, which is hydrogenated coco-glycerides and is available from Hüls America of Somerset, NJ.

[0032] The release rate of nonoxynol-9 from the films prepared and VCF® available from Apothecus Pharmaceutical Corp. of Oyster Bay, NY, in a citrate phosphate buffer having a pH of 4.0 was determined by the USP basket method

(United States Pharmacopeia Method Section <711>). The results are shown in Table 2 below. The time to plateau is the time after which there is no significant increase in the release rate.

Table 2

Formulation	Time to Plateau (minutes)	Release Rate (% by weight per minute)
VCF®[1]	15-20	5.45
Example 6	50-60	2.59
Example 7	50-60	3.76
Example 9	40-50	2.33
Example 10	40-50	2.97
Example 12	40-50	3.15
Example 14	10-15	6.08
Example 15	10-15	6.66
Example 17	10-15	6.01
Example 19	15-20	5.82
Example 20	30-40	4.33
Example 21	30-40	3.93
Example 22	10-15	6.10
Example 23	40-50	2.34
Example 24	30-40	2.72
Example 25	30-40	2.76
Example 26	10-15	7.23
Example 27	5-10	8.47
Example 28	5-10	8.89
Example 29	<15	>6.0
Example 30	<15	>6.0
Example 31	<15	>6.0
Example 32	<15	>16

Examples 33-42

[0033] Water soluble films having the formulations of Table 3 were prepared as described in Examples 1-32. In Examples 33-41, the solution was dried at a temperature of about 60-90° C for less than about 30 minutes. In Example 42, the solution was first dried at a temperature of about 60-75 ° C for less than about 8 minutes and then dried at a temperature of about 75-90° C for less than about 15 minutes. After drying, the film was cured with moisture at a relative humidity of about 30-60% and at about room temperature.

[0034] The substrate for Examples 33-35 was polyester. The substrate for Examples 36-41 was polyester and non-woven fiber. The substrate for Example 42 was a fiber and polyester liner.

[0035] The release rate of miconazole nitrate from the films prepared in a citrate phosphate buffer having a pH of 4.0 was determined by the USP basket method for Examples 33-35 and by the following modified USP method for Examples 36-38, 40, and 41. A dialysis membrane with known molecular weight cut-off and diameter was used instead of a mesh basket for holding the test samples. The membrane limited the amount of dissolution medium which contacted the release layer or composition. This modified dissolution procedure was designed to mimic a vaginal environment where only limited amounts of a medium are typically in contact with the composition. Each release layer and composition was tested in an aqueous medium and in a buffered aqueous medium, which were maintained at a pH of about 4.

[0036] The results are shown in Table 3 below.

Table 3

Example	Casting Device	Polyvinyl alcohol (<30 cps) (% by weight)	Plasticizer (% by weight)	Miconazole Nitrate (% by weight)	Release Rate
33	Resource I	36.2	18.4% Glycerin & 9.2% EB2	36.2	3.3%/min
34	Resource I	40.0	19.9% Glycerin	40.1	4.7%/min
35	Resource I	38.0	19.0% Glycerin & 4.8% EB2	38.2	4.7%/min
36	Resource I & Fiber	36.2	18.4% Glycerin & 9.2% EB2	36.2	3.50%/hr
37	Resource I & Fiber	34.7	17.3% Glycerin & 13.2% EB2	34.8	3.13%/hr
38	Resource I & Fiber	38.0	19.0% Glycerin & 5.0% EB2	38.0	3.33%/hr
39	Resource I & Fiber	39.6	20.6% Glycerin	39.8	-
40	Resource I, Fiber, & OB Tampon	34.7	17.3% Glycerin & 13.2% EB2	34.8	0.81%/hr
41	Resource I, Fiber, & OB Tampon	38.0	19.0% Glycerin & 5.0% EB2	38.0	1.07%/hr
42	Reverse Roller, Scale-up Run, Fiber & Polyester Liner	38.1	19.1% Glycerin & 4.7% EB2	38.1	-
EB2 is Eumulgin B2, which is ceteareth-20 and is available from Henkel Corp. of Hoboken, NJ. The polyvinyl alcohol is a water soluble polyvinyl alcohol, such as Elvanol™ available from DuPont Co. of Wilmington, DE, or Airvol™ available from Air Products & Chemicals, Inc., of Allentown, PA.					

Examples 43-46

[0037] Water soluble films having the formulations of Table 4 were prepared as described in Examples 1-32. In Examples 43-46, the solution was dried at a temperature of about 60-90 ° C for less than about 30 minutes. After drying, the film was cured with moisture at a relative humidity of about 30-60% and at about room temperature. The substrate for Example 43-46 was polyester.

[0038] The time for the dissolution rate to plateau was determined as discussed above.

[0039] The results are shown in Table 4 below.

Table 4

Example	Casting Device	Polymer (% by weight)	Plasticizer (% by weight)	Metro-nidazole (% by weight)	Dissolution (Time to Plateau) (min)
43	Resource I	67.2% PVA 52-22	21.7% PEG 400	11.1	20-30
44	Resource I	58.22% PVA 52-22	18.9% PG & 15.7% EB2	7.2	20-30
45	Resource I	34.9% PVA 52-22 and 11.7% PVA 71-30	20.9% PG & 17.5% EB2	15.0	10-15

Table 4 (continued)

Example	Casting Device	Polymer (% by weight)	Plasticizer (% by weight)	Metro-nidazole (% by weight)	Dissolution (Time to Plateau) (min)
46	Resource I	46.6% HPMC E50LV	20.9% PG & 17.5% EB2	15.0	5-10

PG is propylene glycol

PEG is polyethylene glycol.

EB2 is Eumulgin B2, which is ceteareth-20 and is available from Henkel Corp. of Hoboken, NJ.

PVA is a water soluble polyvinyl alcohol, such as Elvanol™ available from DuPont Co. of Wilmington, DE, or Airvol™ available from Air Products & Chemicals, Inc., of Allentown, PA.

HPMC is hydroxypropyl methylcellulose.

Example 47

[0040] A water soluble film having the formulation of Table 5 was prepared as follows. Glycerin and nonoxynol-9 were added into cold water and mixed until uniform. The solution was heated to about 60-80° C and the film former, *i. e.,* polyvinyl alcohol, was added under constant mixing. The solution was mixed, deaerated, and cooled to about room temperature. The solution was coated onto a stainless steel surface with a web thickness of 0.01 to 0.03 cm. The solution was dried in a multi-zone drying tunnel at a temperature of about 60-90° C for less than about 30 minutes to form a film. The film was then cured with moisture at a relative humidity of about 65-90% and at a temperature of about 40-60° C.

Table 5

Ingredient	% by weight
Polyvinyl Alcohol (5 cps)	66.0
Glycerin	6.0
Nonoxynol-9	28.0

[0041] All patents, publications, applications, and test methods mentioned above are hereby incorporated by reference. Many variations of the present matter will suggest themselves to those skilled in the art in light of the above detailed description. All such obvious variations are within the patented scope of the appended claims.

Claims

1. A method of preparing a water soluble film, the method comprising the steps of:

(a) preparing a solution comprising:

(i) a film former selected from the group consisting of polyacrylic acids, cellulose derivatives, polyethylene oxide, polyvinyl alcohol, and any combination of any of the foregoing,

(ii) a water soluble plasticizer having at least one of a hydroxyl, amido, or amino group and a boiling point greater than about 150° C,

(iii) a pharmaceutically active agent, and

(iv) a solvent;

(b) drying the solution at a temperature of from about 50 to about 100° C to form a film; and

(c) curing the film at a temperature of from about 15 to about 60° C and at a relative humidity of at least about 30%.

2. The method of claim 1, wherein the solution has a viscosity of from about 15,000 to about 30,000 cps at room temperature prior to drying.

3. The method of claim 1, wherein the film former is polyvinyl alcohol.

4. The method of claim 1, wherein the film former is a partially hydrogenated polyvinyl alcohol.

5. The method of claim 1, wherein the plasticizer is a polyhydroxy compound.

6. The method of claim 5, wherein the plasticizer is selected from the group consisting of propylene glycol, polyethylene glycol, glycerin, and any combination of any of the foregoing.

7. The method of claim 1, wherein the pharmaceutically active agent is selected from imidazole antifungal agents, antibacterial agents, antiseptic agents, hormones, anti-inflammatory agents, anesthetics, spermicides, and any combination of any of the foregoing.

8. The method of claim 1, wherein the pharmaceutically active agent is nonoxynol-9.

9. The method of claim 1, wherein the pharmaceutically active agent is miconazole.

10. The method of claim 1, wherein the water soluble film further comprises

(i) a surfactant,
(ii) a preservative,
(iii) a viscosity enhancer,
(iv) a colorant,
(v) a fragrance,
(vi) a flavorant,
(vii) a lubricant,
(viii) a filler,
(ix) a binder,
(x) a wetting agent,
(xi) a penetration agent,
(xii) a pH adjuster,
(xiii) a disintegrant,
(xiv) an excipient, or
(xv) any combination of any of the foregoing.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 00 31 1610

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
X Y	EP 0 466 092 A (LABORATOIRE LUCCHINI) 15 January 1992 (1992-01-15) * claims 1-3 * * page 3; example 1 *	1-3,5-8, 10 9	A61K9/70 A61K9/00
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TECHNICAL FIELDS SEARCHED (Int.Cl.7)
A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	22 February 2001	Ventura Amat, A

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C01)

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 00 31 1610

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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

PCT WELTORGANISATION FÜR GEISTIGES EIGENTUM
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INTERNATIONALE ANMELDUNG VERÖFFENTLICHT NACH DEM VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT)

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(74) Anwalt: UEXKÜLL & STOLBERG; Beselerstr. 4, D-2000 Hamburg 52 (DE).

(81) Bestimmungsstaaten: AT (europäisches Patent), AU, BE (europäisches Patent), BR, CA, CH (europäisches Patent), DE (europäisches Patent), DK (europäisches Patent), ES (europäisches Patent), FI, FR (europäisches Patent), GB (europäisches Patent), GR (europäisches Patent), IT (europäisches Patent), JP, KR, LU (europäisches Patent), NL (europäisches Patent), NO, SE (europäisches Patent), SU, US.

Veröffentlicht
Mit internationalem Recherchenbericht.
Vor Ablauf der für Änderungen der Ansprüche zugelassenen Frist. Veröffentlichung wird wiederholt falls Änderungen eintreffen.

(54) Title: ORAL AND DENTAL HYGIENE PREPARATION

(54) Bezeichnung: MUND- UND ZAHNPFLEGEMITTEL

(57) Abstract

An oral and dental hygiene preparation consists of tensides, polishing agents, flavourings and other usual additives, incorporated in a binder or mixture of binders in the form of water-soluble or water-dilatable, physiologically acceptable foil-forming substances. The mixture is processed to a foil, which is predivided into dosage units.

(57) Zusammenfassung

Ein Mund- und Zahnpflegemittel besteht aus Tensiden, Poliermitteln, Aromastoffen sowie weiteren üblichen Zusatzstoffen welche in ein Bindemittel oder eine Bindemittelmischung aus wasserlöslichen oder -quellenbaren, physiologisch unbedenklichen Folienbildnern eingearbeitet sind. Die Mischung ist zu einer Folie verarbeitet, welche in Dosiseinheiten vorzerteilt ist.

LEDIGLICH ZUR INFORMATION

Code, die zur Identifizierung von PCT-Vertragsstaaten auf den Kopfbögen der Schriften, die internationale Anmeldungen gemäss dem PCT veröffentlichen.

AT	Österreich	ES	Spanien	MG	Madagaskar
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Mund- und Zahnpflegemittel

Zahnpflegemittel werden seit vielen Jahren als Pasten, sogenannte Zahnpasten hergestellt. Dabei ist der wesentliche Ausgangsstoff eine Schlämmkreide, die mit Wasser, Glycerin, waschaktiven Stoffen und Verdickungsmitteln zu einer Paste verarbeitet und in Tuben oder Spendern abgefüllt wird. Die Zahnpasta hat den Markt erobert, während andere Zahnpflegemittel wie Tropfen, Zahnseifen und -pulver oder Granulate kaum noch eine Rolle spielen. Mit den Mitteln soll der bakterielle Zahnbelag entfernt, Kariesprophylaxe betrieben sowie die Reinigung der Zähne schonend und durch die Bürstenbehandlung wesentlich unterstützt durchgeführt und der Mundraum gründlich gereinigt und angenehm erfrischt werden.

In neuerer Zeit hat sich das Bild der Zahnpasten nicht wesentlich verändert, obwohl die Rezepturen in vielerlei Hinsicht abgewandelt wurden. Die Verwendung einer recht groben Kreideform zum mechanischen Reinigen der Zähne wich mehr und mehr modernen, feineren Poliermitteln auf Basis von Aluminiumoxid oder Siliciumdioxid (Kieselgele). Neben Tensiden finden strukturbildende Komponenten und ausgefeilte Geschmackskorrigentien Verwendung. Oft werden Wirkstoffe wie insbesondere verschiedene Fluorderivate oder Mineralsalze zugefügt. Das Volumen konnte teilweise

reduziert werden; sicherlich hat die Einführung und allgemeine Verwendung elektrischer Zahnbürsten hierbei einen starken Einfluß gehabt.

Die Handhabung von Zahnpasten ist jedoch mit einer Reihe von Nachteilen verbunden. Weil die Dosierung aus einfachen Tuben Schwierigkeiten bereitet, hat man in neuerer Zeit Zahnpastaspender entwickelt, welche jeweils eine vorbestimmte Menge Zahnpasta abgeben. Diese Spender sind jedoch verhältnismäßig groß und daher zur Mitnahme auf Reisen wenig geeignet. Tuben sind druckempfindlich und daher auf Reisen ebenfalls nicht ideal. Sowohl in Spendern als auch in Tuben kann Zahnpasta bei längeren Gebrauchsunterbrechungen austrocknen, so daß die angebrauchten Behälter dann weggeworfen werden müssen. Ferner lassen sich sowohl Tuben als auch Spender nicht vollständig entleeren. Nach Verbrauch bleiben die aus Metall oder Plastik hergestellten Behälter zurück und verursachen Umweltprobleme.

Der Erfindung liegt demgegenüber die Aufgabe zugrunde, eine neue Verabreichungs- und Dosierungsform für Mund- und Zahnpflegemittel zu entwickeln, welche die vorstehend genannten Nachteile nicht aufweist. Insbesondere soll eine genaue Dosierung für die einzelne Zahnreinigung ermöglicht und sichergestellt werden, daß das Mittel vollständig aufgebraucht werden kann, ohne daß Reste in der Packung zurückbleiben.

Das erfindungsgemäße Mund- und Zahnpflegemittel auf Basis von Tensiden, Poliermitteln, Aromastoffen sowie weiteren üblichen Zusatzstoffen ist dadurch gekennzeichnet, daß die Wirk- und Zusatzstoffe in ein Bindemittel oder eine Bindemittelmischung eingearbeitet sind, welche aus wasserlöslichen oder -quellbaren, physiologisch unbedenklichen Folienbildern bestehen, und daß diese Mischung zu einer Folie verarbeitet ist, wobei die so gebildete Folie in

Dosiseinheiten vorzerteilt ist.

Als Bestandteile des Mund- und Zahnpflegemittels kommen die Komponenten in Frage, welche üblicherweise zur Herstellung von Zahnpasten Verwendung finden, wobei natürliche Rohstoffe besonders bevorzugt sind. Wichtig ist darüber hinaus, daß alle Bestandteile völlig ungiftig und physiologisch unbedenklich sind, was selbstverständlich auch für die verwendeten Folienbildner gilt. Als wesentliche Bestandteile von Zahnpflegemitteln sind zu nennen:

- Schleifmittel wie Kreide (Calciumcarbonat), Calcium- und Natriumphosphate, Aluminiumoxid oder Siliciumdioxid, insbesondere Kieselgele
- Tenside (Schaummittel) wie Natriumlaurylsulfat, Natriumlaurylsulfoacetat, Sarcoside, Monoglyceridsulfate und andere
- Aromastoffe wie Pfefferminzöl, Krauseminzöl, Anisöl, Zimtöl, Nelkenöl, Menthol und ähnliche
- Süßstoffe wie Saccharin, Cyclamat, Aspartam und ähnliche.

Die in Zahnpasten üblicherweise enthaltenen flüssigen Komponenten wie Glycerin, Propylenglykol oder Sorbitsirup müssen den erfindungsgemäßen Mitteln in Folienform nicht in den üblichen Mengen zugesetzt werden, da hier die für Tuben oder Spender erforderliche Plastizität keine Rolle spielt. Weitere übliche Zusätze wie Fluorverbindungen, Mittel gegen Zahnsteinbildung, antibakterielle Wirkstoffe und ähnliche, wie sie in Mund- und Zahnpflegemitteln üblicherweise Verwendung finden, können auch erfindungsgemäß eingesetzt werden.

Als wasserlösliche bzw. -quellbare Folienbildner eignen sich vor allem Stärken, Gelatinen, Glycerin und/oder Sorbit sowie ferner natürliche oder synthetische Harze und

Gumme. Folgende Rahmenrezeptur hat sich bewährt:

Gelatine	8 - 10 g
Stärke	3 - 8 g
Glycerin	1 - 2 g
Wasser	30 - 50 g.

In dieser Grundmasse werden die Bestandteile des Mund- und Zahnpflegemittels gelöst bzw. dispergiert, um eine gleichmäßige Verteilung der Stoffe zu erreichen. Die so erhaltene Mischung kann erfindungsgemäß in verschiedener Weise zu einem folienförmigen Mund- und Zahnpflegemittel verarbeitet werden:

a) Es ist einmal möglich, die Masse direkt zu einer Folie zu verarbeiten, welche im allgemeinen eine Dicke zwischen 0,1 und etwa 3 mm aufweist. Durch Sollbruchstellen mittels Stanzung oder Perforierung kann diese Folie in Dosiseinheiten vorzerteilt werden, wobei die Streifenbreite und -länge vorzugsweise etwa der Zahnbürstengröße, d.h. der von den freien Borstenenden gebildeten Fläche des Borstenblocks oder der Längsquerschnittfläche des Borstenblocks in der Borstenebene entsprechen sollte.

b) Alternativ kann die Masse auf eine Trägerfolie aufgebracht werden, deren Zusammensetzung derjenigen des Bindemittels der Masse entspricht, wie dies in der EP-OS 219 762 im einzelnen offenbart ist. Auch die auf diese Weise erhaltenen Folien können wie oben angegeben vorzerteilt werden.

c) Es ist ferner möglich, die Masse auf eine Releasefolie oder ein Releasepapier aufzubringen, wie dies aus der DE-PS 36 30 603 bekannt ist. In diesem Fall wird die Beschichtung in einzelne Abschnitte der oben

angegebenen Größe vorzerteilt, welche sich ähnlich wie Haftetiketten von der Trägerfolie vor Gebrauch abziehen lassen.

In allen Fällen erhält man eine Darreichungs- und Dosierungsform, deren Anwendung besonders leicht ist, da die jeweils zu verwendende Menge gleichmäßig vorgegeben ist. Eine Dosis wird in Form eines Folienabschnittes abgetrennt bzw. abgezogen und auf die angefeuchtete Zahnbürste bzw. zwischen die Borsten gelegt, wo sie durch die Feuchtigkeitsberührung haftet und anquillt. Durch das Einführen in die Mundhöhle und in Verbindung mit dem Speichel und der intensiven Zahnbürstenbewegung wird der Streifen an- und aufgelöst, so daß die Inhaltsstoffe zur vollen Wirkung gelangen. Nach der Anwendung und der anschließenden Mundspülung mit Wasser verbleiben keinerlei Rückstände im Mund.

Gewünschtenfalls können die Folien in unterschiedlicher Weise bedruckt, geprägt oder gestanzt werden, wobei beispielsweise für Kinder auch bildliche Darstellungen möglich sind. Es entfällt das Öffnen und Schließen von Tubenverschlüssen, es wird keine Zahnpasta vergeudet und die erfindungsgemäße Darreichungsform läßt sich auch besondes gut auf Reisen einsetzen, da sie leicht ist, ein Auslaufen nicht befürchtet werden muß und sie äußerst wenig Platz beansprucht. Die Verpackung ist umweltfreundlich in Pappschachteln ohne Verwendung von Metallen oder Kunststoff möglich.

Die Mittel der Erfindung eignen sich nicht nur zur Zahnpflege im Mund, sondern bei geeigneter Zusammensetzung auch zur Reinigung und Pflege von künstlichen Zähnen und Gebissen. Für diesen letzteren Einsatzzweck ist eine Mehrfachbeschichtung besonders günstig, bei der sich in einer Schicht die reinigenden, desinfizierenden und sauren

Komponenten befinden, während sich, ggf. getrennt durch eine ebenfalls wasserlösliche Sperrschicht, in einer zweiten Schicht die CO_2 bzw. O_2 abgebenden Substanzen enthalten sind.

Beispiel

Ein erfindungsgemäßes Zahnpflegemittel hat folgende Zusammensetzung:

Amylogum	57,0 g
Honig	25,0 g
Zitronensäure	2,0 g
Titandioxid	1,0 g
Aroma	1,0 g
Siliciumdioxid	3,0 g
Ca-Hydrog-phos.	10,0 g
Na-Laurylsulfat	1,0 g

Mit der erforderlichen Menge Wasser wird ein Brei hergestellt, der zu einer Folie verarbeitet wird, die ca. 0,5 mm dick ist. Durch Perforation wird die Folie in Abschnitte von 8 x 35 mm unterteilt.

Gegebenenfalls kann die Masse auch als Beschichtung auf ein Releasepapier als Träger aufgebracht und durch Stanzung in Abschnitte der angegebenen Größe vorzerteilt werden.

Patentansprüche

1. Mund- und Zahnpflegemittel auf Basis von Tensiden, Poliermitteln, Aromastoffen sowie weiteren üblichen Zusatzstoffen, dadurch gekennzeichnet, daß die Wirk- und Zusatzstoffe in ein Bindemittel oder eine Bindemittel-Mischung eingearbeitet sind, welche aus wasserlöslichen oder -quellbaren, physiologisch unbedenklichen Folienbildnern bestehen, und daß diese Mischung zu einer Folie verarbeitet ist, wobei die so gebildete Folie in Dosiseinheiten vorzerteilt ist.

2. Mund- und Zahnpflegemittel gemäß Anspruch 1, dadurch gekennzeichnet, daß es als Folienbildner Stärken, Gelatinen, Glycerin und/oder Sorbitol oder natürliche und/oder synthetische Harze und Gumme enthält.

3. Mund- und Zahnpflegemittel gemäß Anspruch 1, dadurch gekennzeichnet, daß es als Folienbildner Amylogum enthält.

4. Mund- und Zahnpflegemittel nach den Ansprüchen 1 bis 3, dadurch gekennzeichnet, daß es als Folienbildner eine Mischung aus 8 bis 10 Gewichtsteilen Gelatine, 4 bis 8 Gewichtsteilen Stärke und 1 bis 2 Gewichtsteilen Glycerin enthält.

5. Mund- und Zahnpflegemittel nach den Ansprüchen 1 bis 4, dadurch gekennzeichnet, daß es aus einer Trägerfolie aus dem Bindemittel oder der Bindemittel-Mischung besteht, auf welche eine Schicht aufgebracht ist, welche die Bestandteile des Pflegemittels zusammen mit Bindemittel oder der Bindemittel-Mischung enthält, wobei das Bindemittel oder die Bindemittel-Mischung in der Trägerfolie und in der Beschichtung im wesentlichen die gleiche qualitative

Zusammensetzung aufweisen.

6. Mund- und Zahnpflegemittel nach den Ansprüchen 1 bis 4, dadurch gekennzeichnet, daß eine Beschichtung aus den Bestandteilen des Pflegemittels und dem Bindemittel oder der Bindemittel-Mischung auf eine Trägerfolie in Form eines Trennpapiers, eines Trennfilms oder einer Trennfolie aufgebracht ist, wobei die Beschichtung nach Vorzerteilung in Dosiseinheiten von dem Trägermaterial dosisweise abziehbar ist.

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 90/01936

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.[5] A61K 7/16

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
Int.Cl.[5]	A61K

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III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category * [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
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A	GB, A, 2186190 (COLGATE-PALMOLIVE COMPANY) 12 August 1987 see claims 1,2,4,8	1,2,5,6
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* Special categories of cited documents: [10]

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
15 March 1991 (15.03.91)	11 April 1991 (11.04.91)

International Searching Authority	Signature of Authorized Officer
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ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. EP 9001936 SA 41110

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ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. EP 9001936 SA 41110

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 03/04/91
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB-A- 1476057	10-06-77	None	

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

INTERNATIONALER RECHERCHENBERICHT

Internationales Aktenzeichen PCT/EP 90/01936

I. KLASSIFIKATION DES ANMELDUNGSGEGENSTANDS (bei mehreren Klassifikationssymbolen sind alle anzugeben)[6]

Nach der Internationalen Patentklassifikation (IPC) oder nach der nationalen Klassifikation und der IPC

Int.Cl.[5] A 61 K 7/16

II. RECHERCHIERTE SACHGEBIETE

Recherchierter Mindestprüfstoff[7]

Klassifikationssystem	Klassifikationssymbole
Int.Cl.[5]	A 61 K

Recherchierte nicht zum Mindestprüfstoff gehörende Veröffentlichungen, soweit diese unter die recherchierten Sachgebiete fallen[8]

III. EINSCHLÄGIGE VERÖFFENTLICHUNGEN[9]

Art*	Kennzeichnung der Veröffentlichung[11], soweit erforderlich unter Angabe der maßgeblichen Teile[12]	Betr. Anspruch Nr.[13]
A	EP, A, 0219762 (DESITIN ARZNEIMITTEL GmbH) 29. April 1987 siehe das ganze Dokument in der Anmeldung erwähnt	1,2,5,6
A	GB, A, 2186190 (COLGATE-PALMOLIVE COMPANY) 12. August 1987 siehe Patentansprüche 1,2,4,8	1,2,5,6
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A	GB, A, 2163348 (DENTAB UK LTD) 26. Februar 1986 siehe Patentansprüche 1,4,9,14 ./.	1

* Besondere Kategorien von angegebenen Veröffentlichungen[10]:

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"&" Veröffentlichung, die Mitglied derselben Patentfamilie ist

IV. BESCHEINIGUNG

Datum des Abschlusses der internationalen Recherche	Absendedatum des internationalen Recherchenberichts
15. März 1991	11 APR 1991
Internationale Recherchenbehörde	**Unterschrift des bevollmächtigten Bediensteten**
Europäisches Patentamt	Mme N. KUIPER

Formblatt PCT/ISA/210 (Blatt 2) (Januar 1985)

III. EINSCHLÄGIGE VERÖFFENTLICHUNGEN (Fortsetzung von Blatt 2)

Art *	Kennzeichnung der Veröffentlichung, soweit erforderlich unter Angabe der maßgeblichen Teile	Betr. Anspruch Nr.
A	GB, A, 1476057 (UNICLIFFE LTD) 10. Juni 1977 siehe Seiten 1-3	1,3

ANHANG ZUM INTERNATIONALEN RECHERCHENBERICHT ÜBER DIE INTERNATIONALE PATENTANMELDUNG NR.

EP 9001936
SA 41110

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentdokumente angegeben.
Die Angaben über die Familienmitglieder entsprechen dem Stand der Datei des Europäischen Patentamts am 03/04/91
Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

Im Recherchenbericht angeführtes Patentdokument	Datum der Veröffentlichung	Mitglied(er) der Patentfamilie		Datum der Veröffentlichung
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		US-A-	4925670	15-05-90
GB-A- 2163348	26-02-86	US-A-	4753792	28-06-88

EPO FORM P0473

Für nähere Einzelheiten zu diesem Anhang : siehe Amtsblatt des Europäischen Patentamts, Nr.12/82

ANHANG ZUM INTERNATIONALEN RECHERCHENBERICHT ÜBER DIE INTERNATIONALE PATENTANMELDUNG NR.

EP 9001936
SA 41110

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentdokumente angegeben.
Die Angaben über die Familienmitglieder entsprechen dem Stand der Datei des Europäischen Patentamts am 03/04/91
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Im Recherchenbericht angeführtes Patentdokument	Datum der Veröffentlichung	Mitglied(er) der Patentfamilie	Datum der Veröffentlichung
GB-A- 1476057	10-06-77	Keine	

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(74) Agent: MELOY, Sybil; Foley & Lardner, Suite 403, 501 Brickell Key Drive, Miami, FL 33131 (US).

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(54) Title: COMPOSITIONS AND METHODS FOR TOPICAL ADMINISTRATION OF PHARMACEUTICALLY ACTIVE AGENTS

(57) Abstract

A composition for topical application comprising a therapeutically effective amount of a pharmaceutical agent(s), a flexible, finite, pharmaceutically acceptable, adhesive, and a solvent for the pharmaceutical agent(s) in the adhesive and a method of administering the pharmaceutical agent to a mammal are disclosed.

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COMPOSITIONS AND METHODS FOR TOPICAL ADMINISTRATION OF PHARMACEUTICALLY ACTIVE AGENTS

CROSS-REFERENCE TO RELATED APPLICATION

This application is a continuation-in-part of U.S. Patent Application Serial Number 07/661,827 filed February 27, 1991, and U.S. Serial Number 07/813,196 filed December 23, 1991, both of which applications are hereby incorporated by reference.

Field of the Invention

The present invention relates to compositions and methods for the topical administration of pharmaceutically active agents, namely those having a pharmacological or cosmetic effect, to a mammal in need thereof. The present invention is especially useful with local anesthetic agents for topical administration. In addition, the invention relates to a method for the topical administration of a pharmaceutical agent, especially an anesthetic agent or a combination of anesthetic agents, to prevent or ameliorate a disease or other medical or cosmetic condition, especially pain.

There is no limitation on the type of pharmaceutical agent that can be used in the present invention, provided that the agent can be absorbed percutaneously. Thus, the pharmaceutical agents can be drugs that can be topically applied for local effects and those which can be topically applied for systemic effects.

Background of the Invention

Anesthetic agents are pharmacologically active agents that block nerve conduction when applied in therapeutically effective amounts. They can be used for local or systemic effects. Anesthetic agents

have been used extensively in the medical field to obtain topical anesthesia. Topical administration or application means the direct contact of the anesthetic with tissue to be anesthetized, such as skin or membrane, particularly the oral or buccal mucosa. Previous methods of applying topical anesthetic agents to the skin or mucosa have used "nonfinite" or semi-liquid carriers or spreading substances such as creams, gels or ointments, or "finite" carriers, non-spreading substances which retain their form, e.g. patches, dressings and bandages. The finite carriers are flexible in the sense that they can bend to conform to the configuration of the skin or mucosa where they are applied.

Local anesthetics generally are esters or amides of benzoic acid derivatives, administered either as the free base or the acid-addition salt. Free bases tend to be irritating at high concentrations. Acid-addition salts have low skin permeability.

To be effective, a topical, local anesthetic should contain sufficient concentration of the active agent to produce an anesthetic effect, it should penetrate intact skin or mucosa sufficiently to deliver a therapeutic dose, and it should exhibit rapid onset of anesthetic action and have a prolonged anesthetic effect. In achieving the foregoing, it is often desirable to have the anesthetic agent present in a high concentration in the dosage form to effect a rapid onset and, additionally or alternatively, in excess of the amount that can be immediately absorbed through the dermis at the site of application, so as to prolong the duration or effect of anesthesia. On the other hand, the presence of the anesthetic agent in crystalline form may irritate sensitive tissues such as mucosal tissues. This is particularly true

with regard to lidocaine. The usefulness of topical anesthetics has been limited by the concentration of drug achievable in the dosage form. The same considerations also apply generally to other pharmaceutically active agents.

Anesthetic agents have been used in nonfinite form. United States Patent No. 4,894,232 to Reül, et al. discloses a base for mucosal or denture adhesive pastes and a process for the preparation thereof. A lidocaine salt is named as suitable for this paste.

Finite local anesthetic compositions are reported in the literature. Some compositions are solvent free. For instance, Swedish Patent Publication No. 352,239 published December 27, 1972 in the name of S.G. Davis et al., assigned to Astra Pharmaceutical Products, Inc., and based on Swedish patent application No. 17744/70 filed December 30, 1970, discloses a local anesthetic film containing up to 50% lidocaine in crystallized, microdispersed form. In its final form, this composition lacks a solvent for the anesthetic agent. The preparation is prepared by adding a solution of lidocaine in an organic solvent or an acid addition salt in water, under heat and agitation, to a solution or suspension of a film-forming material, namely carboxymethyl cellulose, polyvinyl alcohol, or a mixture of polyvinyl alcohol and polyvinyl pyrrolidone in water, followed by heating to remove any solvent present.

United States Patent No. 4,900,552 of Sanvordeker et al., disclose a trilaminate film suitable for prolonged and sustained delivery of an active ingredient in a buccal cavity. Specifically a hydratable mucoadhesive base layer, a non-adhesive reservoir layer containing the drug and a water-impermeable carrier film sandwiched between and bonded

to the base layer and the reservoir layer form the trilaminate film.

Some finite anesthetic compositions contain polyhydric alcohol solvents. United States Patent Nos. 4,572,832 and 4,695,465 to Kigasawa and 3,249,109 to Maeth all describe the use of water soluble protein based systems which incorporate anesthetics, and which also contain a tackifier and a polyhydric alcohol.

Some finite anesthetic agent compositions have a separate adhesive. United States Patent No. 3,814,095 to Lubens describes an absorbent pad for topical application of an anesthetic agent having a peripheral adhesive.

Glycerol (glycerin) has been used as a plasticizer for karaya gum. United States Patent Nos. 4,307,717 and 4,675,009 to Hymes et. al., describe a drug in a solid phase formed of a synthetic polymer and/or a long chain natural or synthetic polysaccharide or a combination thereof and a liquid phase of water or an alcohol or a combination thereof. The amount of drug in the preparation (excluding solvent or carrier) is low. The cross-linked polysaccharide plasticized with water and/or a polyhydric alcohol is said to be not self-adhering. The formulations do not include both a solvent for the drug and a plasticizer for the polysaccharide.

It is also known to combine two local anesthetic free bases with different melting points. By mixing the two anesthetic bases, an eutectic mixture has been reported that is liquid at room temperature, making it possible to attain higher concentrations of the active bases. United States Patent No. 4,888,354 to Chang relates to a combination of the free base and an acid addition salt or a variety of drugs, typically in a liquid carrier, to increase skin penetration rates. Anesthetics, along

with a list of other suitable drugs are mentioned. This reference specifically teaches that base and acid-addition forms of the same drug be used in carrier.

United States Patent No. 2,352,691 to Curtis teaches the use of salicylate salts of alkamine esters of aminobenzoic acid to enhance the water solubility of anesthetic agents. In one example, this reference discloses a solution of procaine acetyl salicylate containing insoluble anesthetics such as benzocaine, butesin, orthoform, or their salts, in certain glycols, which are combined with a volatile solvent, and then used to saturate gauze bandages or other suitable fabrics.

United States Patent No. 2,142,537 to Tisza describes an ointment containing isoamylhydrocupreine in combination with a quick acting local anesthetic to overcome the undesirable irritation caused by the prolonged acting anesthetic isoamylhydrocupreine or its salts. The preparation of Tisza combines short and long acting anesthetic agents.

United States Patent No. 2,277,038 to Curtis relates to preparations containing a mixture of two or more anesthetic agent salts having different pH values in solution, whereby the pH value of the combined mixture in solution may be adjusted to obtain a higher degree of stability of the solution, and at relatively higher pH, a more rapid onset of anesthetic action. The anesthetic agents in Curtis are not in highly dispersed form and are used in a liquid-soaked fabric.

Commonly, prolongation of anesthesia with topical anesthetics has been achieved by the addition of vasoconstrictors, such as the catecholamine, epinephrine, which caused constriction of blood vessels. Since catecolamines are not particularly effective when applied topically, such a prolongation

is of minimal usefulness for topical anesthetics. The primary drawbacks of this approach are the potential adverse side effects of catecolamines, and the prolongation itself.

Although many local anesthetic compositions have been proposed, it has been discovered that the incorporation of one or more anesthetic agents in a solvent for the anesthetic agent or agents into a flexible, finite, pharmaceutically acceptable carrier, permits an exceptionally high loading of anesthetic agent in the carrier, permitting more rapid delivery of the anesthetic agent to the dermal membrane and a greater extent of anesthesia without crystallization of the anesthetic agent or agents which can limit absorption by the skin and which can cause irritation of the skin or other dermal membrane.

It has also surprisingly been found that concentrations of substantially dissolved anesthetic agent as high as 50% by weight of the total composition can be achieved in a system in which the adhesion of the adhesive is not hindered. Prolongation of anesthesia can thus be achieved by increasing the amount of time the composition is applied, without detrimental irritation.

The compositions of the present invention are in convenient form for topical application of the anesthetic agents, thereby enabling such anesthetics to penetrate the dermis, for example, intact skin or a mucous membrane. Moreover, the anesthetic action is highly localized. Because the drug is substantially microdispersed in the carrier, it is more readily available for permeation into the skin or dermal membrane.

It still further has surprisingly been found that the use of two different local anesthetic agents, the first in base form and the second in acid-addition

salt form, in a finite, flexible, adhesive, pharmaceutically acceptable carrier, including a solvent for the anesthetic agents, permits the attainment of anesthetic agent concentrations in the final product of up to 50% by weight in microdispersed form, without crystallization of the anesthetic agents which can cause irritation of the skin or other dermal membrane.

Thus, in one embodiment, the present invention is in convenient form for topical application of the anesthetic agents, thereby enabling such anesthetics to penetrate intact skin or mucous membranes and have a highly localized effect. Furthermore, the combination of the salt and base forms, advantageously results in rapid onset of anesthetic action with prolonged anesthetic effect.

Summary of the Invention

The invention relates to a flexible, finite bioadhesive composition, for topical application comprising:

a therapeutically effective amount of at least one local anesthetic or other pharmaceutically active agent which is in solid form at ambient temperatures and pressures;

a pharmaceutically acceptable solvent for the anesthetic or other pharmaceutically active agent, in an amount from about 5 to about 70 weight percent based on the weight of the whole composition, said solvent including about 5 to about 50 weight percent based on the weight of the whole composition of a plasticizer for the bioadhesive;

in admixture with the anesthetic agent or other pharmaceutically active agent in the solvent, a flexible, finite, pharmaceutically acceptable polysaccharide bioadhesive in an amount from about 20

to about 50 weight percent based on the weight of the whole composition;

wherein the composition is substantially free of water, substantially water insoluble and self-adhesive; and wherein the pharmaceutically active agent is present in non-crystallized form in the composition.

In another embodiment, the flexible, finite composition of the invention is comprised of two anesthetic agents, that is:

a therapeutically effective amount of a first local anesthetic agent in base form;

a therapeutically effective amount of a different, second local anesthetic agent in acid-addition salt form;

a solvent for the first and second local anesthetic agents, preferably in an amount from about 5 to about 70 weight percent based on the weight of the whole composition; and

in an admixture with the anesthetic agents and the solvent, a pharmaceutically acceptable adhesive, preferably a bioadhesive, preferably in an amount from about 20 to about 50 weight percent based on the weight of the whole composition;

wherein the composition is preferably substantially free of water, substantially water insoluble and self-adhesive; and wherein the anesthetic agents preferably are in non-crystallized form in the composition.

The compositions of the invention may be further include a backing material which conforms to the size and shape of a single dosage of the composition.

The present invention further relates to a method of administering one or more pharmaceutically active agents in a bioadhesive to a subject comprising the steps of:

providing a composition comprising a therapeutically effective amount of at least one pharmaceutically active agent which is in solid form at ambient temperatures and pressures; a pharmaceutically acceptable solvent for the pharmaceutically active agent, preferably in an amount from about 5 to about 70 weight percent based on the weight of the whole composition, said solvent preferably including about 5 to about 50 weight percent of a plasticizer for the bioadhesive; and in admixture with the pharmaceutically active agent in the solvent, a pharmaceutically acceptable polysaccharide bioadhesive, preferably in an amount from about 20 to about 50 weight percent based on the weight of the whole composition; wherein said composition is substantially free of water, is substantially water insoluble and is self-adhesive; and wherein the pharmaceutically active agent is in non-crystallized form in the composition; and

contacting an area of skin or mucous membrane with the composition to administer the pharmaceutically active agent.

The invention further relates to a method of administering two local anesthetic agents to a subject comprising the steps of:

providing a composition comprising a therapeutically effective amount of a first local anesthetic agent in base form; a therapeutically effective amount of a different, second local anesthetic agent in acid-addition salt form; a pharmaceutically acceptable solvent for the anesthetic preferably in an amount which ranges from about 50 to about 70 weight percent based on the weight of the whole composition, said solvent preferably including about 5 to about 50 weight percent of a plasticizer for the bioadhesive carrier; and in admixture with the

pharmaceutically active agent in the solvent, a pharmaceutically acceptable preferably polysaccharide bioadhesive, preferably in an amount from about 20 to about 50 weight percent based on the weight of the whole composition; wherein said composition is preferably substantially free of water, substantially water insoluble and self-adhesive; and wherein the pharmaceutically active agent is in non-crystallized form in the composition; and

contacting an area of skin or mucous membrane with the composition thereby administering the local anesthetic agent.

The compositions of this invention permit a far higher loading of drug than conventional dosage forms. This loading in the case of anesthetic agents can result in an extent (depth) of anesthesia which numbs the teeth when applied buccally, not a typical result for a topical anesthetic cream or ointment.

Detailed Description of the Invention

This invention provides a composition which adheres to an area of the skin or mucosa, and permits delivery at elevated levels of pharmaceutical agent or a combination of agents to produce a local or systemic effect over a prolonged period of time.

In accordance with one embodiment of the present invention, a local anesthetic in solution with a solvent for the anesthetic, containing a plasticizer for the adhesive, is in admixture with a pharmaceutically acceptable adhesive, which is preferably a bioadhesive, and more preferably a polysaccharide bioadhesive, is provided in a finite, flexible form for topical application to the skin or dermal membrane of a mammal.

In accordance with a further embodiment of the present invention, a combination of local anesthetic agents, a solvent for the anesthetic agents

and a flexible, preferably adhesive pharmaceutically acceptable adhesive carrier is provided for topical application to the skin or mucosa of a mammal.

The anesthetic agents of this invention are those known, or of a type known, in the art. The local anesthetic bases encompassed by this invention are weak organic bases which are lipophilic in nature and thus poorly soluble in water. However, these bases will react with organic or inorganic acids to form acidic, water soluble acid-addition salts.

The base form and the salt form of the anesthetic agent incorporated in the combination composition of this invention must be different anesthetic agents, to achieve maximum duration of the anesthetic effect. By the term "different" is meant that the salt form in any combination is not a salt of the base form used in the given combination.

Local anesthetic agents suitable for use in the practice of this invention include amides and esters. Examples of the amides are lidocaine, prilocaine, mepivacaine, bupivacaine, dibucaine and etidocaine. Esters include procaine, tetracaine, propoxycaine, chloroprocaine, benzocaine, butamben picrate, cocaine, hexylcaine, piperocaine, oxyprocaine and proparacaine. Other suitable local anesthetics for use in the practice of this invention include cyclomethycaine, dimethisoquin, ketocaine, diperodon, dyclonine and pramoxine, all typically administered in the form of the acid addition hydro-chloride or sulfate salts.

The acid-addition salts of the present invention are any non-toxic, pharmaceutically acceptable organic or inorganic salts. Typical inorganic salts are the hydrogen halides, especially the hydrochlorides, carbonates, borates, phosphates, sulfates, hydrogen sulfates, hydrobromides, nitrates,

sulfides, and arsenates. Typical organic salts are salts of mono- and polycarboxylic acids such as the citrate, tartrate, malate, cinnamate, oxalate, formate, succinate and phthalates.

The solvents for the anesthetic agents or other drugs are non-toxic, pharmaceutically acceptable substances, preferably liquids, which do not substantially negatively affect the adhesion properties of the system and in which the anesthetic agents or other drugs in the amounts employed are fully soluble. Preferably, the solvent is or is primarily a polyhydric alcohol or combination of polyhydric alcohols, particularly when the adhesive is a gum. The term polyhydric alcohol means any organic polyol. Other suitable solvents include carboxlyic acids and their derivatives and analogs such as fatty acids such as oleic acid, linoleic acid, capric acid and the like, as well as fatty esters or alcohols and ketones such as polyvinylpyrrolidone. Further suitable solvents include other non-toxic, non-volatile solvents commonly used in dermal or transdermal compositions for dissolving like compounds. As apparent to one skilled in the art what is a suitable solvent varies with the solubility of the drug in question.

The above mentioned polyhydric alcohols may include those having 2 to 6 alcoholic hydroxyl groups. Such polyhydric alcohols include glycols, triols and polyols having 4 to 6 alcoholic hydroxyl groups. Typical of said glycols are glycols containing 2 to 6 carbon atoms, e.g. ethylene glycol, propylene glycol, butylene glycol, polyethylene glycol (average molecular weight about 200 - 8,000, preferably about 200 to 6,000), dipropylene glycol, hexylene glycol, polyoxyethylene, polypropylene glycol, sorbitol, and the like. Examples of said triols include glycerin,

trimethylolpropane. Said polyols are exemplified by cycloalkanepolyols such as polyols derived from monosaccharides such as sorbitol (sorbit). These polyhydric alcohols may be used either singly or in combination (preferably, of two or three). Thus, for example, glycerin alone or a mixture of glycerin and butylene glycol is employed. In general, when an anesthetic agent, especially an anesthetic base is used, there are limits to the amounts of lipophilic polyhydric alcohols containing more than two alcoholic hydroxyl groups that can be present in the solvent and yet not result in precipitation of the drug as crystals.

Among those polyhydric alcohols, those which satisfy the requirements relevant to the adjustment and maintenance of softness of the external drug of the invention, the compatibility or co-dispersibility with the other components, and provide a proper consistency of the composition, may be freely used. Those which are low in volatility and plastic, are generally preferred and, in this regard, dipropylene glycol, glycerin, propylene glycol, butylene glycol, and sorbitol are appropriate solvents, according to the invention. Since solvent is to remain, at least in part, in the composition, the solvent should include components that do not substantially volatilize under the drying conditions used in preparing the composition. In other words, the solvent for the drug should be non-volatile.

Solvent selection for a single anesthetic agent or a combination of anesthetic agents in either the free base form or in the acid-addition salt form, depends on the form of the anesthetic agent, namely whether it is in free base form or acid-addition salt form. Solvents for the salt form of anesthetic agent are polar organic solvents. Polar organic solvents

are preferably polyhydric alcohols, as discussed above. Various other solvents suitable for either the base or acid-addition form of the anesthetic agent are those solvents known to dissolve either or both of these two types of forms including cyclic ketones such as 2-pyrrolidone; N-(2-hydroxyethyl) pyrrolidone, N-methylpyrrolidone, 1-dodecylazacycloheptan-2-one and other n-substituted alkyl-azacycloalkyl-2-ones (azones) dimethylformadide, and dimethylsulfoxide.

Other suitable solvents for the free base form of the anesthetic agent are cell envelope disordering compounds known to be useful in topical pharmaceutical preparation, which compounds are thought to assist in skin penetration by disordering the lipid structure of the stratum corneum cell-envelopes. Some of these compounds are generally encompassed by the formula:

R-X

wherein R is a straight-chain alkyl of about 7 to 16 carbon atoms, a non-terminal alkenyl of about 7 to 22 carbon atoms, or a branched-chain alkyl of from about 13 to 22 carbon atoms, and X is -OH, -$COOCH_3$, -$COOC_2H_5$, -$OCOCH_3$, -$SOCH_3$, -$P(CH_3)_2O$, -$COOCH_2H_4OC_2H_4OH$, -$COOCH(CHOH)_4CH_2OH$, -$COOCH_2CHOHCH3$, -$COOCH_2CH(OR")CH_2OR"$. -$(OCH_2CH_2)_mOH$, -COOR', or -$CONR'_2$ where R; is -H, -CH_3, -C_2H_5, -C_3H_7 OR -C_2H_4OH; R" is -H, or a non-terminal alkenyl of about 7 to 22 carbon atoms; and m is a positive integer from 2 to 6; provided that when R" is an alkenyl and X is -OH or -COOH, at least one double bond is in the cis-configuration.

Although the exact amount of the polyhydric alcohol or alcohols in the composition depends on the nature of other components, and therefore cannot be stated in specific terms, the proportion may range

from about 5 to about 70 weight percent based on the whole composition.

The solvent includes from about 5% to about 50% and more preferably about 10% to about 30% of a polyhydric alcohol known to plasticize the bioadhesive carrier. A particularly useful plasticizer is glycerine.

The high concentrations of microdispersed drug, for example anesthetic agent, of this invention are achieved typically by mixing the anesthetic agents with the solvent, preferably at an elevated temperature, for example about 70° to 100°C, to obtain a mixture, preferably a solution, of the anesthetic agents which is then added to the pharmaceutically acceptable adhesive.

Preferably the anesthetic agent is substantially dissolved in the solvent so that when mixed with the adhesive, the anesthetic is microdispersed in the composition. The term "microdispersed" is intended to mean that in the solvent, and subsequently in the carrier, there is an intimate dispersion of the anesthetic agent at the molecular or ionic level, such that crystals of the anesthetic agent cannot be detected using a microscope having a magnification of roughly 25X. As such, the pharmaceutically active agent is in "non-crystallized" form when in the compositions of the present invention.

It has been discovered that high concentrations of a combination of microdispersed anesthetic agents, namely up to 50% by weight of the finite, flexible composition, require the use of a solvent as herein described. Omission of the solvent in the procedure of Example 1 below yields a product filled with crystals or crystalline mass.

In particularly preferred embodiments of this invention, the free base local anesthetic agent is selected from the group comprising lidocaine, procaine, propoxycaine, mepivacaine, prilocaine, dyclonine, pramoxine, benzocaine and chloroprocaine. The salt form is preferably one selected from the group comprising prilocaine, tetracaine, bupivacaine, dyclonine, dibucaine, etidocaine and lidocaine salts. The aforementioned bases and salts can be used alone or in combination with other anesthetic bases and salts as needed to achieve therapeutically affective levels when administered transdermally.

The term "therapeutically effective amount" is intended to mean the amount of drug as a minimizer sufficient to produce a therapeutic effect, for example, an anesthetic effect when applied topically. These amounts are known in the art or may be determined by methods known in the art, and typically range from about 1 to 20,000 mg per human adult and preferably about 10 to 10,000 mg and most preferably range from about 20 to 5,000 mg of the anesthetic agent per application, depending upon the anesthetic agents chosen, and whether the skin or mucous membrane is the site of action. The only upper limit on the amount of anesthetic in the composition is that the preparation is substantially free of crystals of anesthetic agent or other drug and the amount of solvent used is not sufficient to undesirably affect the adhesive properties of the whole composition. Thus, the single ingredient anesthetic agent contains as a minimizer a therapeutically effective amount of anesthetic agent within the foregoing range.

The concentration as well as the quantity of anesthetic per square centimeter can be varied independently in order to achieve the desired effect. Higher concentrations of anesthetic base contained in

a dosage form of decreased thickness will result in a anesthetic with fast onset and short duration. High concentrations of the anesthetic base contained in a dosage form of increased thickness (higher mg of anesthetic per square centimeter) will result in potent anesthesia with fast onset and long duration. Low concentrations of the anesthetic base in a dosage form of decreased thickness will result in mild anesthesia with longer onset and short duration. Low concentrations of the anesthetic base contained in a dosage form of increased thickness will have mild anesthesia with longer onset and longer duration. As shown in the above explanation, the ability to vary the concentration of anesthetic from very low (about 1%) to high (40% or higher) of the total composition, when combined with the ability to coat thin (about 0.001 inches) or thick (about 0.500 or more inches) enables the practitioner of the invention to vary the dosage of the system as needed for particular anatomical sites of interest.

As a general rule, in the case of mucosal application, the anesthetic drug selected, the concentration and thickness and the duration of the application is determined based upon the anesthetic's ability to penetrate the mucosa and to be at peak effectiveness within about 2 to 30 minutes. The duration of the effect of the anesthetic on the oral mucosa should range between about 2 to 240 minutes, depending on the anesthetic agent selected, the concentration of the anesthetic and the thickness of application. Longer or shorter durations can also be selected dependent on need, as will be apparent to one skilled in the art.

The ratio of the free base form to the salt form in the alternate composition of this invention will depend on several factors, namely: (1) the

identity of the salt and base used; (2) the desired duration of action; and (3) the desired rapidity of anesthetic effect. As a general rule in the case of mucosal application, the ratios of base to salt are such that the free base form preferably should penetrate the mucosa and be at its peak effectiveness within about a 2 to 30 minute period, whereas, the salt form should preferably penetrate the mucosa and be at its peak effectiveness within a period of about 10 to 75 minutes. The duration of the effect of these on the oral mucosa will range between about 2 to 240 minutes depending on the base/salt combination selected and the length of application time.

The term "onset of anesthesia" is intended to mean the time to peak effect on the individual nerves. Onset of anesthesia principally depends upon the lipid solubility, molecular size, and quantity of available, un-ionized form of the local anesthetic. Thus, anesthetics with a high lipid solubility or a low pK_a, or both, have a more rapid onset of anesthesia.

The term "duration of anesthesia" as used herein means the period of time during which the local anesthetic measurably blocks nerve conduction. The foregoing depends upon all of the factors listed for onset of anesthesia, as well as on the extent of protein binding of the anesthetic agent.

The anesthetic agent free base can penetrate intact skin to a limited degree, and will more rapidly penetrate the skin if the keratin layers are abraded. In the case of the oral mucosa, the anesthetic base will penetrate much more readily due to the different keratin composition and the resulting difference in the hydrophilicity as compared to the stratum corneum of intact skin.

As a general rule, the salt forms of the aforementioned anesthetics do not appreciably penetrate intact skin, but the un-ionized base form do penetrate to a limited degree. Both forms, salt and base, will penetrate abraded keratin layers. The salt as well as the base will penetrate, to a differing degree, the buccal mucosa due to the buccal mucosa's hydrophilicity, as compared to the stratum corneum of intact skin. Generally, the higher the lipid content of the mucosal membrane, the more rapidly the base form of the anesthetic agent will be absorbed. Therefore, when the composition is used for application to oral or buccal mucosa, the different lipid contents of the gum (gingiva) and the alveolar mucosa must be kept in mind in order to obtain the optimal penetration rate.

Although applicants do not intend to be bound by any theory or proposed mechanism of operation, it is believed that the base which is lipid soluble has a rapid onset of anesthesia since it enters the lipo-protein nerve membrane preventing the depolarization and ion exchange involved in stimulus conduction. On the other hand, the salt which is not lipid soluble, penetrates to the lipo-protein nerve membrane only after the buffering capacity of the skin or mucosal tissue converts the salt to the base, the final result being a delayed onset of anesthesia.

The salts of this invention in the combination composition are selected on the basis of onset of anesthesia and duration of anesthesia. Adjusting the ratio of base to salt affects the relative onset as well as the duration of anesthetic action. The greater the amount of anesthetic agent having a rapid onset of action, the shorter the onset of anesthesia. Similarly, the greater the amount of the anesthetic agent having a prolonged duration of

anesthesia, the more prolonged the duration of anesthesia. More than two anesthetic agents may be used to have a broader spectrum of activity. Moreover, the composition can include other drugs used concomitantly.

Generally, the concentration of solubilized anesthetic agent can range, on a weight basis, between about 1 and about 50% or more, preferably between 2.5 and 40% and more preferably between 5 and 30% of the total weight of the composition. In a preferred embodiment of the combination of this invention, the concentration of dissolved base is 20% by weight of the total composition. The base used in the preferred embodiment for a single ingredient preparation is lidocaine.

Generally, for the hydrochloride salts the ratio by weight of base to salt is about 90:10 to about 60:40, preferably about 75:25 to about 60:40, and more preferably about 70:30 to about 60:40. For other salts, the ratios are comparable based on relative molar amounts. In a preferred embodiment of the invention, the ratio is about 2:1 base to salt, respectively. The base used in the preferred embodiment is lidocaine and the preferred salt is a salt of prilocaine, bupivacaine, dyclonine, mepivacaine, or tetracaine, preferably the hydrochloride salt.

Table 1 below summarizes the peak and duration of action of selected local anesthetics based primarily on application to skin or mucous membranes:

TABLE 1

Local Anesthetic	Minimum Adult Dose	Maximum Adult Dose (mg)	Peak Effect (minutes)	Duration of Effect (minutes)
Dibucaine		25	< 15	120-240
Lidocaine		750	2-5	30-60
Benzocaine		5000	1	30-60
Cocaine		50	2-5	30-120
Tetracaine		50	3-8	30-60
Dyclonine		100	< 10	< 60
Pramoxine		200	3-5	NA

NA: Not Available.

Source: Drug Facts and Comparisons, 1990 edition, J.B. Lippincott Company, St. Louis, MO. Page 601.

In general, the relative speed of onset of anesthesia and duration of anesthesia for any given form of anesthetic agent is available in the literature or can be calculated by standard tests.

Onset time, as well as duration of anesthesia, will vary from individual to individual as well as on the basis of the site of application. When applying the composition to highly keratinized dermal tissues, the onset of anesthesia may take as long as 2 to 4 hours.

The composition of this invention can be manufactured by numerous methods known in the art which permit the achievement of a microdispersed anesthetic agent, including extruding, molding, solvent casting, coating, and all other methods which employ a solvent to disperse the drug in a carrier prior to shaping of the carrier.

Contrary to the typical method for manufacturing a drug in a solvent containing adhesive, the preparation is either not dried so as to force removal of the solvent from the adhesive or a solvent

is used which is not substantially evaporated during the conditions of manufacture. The composition in question can then be applied to a flexible backing or a combination of backings which will serve to define the size and shape of a single dosage of the composition. Such backing may be a three dimensional material such as paper, a non-woven fabric or natural or synthetic polymer substance. Methods of coating backings are well-known in the art and include techniques involving Mayer rod, gravure, and knife-over roll. Further processing of backings may involve the use of converting equipment for die cutting.

The finished dosage form will be substantially occlusive to water permeation in in-vivo.

For example, the anesthetic agents are dissolved in a solvent, preferably a polyhydric alcohol, and then the resulting mixture is added to an adhesive prior to being placed onto the flexible form or backing. The final form in which the composition of the invention will be applied depends upon the anatomical site of application.

The phrase "flexible, finite" with reference to the pharmaceutically acceptable carrier, is intended to mean a solid capable of conforming to a surface with which it comes into contact and capable of maintaining the contact so as to facilitate topical application without any adverse physiological response, and which can be used to establish the compositions herein in their preferred solid form without being appreciably decomposed by aqueous contact during administration to a patient.

An important characteristic of the present invention relates to the substantially water-free and water-insoluble nature of the composition. By the term "substantially water-free" is meant that the

preparation contains less than about 10% by weight water, and preferably less than 5%, and most preferably less than 3%. In general, it is desirable to avoid the addition of water entirely and to eliminate, as far as possible, the presence of water in the other ingredients of the composition. By the term "substantially water insoluble" is meant that the composition remains "finite" and does not generally detach from the skin or other dermal membrane at the site of application and under the conditions of regular, intended use for a period of at least 3 hours. The advantages to be derived from the substantially water-free and water-insoluble nature of the compositions of the present invention include achievement of higher concentrations of drug. Another advantage of these compositions is minimization of precipitation of drug into crystals, which precipitation affects processing of the composition, affects rate of delivery of the drugs and in certain cases can affect sensitivity of the subject to be treated to the drug.

Suitable adhesive carriers include any of the non-toxic polymers, particularly those of the type used to carry drugs for transdermal delivery including natural or synthetic elastomers, such as polyisobutylene, styrene, butadiene, styrene isoprene block copolymers, acrylics, urethanes, silicones, styrene butadiene copolymers, methyl acrylate copolymers, acrylic acid, polyacrylates, and polysacchrides such as, karaya gum, tragacanth gum, pectin, guar gum, cellulose, and cellulose derivatives such as methyl cellulose, propyl cellulose, cellulose acetate and the like, along with other substances known for use in transdermal preparations capable of forming a solid colloid that can adhere to skin and mucosa, used alone or in

combination with other suitable carriers. A particularly preferred carrier is a bioadhesive and more preferably a polysaccharide bioadhesive for application to the dermis, preferably the mucosa. The adhesive can be modified so as to adhere to the skin or mucosal tissue, depending on the intended application site.

The term "adhesive" as used herein means a substance, inorganic or organic, natural or synthetic, that is capable of surface attachment to the intended application site.

The term "bioadhesive" as used herein means an adhesive which attaches and preferably strongly attaches to a live or freshly killed biological surface such as skin or mucosal tissue upon hydration. Indeed, to qualify as a bioadhesive, a substance must be capable of maintaining adhesion in moist or wet in *in-vivo* or *in-vitro* environments. The final composition of the present invention is "self-adhesive" in that it attaches to the site of interest without the need to reinforce its attachment by way of another adhesive which is applied to the composition.

The strength of adherence can be measured by standard tests for measuring the force, e.g. in dynes per square centimeter, as disclosed in U.S. 4,615,697. Suitable bioadhesives include those prepared from optionally partially esterified or etherified polyacrylic acid polymers, including but not limited to, polyacrylic acid polymers lightly cross-linked with a polyalkenyl polyether or other cross-linking agent such as those commercially available from B.F. Goodrich, Cincinnati, Ohio, under the trademarks Carbopol 934, 934P, 940 and 941.

Other suitable bioadhesives include natural or synthetic polysaccharides. The term "polysaccharide" as used herein means a carbohydrate

decomposable by hydrolysis into two or more molecules of natural or synthetic monosaccharides or their analogs or derivatives. Suitable polysaccharides include cellulose derivatives such as methylcellulose, cellulose acetate, carboxymethylcellulose, hydroxyethylcellulose and the like. Other suitable bioadhesives are pectin, a mixture of sulfated sucrose and aluminum hydroxide, hydrophilic polysaccharide gums such as natural plant exudates, including karaya gum, ghatti gum, tragacanth gum, xanthan gum, jaraya gum and the like, as well as seed gums such as guar gum, locust bean gum, psillium seed gum and the like.

In addition to the above ingredients, there may also be incorporated other additives selected from among the various pharmaceutically acceptable additives available to those skilled in the art. These additives include binders, stabilizers, preservatives, penetration enhancers, flavorings and pigments. In the preferred embodiment, the compositions of the present invention also contain a binder or emulsifier such as lecithin which promotes dispersion of the other ingredients having differing solubilities, thereby enhancing the uniform consistency of the final composition.

The composition is administered in appropriate sizes, typically having a surface area of from about 0.1 to about 200 cm^2 or conveniently 0.2 to 100 cm^2. The anesthetic agent is loaded into the composition in as high a concentration as necessary to effect therapy, e.g., in a range from about 0.1 mg/cm^2 to about 50 or more mg/cm^2.

In general, the composition can have the following types and amounts of ingredients:

Ingredient	Typical Range (% by weight)	Preferred Range (% by weight)	Optimum Range (% by weight)
Adhesive	15 to 60	20 to 50	20 to 35
Solvent	2 to 75	5 to 70	20 to 40
(plasticizer included in solvent)	1 to 50	5 to 50	10 to 30
Anesthetic agent (single ingredient)	1 to 50	5 to 40	10 to 30
Anesthetic agent (multiple ingredient)	1 to 50	5 to 40	10 to 30
(a) Anesthetic base	.7 to 50	5 to 40	7 to 20
(b) Anesthetic salt	.3 to 25	2 to 30	3 to 20

In one embodiment, the flexible, finite, bioadhesive composition for topical application comprises:

a therapeutically effective amount of at least one pharmaceutically active agent which is in solid form at ambient temperatures and pressures;

a pharmaceutically acceptable solvent for the pharmaceutically active agent, in an amount from about 5 to about 70 weight percent based on the weight of the whole composition, said solvent including about 5 to about 50 weight percent of a plasticizer for the bioadhesive;

in admixture with the pharmaceutically active agent in the solvent, a pharmaceutically acceptable polysaccharide bioadhesive in an amount from about 20 to about 50 weight percent based on the weight of the whole composition;

wherein the composition is substantially free of water, substantially water insoluble and self-adhesive; and wherein the pharmaceutically active

agent is present in non-crystallized form in the composition.

In another embodiment, the flexible, finite composition of the invention comprises;

a composition for topical application comprising a therapeutically effective amount of a first local anesthetic agent in base form and a therapeutically effective amount of a different, second local anesthetic agent in salt form in a pharmaceutically acceptable, adhesive-containing carrier containing a solvent for the first and second local anesthetic agents.

wherein the composition is preferably substantially free of water, and substantially water insoluble and is self-adhesive; and wherein the anesthetic agents are in non-crystallized form in the composition.

Preferably, the pharmaceutically acceptable solvent is in an amount from about 20 to about 53 weight percent based on the weight of the whole composition of which the plasticizer represents about 10 to about 30 weight percent based on the weight of the whole composition, and the bioadhesive carrier is in an amount from about 20 to about 34 weight percent based on the weight of the whole composition. More preferably, the composition is comprised of 20 to 34 weight percent of karaya gum, about 20 to 53 weight percent of at least one glycol, and about 10 to 25 weight percent of lidocaine base and is further comprised of a binder in or emulsifier an amount sufficient to bind the other ingredients.

Another embodiment of the invention relates to a method of administering one or more local anesthetics to a subject in need of such local anesthetic. The term "administering" is intended to mean any mode of application which results in the physical contact of the composition with an anatomical

site in need of anesthesia. The term "subject" is intended to include all warm-blooded mammals, including humans.

The following examples will further describe the instant invention, and are used for the purposes of illustration only, and should not be considered as limiting in any way the invention being disclosed herein. Percent (%) as used in these examples refer to percentage of the liquid formulation on a weight to weight basis and temperatures are given in degrees celsius (°C).

Example 1

Ingredient	% (w/w)
Adhesive (karaya gum)	21
Binder (lecithin)	11
Solvent (propylene glycol)	7
Solvent/plasticizer (glycerin)	19
Anesthetic agent base (lidocaine base)	28
Anesthetic agent salt (prilocaine hydrochloride)	14

The final product is manufactured by first blending the lidocaine base, prilocaine hydrochloride, propylene glycol, lecithin and glycerin at about 70 to 90°C until all of the drug is dissolved. The solution is then cooled to 20 to 35°C prior to adding the karaya gum. Once the karaya gum is added, the final composition is applied to a suitable backing material such as a non-woven, polyester film (for example, the film sold under the trademark Sontara 8100, manufactured by DuPont de Nemours, E.I. and Co., Wilmington, DE) and warmed to about 100°C to accelerate the formation of the gel into its final, finite form.

Example 2

Ingredient	% (w/w)
Adhesive (karaya gum)	30
Solvent/plasticizer (glycerin)	30
Solvent (propylene glycol)	39
Anesthetic agent base (lidocaine base)	0.7
Anesthetic agent salt (prilocaine hydrochloride)	0.3

The procedure set forth in Example 1 is used with appropriate substitutions of quantities to prepare this formulation.

Example 3

Ingredient	% (w/w)
Adhesive (karaya gum)	21
Binder (lecithin)	4
Solvent (propylene glycol)	3
Solvent (isocetyl alcohol)	7
Solvent/plasticizer (glycerin)	26
Anesthetic agent base (lidocaine base)	26
Anesthetic agent salt (tetracaine hydrochloride)	13

The procedure of Example 1 is used with appropriate substitution of ingredients to prepare this formulation.

Example 4

Ingredient	% (w/w)
Adhesive (karaya gum)	27
Solvent (propylene glycol)	29
Solvent/plasticizer (glycerin)	4
Anesthetic agent base (lidocaine base)	28
Anesthetic agent salt (dyclonine hydrochloride)	12

The procedure of Example 1 is used with appropriate substitution of ingredients to prepare this formulation.

Example 5

Ingredient	% (w/w)
Adhesive (karaya gum)	26
Binder (lecithin)	10
Solvent (propylene glycol)	7
Solvent (butylene glycol)	17
Solvent/plasticizer (glycerin)	10
Anesthetic agent base (lidocaine base)	20
Anesthetic agent salt (dyclonine hydrochloride)	10

The procedure of Example 1 is used with appropriate substitution of ingredients to prepare this formulation.

Example 6

Ingredient	% (w/w)
Adhesive (karaya gum)	27
Binder (lecithin)	12
Solvent (propylene glycol)	8
Solvent/plasticizer (glycerin)	13
Anesthetic agent base (lidocaine base)	27
Anesthetic agent salt (bupivacaine hydrochloride)	13

The procedure of Example 1 is used with appropriate substitution of ingredients to prepare this formulation.

Example 7

Ingredient	% (w/w)
Adhesive (karaya gum)	27
Binder (lecithin)	12
Solvent (propylene glycol)	8
Solvent/plasticizer (glycerin)	13
Anesthetic agent base (lidocaine base)	13
Anesthetic agent salt (bupivacaine hydrochloride)	27

The procedure of Example 1 is used with appropriate substitution of ingredients to prepare this formulation.

Example 8

Ingredient	% (w/w)
Adhesive (karaya gum)	21
Binder (lecithin)	11
Solvent (propylene glycol)	7
Solvent/plasticizer (glycerin)	19
Anesthetic agent base (lidocaine base)	28
Anesthetic agent salt (mepivacaine hydrochloride)	14

The procedure of Example 1 is used with appropriate substitution of ingredients to prepare this formulation.

Example 9

Ingredient	% (w/w)
Adhesive (Carbopol 934P, a polycarboxylic acid sold by B.F. Goodrich Chemical Company)	20
Solvent (propylene glycol)	15
Solvent/plasticizer (glycerin)	20
Anesthetic agent base (lidocaine base)	30
Anesthetic agent salt (bupivacaine hydrochloride)	15

The procedure of Example 1 is used with appropriate substitution of ingredients to prepare this formulation.

Example 10

Ingredient	% (w/w)
Adhesive (karaya gum)	24
Solvent (propylene glycol)	3
Solvent/plasticizer (glycerin)	14
Solvent (isocetyl alcohol)	7
Binder (lecithin)	4
Anesthetic agent base (lidocaine base)	32
Anesthetic agent salt (tetracaine hydrochloride)	16

The above formulation is prepared by a procedure which is analogous to that set forth in Example 1.

The addition of up to 2% by weight water in this formulation did not result in precipitation of the anesthetic agent(s) prior to addition of the karaya gum. The addition of 3% to 10% water results in increased precipitation, which at 10% water results in a crystalline mass.

Example 11

Ingredient	% (w/w)
Adhesive (tragacanth gum)	24
Adhesive (pectin)	5
Solvent (propylene glycol)	12
Solvent/plasticizer (glycerin)	12
Anesthetic agent base (mepivacaine base)	35
Anesthetic agent salt (lidocaine hydrochloride)	12

The above formulation is prepared by a procedure analogous to that of Example 1.

Example 12

Ingredient	% (w/w)
Bioadhesive (karaya gum)	33
Binder (lecithin)	9
Solvent (propylene glycol)	6
Solvent (dipropylene glycol)	15
Solvent/plasticizer (glycerin)	17
Anesthetic agent base (lidocaine base)	20

The final product is manufactured by first blending the lidocaine base, lecithin, propylene glycol, dipropylene glycol and glycerine at about 70 to 90°C until all of the drug is dissolved. The solution is then chilled to about 20 to 40°C prior to adding the karaya gum. Once the karaya gum is added, the final composition is applied to a suitable backing material such as a non-woven polyester film (for example the film sold under the trademark Sontata 8100 manufactured by DuPont de Nemours, E.I. and Co., Wilmington, DE) and warmed at about 70 to 130°C to accelerate the formation of the gel into its final

solid form. This gel can be directly applied to the oral mucosa or overlaid with a skin contact adhesive for skin adhesion.

Example 13

Ingredient	% (w/w)
Bioadhesive (karaya gum)	33
Binder (lecithin)	5
Solvent (propylene glycol)	7
Solvent (dipropylene glycol)	12
Solvent/plasticizer (glycerin)	33
Anesthetic agent base (lidocaine base)	10

The procedure of Example 12 is used with appropriate substitution of ingredients to prepare this formulation.

Example 14

Ingredient	% (w/w)
Bioadhesive (karaya gum)	35
Binder (lecithin)	5
Solvent (propylene glycol)	7
Solvent (dipropylene glycol)	12
Solvent/plasticizer (glycerin)	36
Anesthetic agent base (lidocaine base)	5

The procedure of Example 12 is used with appropriate substitution of ingredients to prepare this formulation.

Example 15

Ingredient	% (w/w)
Bioadhesive (karaya gum)	30
Binder (lecithin)	9
Solvent (propylene glycol)	6
Solvent (dipropylene glycol)	15
Solvent/plasticizer (glycerin)	15
Anesthetic agent base (lidocaine base)	25

The procedure of Example 12 is used with appropriate substitution of ingredients to prepare this formulation.

Example 16

Ingredient	% (w/w)
Bioadhesive (karaya gum)	20
Binder (lecithin)	9
Solvent (propylene glycol)	6
Solvent (dipropylene glycol)	10
Solvent/plasticizer (glycerin)	10
Solvent (benzyl alcohol)	5
Anesthetic agent base (lidocaine base)	40

The procedure of Example 12 is used with appropriate substitution of ingredients to prepare this formulation.

Example 17

Ingredient	% (w/w)
Bioadhesive (karaya gum)	25
Binder (lecithin)	8
Solvent (isocetyl alcohol)	5
Solvent (propylene glycol)	12
Solvent/plasticizer (glycerin)	10
Anesthetic agent base (prilocaine base)	40

The procedure of Example 12 is used with appropriate substitution of ingredients to prepare this formulation.

Example 18

Ingredient	% (w/w)
Bioadhesive (karaya gum)	25
Binder (lecithin)	4
Solvent (propylene glycol)	6
Solvent (benzyl alcohol)	10
Solvent (dipropylene glycol)	10
Solvent/plasticizer (glycerin)	5
Anesthetic agent base (tetracaine base)	40

The procedure of Example 12 is used with appropriate substitution of ingredients to prepare this formulation.

Example 19

Ingredient	% (w/w)
Bioadhesive (karaya gum)	30
Binder (lecithin)	8
Solvent (propylene glycol)	12
Solvent (dipropylene glycol)	25
Solvent (benzyl alcohol)	5
Solvent/plasticizer (glycerin)	10
Anesthetic agent base (dibucaine base)	10

The procedure of Example 12 is used with appropriate substitution of ingredients to prepare this formulation.

Example 20

Ingredient	% (w/w)
Bioadhesive (karaya gum)	28
Bioadhesive (Carbopol 934 Trademark of B.F. Goodrich)	2
Solvent (propylene glycol)	6
Solvent (dipropylene glycol)	15
Solvent/plasticizer (glycerin)	15
Binder (lecithin)	9
Anesthetic agent base (lidocaine base)	25

The procedure of Example 12 is used with appropriate substitution of ingredients to prepare this formulation. The only difference is that the carbopol 934 is added to the original blend prior to heating it.

Example 21

Ingredient	% (w/w)
Bioadhesive (tragacanth gum)	27
Bioadhesive (pectin)	6
Binder (lecithin)	9
Solvent (propylene glycol)	6
Solvent (dipropylene glycol)	15
Solvent/plasticizer (glycerin)	17
Anesthetic agent base (lidocaine base)	20

The procedure of Example 12 is used with the solvents and anesthetic agent base added in the initial step followed later by the adhesives addition.

Example 22

Ingredient	% (w/w)
Bioadhesive (cellulose acetate)	27
Solvent (dipropylene glycol)	33
Anesthetic agent base (prilocaine base)	20
Solvent/plasticizer (glycerin)	10

This formulation is prepared according to the procedure which is analogous to the procedure set forth in Example 1.

Example 23

Ingredient	% (w/w)
Bioadhesive (Xanthan gum)	27
Bioadhesive (Pectin)	6
Binder (lecithin)	9
Solvent (propylene glycol)	6
Solvent (dipropylene glycol)	15
Solvent/plasticizer (glycerin)	17
Anesthetic agent base (lidocaine base)	20

The procedure of Example 12 is followed with the appropriate substitution of ingredients.

Example 24

Ingredient	% (w/w)
Drug (miconazole nitrate)	2
Solvent (propylene glycol)	67
Thickener (hydroxymethylcellulose)	1
Adhesive (karaya gum)	30

This formulation is prepared by dispersing the hydroxymethylcellulose into the propylene glycol. Once the hydroxymethylcellulose is dispersed, the drug is added at a temperature between 50 and 80°C and mixed until dissolved. The sample is then cooled to approximately 20 to 35°C prior to adding the karaya gum. Once the karaya gum is added, the formulation is applied to a sheet of backing material, then the individual dosage forms are cut to the desirable shape to contain the desired amount of drug.

Example 25

Ingredient	% (w/w)
Drug (miconazole base)	5.0
Solvent (dipropylene glycol)	32.5
Plasticizer (glycerin)	32.5
Adhesive (karaya gum)	30.0

Example #25 is prepared just as Example #24.

Example 26

Ingredient	% (w/w)
Drug (miconazole base)	5.0
Solvent (dipropylene glycol)	17.5
Plasticizer (glycerin)	30.0
Solvent (propylene glycol)	7.0
Binder (lecithin)	10.5
Adhesive (karaya gum)	30.0

Example #26 is prepared just as Example #24.

Example 27

Ingredient	% (w/w)
Drug (miconazole base)	10
Solvent (propylene glycol)	35
Plasticizer (glycerin)	25
Adhesive (karaya gum)	30

Example #27 is prepared just as Example #24.

Example 28

Ingredient	% (w/w)
Drug (clotrimazole)	1.0
Solvent (propylene glycol)	41.3
Plasticizer (glycerin)	24.7
Adhesive (karaya gum)	33.0

Example #28 is prepared just as Example #24.

Example 29

Buccal formulations containing, respectively, 5%, 10%, 20%, and 25% lidocaine were prepared according to the procedure of foregoing

examples. A patch containing no drug (placebo patch) was also used.

The patches were tested on nine human subjects. The patch was applied to the buccal cavity of the mouth and removed after 15 minutes. The patch was placed on the gingival surface, since the gingival surface was found to be the best site to examine for a dose response relationship.

The extent of anesthesia at 5, 10, 15, 30, 45, and 60 minutes after application was determined by measurement of the extent of anesthesia. The exent of anesthesia was determined by a base line discomfort tolerance limit determined by application of a tip of a periodontal probe, to the treated surface. The patient was asked to determine the depth penetration they could tolerate at the various timed intervals.

Five minutes after initiation of treatment there was no statistical differences in pain toleration between the treatment groups, including the placebo and no-patch.

At ten minutes post application the 25% lidocaine patch produced the greatest mean change in response threshold followed by the 10 and 20% lidocaine patches. There was little difference between the 5% lidocaine and placebo patch. Lidocaine concentrations greater than 5% were necessary to produce a significant increase in pain threshold responses, and there was a distinct trend in dose proportionality in the range of 10% - 25% lidocaine.

The median change in response thresholds for the gingival surface group displayed the same relationship. The 25% lidocaine patch provided the greatest anesthetic effect followed by the 10% and 20% lidocaine patches.

When all the sites were combined into one group and the median change from baseline was plotted,

the graph revealed a dose response profile where the doses appear in order of concentration from 10 to 30 minutes post application. The 25% lidocaine patch provided the greatest increase in response threshold. The 10% and 20% lidocaine patch responses were similar with the 20% lidocaine patch being slightly better.

There were no signs of inflammation, tissue damage, or other adverse effects associated with application of the patches.

Similar studies were conducted in which the patch was applied to the gingival sulcus and the interproximal sulcus.

Certain of the lidocaine preparations were distinguised in that they resulted in the numbness of the teeth, an effect not generally observed with topical anesthetics applied in fluid vehicles.

The foregoing examples are illustrative embodiments of the invention and are merely exemplary. A person skilled in the art may make variations and modification without departing from the spirit and scope of the invention. All such modifications and variations are intended to be included within the scope of the invention as described in this specification and the appended claims.

Indeed, the present invention is intended to encompass and be suitable for any pharmaceutically active agent, especially any of the following drugs as the pharmaceutically active agent in the composition:

1. Analgesic anti-inflammatory agents such as, acetaminophen, aspirin, salicylic acid, methyl salicylate, choline salicylate, glycol salicylate, l-menthol, camphor, mefenamic acid, fluphenamic acid, indomethacin, diclofenac, alclofenac, ibuprofen, ketoprofen, naproxene, pranoprofen, fenoprofen, sulindac, fenbufen, clidanac, flurbiprofen, indoprofen, protizidic acid, fentiazac, tolmetin,

tiaprofenic acid, bendazac, bufexamac, piroxicam, phenylbutazone, oxyphenbutazone, clofezone, pentazocine, mepirizole, and the like;

2. Drugs having an action on the central nervous system, for example sedatives, hypnotics, antianxiety agents, analgesics and anesthetics, such as, chloral, buprenorphine, naloxone, haloperidol, fluphenazine, pentobarbital, phenobarbital, secobarbital, amobarbital, cydobarbital, codeine, lidocaine, tetracaine, dyclonine, dibucaine, cocaine, procaine, mepivacaine, bupivacaine, etidocaine, prilocaine, benzocaine, fentanyl, nicotine, and the like;

3. Antihistaminics or antiallergic agents such as, diphenhydramine, dimenhydrinate, perphenazine, triprolidine, pyrilamine, chlorcyclizine, promethazine, carbinoxamine, tripelennamine, brompheniramine, hydroxyzine, cyclizine, meclizine, clorprenaline, terfenadine, chlorpheniramine, and the like;

4. Acetonide anti-inflammatory agents, such as hydrocortisone, cortisone, dexamethasone, fluocinolone, triamcinolone, medrysone, prednisolone, flurandrenolide, prednisone, halcinonide, methylprednisolone, fludrocortisone, corticosterone, paramethasone, betamethasone, ibuprophen, naproxen, fenoprofen, fenbufen, flurbiprofen, indoprofen, ketoprofen, suprofen, indomethacin, piroxicam, aspirin, salicylic acid, diflunisal, methyl salicylate, phenylbutazone, sulindac, mefenamic acid, meclofenamate sodium, tolmetin, and the like;

5. Steroids such as, androgenic steriods, such as, testosterone, methyltestosterone, fluoxymesterone, estrogens such as, conjugated estrogens, esterified estrogens, estropipate, 17β-estradiol, 17β-estradiol esters such as 17ß- estradiol

valerate, equilin, mestranol, estrone, estriol, 17β-estradiol derivatives such as 17ß-ethinyl estradiol, diethylstilbestrol, progestational agents, such as, progesterone, 19-norprogesterone, norethindrone, norethindrone acetate, melengestrol, chlormadinone, ethisterone, medroxyprogesterone acetate, hydroxyprogesterone caproate, ethynodiol diacetate, norethynodrel, 17α-hydroxyprogesterone, dydrogesterone, dimethisterone, ethinylestrenol, norgestrel, demegestone, promegestone, megestrol acetate, and the like;

6. Respiratory agents such as, theophylline and β_2-adrenergic agonists, such as, albuterol, terbutaline, metaproterenol, ritodrine, carbuterol, fenoterol, quinterenol, rimiterol, solmefamol, soterenol, tetroquinol, and the like;

7. Sympathomimetics such as, dopamine, norepinephrine, phenylpropanolamine, phenylephrine, pseudoephedrine, amphetamine, propylhexedrine, arecoline, and the like;

8. Antimicrobial agents including antibacterial agents, antifungal agents, antimycotic agents and antiviral agents; tetracyclines such as, oxytetracycline, penicillins, such as, ampicillin, cephalosporins such as, cefalotin, aminoglycosides, such as, kanamycin, macrolides such as, erythromycin, chloramphenicol, iodides, nitrofrantoin, anti fungals, such as, clotrimazole, miconazole, chloramphenicol, nystatin, amphotericin, fradiomycin, sulfonamides, purrolnitrin, sulfacetamide, sulfamethazine, sulfadiazine, sulfamerazine, sulfamethizole and sulfisoxazole; antivirals, including idoxuridine; clarithromycin; and other anti-infectives including nitrofurazone, and the like;

9. Antihypertensive agents such as, clonidine, α-methyldopa, reserpine, syrosingopine, rescinnamine, cinnarizine, hydrazine, prazosin, and the like;

10. Antihypertensive diuretics such as, chlorothiazide, hydrochlorothrazide, bendoflumethazide, trichlormethiazide, furosemide, tripamide, methylclothiazide, penfluzide, hydrothiazide, spironolactone, metolazone, and the like;

11. Cardiotonics such as, digitalis, ubidecarenone, dopamine, and the like;

12. Coronary vasodilators such as, organic nitrates such as, nitroglycerine, isosorbitol dinitrate, erythritol tetranitrate, and pentaerythritol tetranitrate, dipyridamole, dilazep, trapidil, trimetazidine, and the like;

13. Vasoconstrictors such as, dihydroergotamine, dihydroergotoxine, and the like;

14. β-blockers or antiarrhythmic agents such as, timolol pindolol, propranolol, and the like;

15. Calcium antagonists and other circulatory organ agents, such as, aptopril, diltiazem, nifedipine, nicardipine, verapamil, bencyclane, ifenprodil tartarate, molsidomine, clonidine, prazosin, and the like;

16. Anti-convulsantants such as, nitrazepam, meprobamate, phenytoin, and the like;

17. Agents for dizziness such as, isoprenaline, betahistine, scopolamine, and the like;

18. Tranquilizers such as, reserprine, chlorpromazine, and antianxiety benzodiazepines such as, alprazolam, chlordiazepoxide, clorazeptate, halazepam, oxazepam, prazepam, clonazepam, flurazepam, triazolam, lorazepam, diazepam, and the like;

19. Antipsychotics such as, phenothiazines including thiopropazate, chlorpromazine, triflupromazine, mesoridazine, piperracetazine, thioridazine, acetophenazine, fluphenazine, perphenazine, trifluoperazine, and other major tranqulizers such as, chlorprathixene, thiothixene, haloperidol, bromperidol, loxapine, and molindone, as well as, those agents used at lower doses in the treatment of nausea, vomiting, and the like;

20. Muscle relaxants such as, tolperisone, baclofen, dantrolene sodium, cyclobenzaprine;

21. Drugs for Parkinson's disease, spasticity, and acute muscle spasms such as levodopa, carbidopa, amantadine, apomorphine, bromocriptine, selegiline (deprenyl), trihexyphenidyl hydrochloride, benztropine mesylate, procyclidine hydrochloride, baclofen, diazepam, dantrolene, and the like;

22. Respiratory agents such as, codeine, ephedrine, isoproterenol, dextromethorphan, orciprenaline, ipratropium bromide, cromglycic acid, and the like;

23. Non-steroidal hormones or antihormones such as, corticotropin, oxytocin, vasopressin, salivary hormone, thyroid hormone, adrenal hormone, kallikrein, insulin, oxendolone, and the like;

24. Vitamins such as, vitamins A, B, C, D, E and K and derivatives thereof, calciferols, mecobalamin, and the like for dermatologically use;

25. Antitumor agents such as, 5-fluorouracil and derivatives thereof, krestin, picibanil, ancitabine, cytarabine, and the like;

26. Enzymes such as, lysozyme, urokinaze, and the like;

27. Herb medicines or crude extracts such as, glycyrrhiza, aloe, Sikon (Lithospermi radix), and the like;

28. Miotics such as pilocarpine, and the like;

29. Cholinergic agonists such as, choline, acetylcholine, methacholine, carbachol, bethanechol, pilocarpine, muscarine, arecoline, and the like;

30. Antimuscarinic or muscarinic cholinergic blocking agents such as, atropine, scopolamine, homatropine, methscopolamine, homatropine methylbromide, methantheline, cyclopentolate, tropicamide, propantheline, anisotropine, dicyclomine, eucatropine, and the like;

31. Mydriatics such as, atropine, cyclopentolate, homatropine, scopolamine, tropicamide, eucatropine, hydroxyamphetamine, and the like;

32. Psychic energizers such as, 3-(2-aminopropy)indole, 3-(2-aminobutyl)indole, and the like;

33. Humoral agents such as, the prostaglandins, natural and synthetic, for example PGE_1, $PGE_{2\alpha}$, and $PGF_{2\alpha}$, and the PGE_1 analog misoprostol.

34. Antispasmodics such as, atropine, methantheline, papaverine, cinnamedrine, methscopolamine, and the like;

35. Antidepressant drugs such as, isocarboxazid, phenelzine, tranylcypromine, imipramine, amitriptyline, trimipramine, doxepin, desipramine, nortriptyline, protriptyline, amoxapine, maprotiline, trazodone, and the like;

36. Anti-diabetics such as, insulin, and anticancer drugs such as, tamoxifen, methotrexate, and the like;

37. Anorectic drugs such as, dextroamphetamine, methamphetamine, phenylpropanolamine, fenfluramine, diethylpropion, mazindol, phentermine, and the like;

38. Anti-allergenics such as, antazoline, methapyrilene, chlorpheniramine, pyrilamine, pheniramine, and the like;

39. Decongestants such as, phenylephrine, ephedrine, naphazoline, tetrahydrozoline, and the like;

40. Antipyretics such as, aspirin, salicylamide, and the like;

41. Antimigrane agents such as, dihydroergotamine, pizotyline, and the like;

42. Anti-malarials such as, the 4-aminoquinolines, alphaaminoquinolines, chloroquine, pyrimethamine, and the like;

43. Anti-ulcer agents such as, misoprostol, omeprazole, enprostil, allantoin, aldioxa, alcloxa, N-methylscopolamine methylsuflate, and the like;

44. Peptides such as, growth releasing factor, and the like;

45. Anti-estrogen or anti-hormone agents such as, tamoxifen or human chorionic gonadotropin, and the like.

The drugs mentioned above can be used in combination as required. Moreover, the above drugs may be used either in the free form or, if capable of forming salts, in the form of a salt with a suitable acid or base. If the drugs have a carboxyl group, their esters can be employed.

All the drugs used are in solid form at ambient, namely room, temperatures and pressures. However liquid drugs can also be employed to the extent that such drugs, in the forms and amounts used do not undesirably affect the adhesive properties of the carrier.

The acid mentioned above may be an organic acid, for example, methanesulfonic acid, lactic acid, tartaric acid, fumaric acid, maleic acid, acetic acid,

or ann inorganic acid, for example, hydrochloric acid, hydrobromic acid, phosphoric acid or sulfuric acid. The base may be an organic base, for example, ammonia, triethylamine, or an inorganic base, for example, sodium hydroxide or potassium hydroxide. The esters mentioned above may be alkyl esters, aryl esters, aralkyl esters, and the like.

When a drug different than an anesthetic agent is used the solvent selected is one in which the drug is soluble. In generally the polyhydric alcohol can be used as a solvent for a wide variety of drugs. Other useful solvents are those known to solubilize the drugs in question.

CLAIMS

1. A flexible, finite, bioadhesive composition for topical application comprising:

a therapeutically effective amount of at least one pharmaceutically active agent which is in solid form at ambient temperatures and pressures;

a pharmaceutically acceptable solvent for the pharmaceutically active agent, in an amount from about 5 to about 70 weight percent based on the weight of the whole composition, said solvent including about 5 to about 50 weight percent of a plasticizer for the bioadhesive;

in admixture with the pharmaceutically active agent in the solvent, a pharmaceutically acceptable polysaccharide bioadhesive in an amount from about 20 to about 50 weight percent based on the weight of the whole composition;

wherein the composition is substantially free of water, substantially water insoluble and self-adhesive; and wherein the pharmaceutically active agent is present in non-crystallized form in the composition.

2. The composition of claim 1, wherein the pharmaceutically acceptable solvent is in an amount from about 20 to about 53 weight percent based on the weight of the whole composition, of which the plasticizer represents about 10 to about 30 weight percent based on the weight of the whole composition, and the bioadhesive is in an amount from about 20 to about 34 weight percent based on the weight of the whole composition.

3. The composition of claim 1, wherein the pharmaceutically active agent is at least one local anesthetic in an amount of about 10 to about 40 weight percent based on the weight of the total composition.

4. The composition of claim 1, wherein the pharmaceutically active agent is from a class of drugs selected from the group consisting of analgesic anti-inflammatory drugs, central nervous system drugs, antihistaminic or antiallergic drugs, acitonide anti-inflammatory drugs, androgenic and estrogenic steroids, respiratory drugs, sympathomimetic drugs, antimicrobial drugs, antihypertensive drugs, cardiotonic drugs, coronary vasodilators, vasoconstrictors, beta blocking and antiarrhythemic drugs, calcium antagonistic and other circulatory anticonvulsants, anti-vertigo-tranquilizing drugs, antipsychotic drugs, muscle-reactants drugs, anti-Parkinson drugs, non-steroidal hormones, anti-hormones, vitamins, anti-tumor, enzymes, herb medicines or crude extracts, miotics, cholinergic agonists, antimuscarinic or muscarinic cholinergic blocking drugs, mydriatics, psychic energizers, humoral agents, antispasmodic drugs, antidepressants, antidiabetics, anorexic drugs, anti-allergic drugs, decongestants, antipyretics, anti-migraine drugs, antimalarial, antiulcer drugs, peptides, and anti-estrogens.

5. The composition of claim 4, wherein the antimicrobial drugs is an antifungal agent selected from the group consisting of chlotrimazole, miconazale and chloramphenicol

6. The composition of claim 4, in which the pharmaceutically active agent is one or more steroids selected from the group consisting of androgenic steroids, including testosterone; methyltestosterone; fluoxymesterone; estrogenic steroids, including conjugated estrogens, esterified estrogens, estropipate, 17ß-estradiol, 17ß-estradiol esters such as 17ß-estradiol valerate, equilin, mestranol, estrone, estriol; 17ß- estradiol derivatives such as

17ß-ethinyl estradiol; diethylstilbestrol, progestational agents, including progesterone and progesterone analogs such as 19-norprogesterone, hydroxyprogesterone caproate, 17α-hydroxyprogesterone, dydrogesterone, medroxyprogesterone acetate; and norethindrone, norethindrone acetate, melengestrol, chlormadinone; ethynodiol diacetate, norethynodrel, dydrogesterone, dimethisterone, ethinylestrenol, norgestrel, demegestone, promegestone, megestrol acetate, and anti-estrogen or anti-androgenic steroids.

7. The composition of claim 3, wherein the anesthetic agent is selected from the group consisting of procaine, lidocaine, prilocaine, mepivacaine, dyclonine, dibucaine, benzocaine, chloroprocaine, tetracaine, bupivacaine, and etidocaine and is in the form of the base or an acid-addition salt or both forms.

8. The composition of claim 7, wherein the acid-addition salt is hydrochloride.

9. The composition of claim 1, wherein the bioadhesive is selected from the group consisting of polyacrylates, polyacrylic acids, gums and celluloses.

10. The composition of claim 9, wherein the gum is selected from the group consisting of karaya gum, tragacanth gum, pectin gum, xanthan gum, guar gum, cellulose, and cellulose derivatives.

11. The composition of claim 1, wherein the solvent for the anesthetic agent is at least one polyhydric alcohol.

12. The composition of claim 11, wherein the polyhydric alcohol is a polyalkylene glycol.

13. The composition of claim 12, wherein the glycol is selected from the group consisting of dipropylene glycol, propylene glycol, ethylene glycol,

polyethylene glycol, glycerin, butylene glycol, hexylene glycol, polypropylene glycol, and sorbitol.

14. The composition of claim 1, further comprising a backing material conforming to the size and shape of a single dosage of the composition.

15. The composition of claim 1 comprising about 20 to 34 weight percent of karaya gum, about 20 to 53 weight percent of at least one glycol, and about 10 to 25 weight percent of lidocaine base and further comprising a binder in an amount sufficient to bind the other ingredients.

16. The composition of claim 15 comprising about 30 weight percent of karaya gum, about 6 weight percent propylene glycol, about 15 weight percent of dipropylene glycol, about 15 weight percent of glycerine, about 25 weight percent of lidocaine base and about 9 weight percent of lecithin.

17. The composition of claim 15, comprising about 33 weight percent of karaya gum, about 7 weight percent of propylene glycol, about 12 weight percent of dipropylene glycol, 33 weight percent of glycerin, about 10 weight percent lidocaine base and about 5 weight percent lecithin.

18. The composition of claim 1 wherein the pharmaceutical agent comprises a therapeutically effective amount of a first local anesthetic agent in base form and a therapeutically effective amount of a different, local anesthetic agent in acid-addition salt form.

19. The composition of claim 18, wherein the first local anesthetic agent in base form is selected from the group consisting of procaine, dyclonine, lidocaine, prilocaine, mepivacaine, benzocaine, propoxycaine and chloroprocaine and the local anesthetic agent in acid-addition salt form is selected from the group consisting of a dyclonine

salt, a prilocaine salt, a tetracaine salt, a bupivacaine salt, a mepivacaine salt, a lidocaine salt, a procaine salt, an etidocaine salt, and a dibucaine salt.

20. The composition of claim 21, wherein the acid-addition salt is the hydrochloride.

21. The composition of claim 20, wherein the bioadhesive is selected from the group consisting of polyacrylates, polyacrylic acids, gums and celluloses.

22. The composition of claim 21, wherein the gum is selected from the group consisting of karaya gum, tragacanth gum, pectin gum, xanthan gum and guar gum.

23. The composition of claim 22, wherein the solvent for the anesthetic agents is at least one polyhydric alcohol.

24. The composition of claim 23, wherein the polyhydric alcohol is a polyalkylene glycol.

25. The composition of claim 24, wherein the glycol is selected from the group consisting of dipropylene glycol, propylene glycol, ethylene glycol, polyethylene glycol, butylene glycol, hexylene glycol, polypropylene glycol, and sorbitol.

26. A method of administering one or more pharmaceutically active agent to a subject comprising the steps of:

providing the composition set forth in claim 1; and

contacting an area of skin or mucous membrane with the composition to administer the pharmaceutically active agent.

27. The method of claim 26, wherein the pharmaceutically active agent is an anesthetic agent selected from the group consisting of procaine, dyclonine, lidocaine, prilocaine, mepivacaine, benzocaine, propoxycaine, chloroprocaine, tetracaine, bupivacaine, etidocaine, and dibucaine.

28. The method of claim 27, wherein the anesthetic agent is administered in the form of a free base.

29. The method of claim 28, wherein the anesthetic agent is administered in the form of an acid-addition salt.

30. The method of claim 29, wherein the solvent is at least one polyhydric alcohol.

31. The method of claim 30, wherein the polyhydric alcohol is a glycol or cycloalkanepolyol.

32. The method of claim 31, wherein the glycol is selected from the group consisting of dipropylene glycol, propylene glycol, polyethylene glycol, glycerin, butylene glycol, hexylene glycol, polypropylene glycol, sorbitol, and ethylene glycol.

33. The method of administering a pharmaceutically active agent of claim 26, wherein the pharmaceutically active agent is a combination of a therapeutically effective amount of a first local anesthetic agent in base form; and a therapeutically effective amount of a different, second local anesthetic agent in an acid-addition salt form.

34. The method of claim 33, wherein the first local anesthetic agent in base form is selected from the group consisting of procaine, dyclonine, lidocaine, prilocaine, mepivacaine, benzocaine, propoxycaine and chloroprocaine and the second local anesthetic agent in acid-addition salt form is selected from the group consisting of a dyclonine salt, a prilocaine salt, a tetracaine salt, a bupivacaine salt, a mepivacaine salt, a lidocaine salt, a procaine salt, an etidocaine salt, and a dibucaine salt.

35. The method of claim 34, wherein the acid-addition salt is hydrochloride.

36. The method of claim 35, wherein the bioadhesive is selected from the group consisting of polyacrylates, polyacrylic acids, gums and celluloses.

37. The method of claim 36, wherein the gum is selected from the group consisting of karaya gum, tragacanth gum, pectin gum, xanthan gum and guar gum.

38. The method of claim 37, wherein the solvent for the anesthetic agents is at least one polyhydric alcohol.

39. The method of claim 38, wherein the polyhydric alcohol is a polyalkylene glycol or cycloalkanepolyol.

40. The method of claim 39, wherein the glycol or polyol is selected from the group consisting of dipropylene glycol, propylene glycol, ethylene glycol, polyethylene glycol, and sorbitol.

41. The composition of claim 1, wherein the pharmaceutically active agent is an anti-microbial agent.

42. The composition of claim 41, in which the anti-microbial agent in an antifungal agent.

43. The composition of claim 42 in which the anti-microbial agent is clotrimazole.

44. The composition of claim 43 in which the anti-microbial agent is miconazole.

45. A composition for topical application comprising a therapeutically effective amount of a first local anesthetic agent in base form and a therapeutically effective amount of a different, second local anesthetic agent in salt form in a flexible, finite, pharmaceutically acceptable adhesive-containing solvent for the first and second local anesthetic agents.

46. The composition of claim 45, wherein the first local anesthetic agent in base form is selected from the group consisting of procaine, lidocaine,

prilocaine, mepivacaine, dyclonine, dibucaine, benzocaine, propoxycaine, and chloroprocaine.

47. The composition of claim 45, wherein the second local anesthetic agent is selected from the group consisting of a dyclonine salt, a prilocaine salt, a tetracaine salt, a bupivacaine salt, a mepivacaine salt, a lidocaine salt, a procaine salt, an etidocaine salt and a dibucaine salt.

48. The composition of claim 45, wherein the first local anesthetic agent in base form is selected from the group consisting of procaine, dyclonine, lidocaine, prilocaine, mepivacaine, benzocaine, propoxycaine and chloroprocaine and the second local anesthetic agent in salt form is selected from the group consisting of a dyclonine salt, a prilocaine salt, a tetracaine salt, a bupivacaine salt, a mepivacaine salt, a lidocaine salt, a procaine salt, an etidocaine salt, and a dibucaine salt.

49. The composition of claim 48, wherein the salt is the hydrochloride.

50. The composition of claim 45, wherein the adhesive is a bioadhesive.

51. The composition of claim 50, wherein the first local anesthetic agent is selected from the group consisting of procaine, lidocaine, prilocaine, mepivacaine, dyclonine, dibucaine, benzocaine, propoxycaine and chloroprocaine.

52. The composition of claim 50, wherein the second local anesthetic agent is selected from the group consisting of a dyclonine salt, a prilocaine salt, a tetracaine salt, a bupivacaine salt, a mepivacaine salt, a lidocaine salt, a procaine salt, an etidocaine salt, and a dibucaine salt.

53. The composition of claim 50, wherein the bioadhesive is karaya gum.

54. A method of delivering local anesthetic agents which comprises the topical administration to a mammal of a composition comprising:

a therapeutically effective amount of a first local anesthetic agent in base form and

a therapeutically effective amount of a different, second local anesthetic agent in salt form

in admixture with a flexible, finite, pharmaceutically acceptable, adhesive; and

a solvent in the adhesive for the first and second local anesthetic agents.

55. The method of claim 54, wherein the first local anesthetic agent is selected from the group consisting of procaine, dyclonine, lidocaine, prilocaine, mepivacaine, benzocaine, propoxycaine and chloroprocaine and the second local anesthetic agent is selected from the group consisting of a dyclonine salt, a prilocaine salt, a tetracaine salt, a bupivacaine salt, a mepivacaine salt, a lidocaine salt, a procaine salt, an etidocaine salt, and a dibucaine salt.

56. The method of claim 55, wherein the salt is a hydrochloride.

57. The method of claim 54, wherein the adhesive is a bioadhesive.

58. The method of claim 57, wherein the first local anesthetic agent is selected from the group consisting of procaine, lidocaine, prilocaine, mepivacaine, dyclonine, dibucaine, benzocaine, propoxycaine and chloroprocaine.

59. The method of claim 57, wherein the second local anesthetic agent is selected from the group consisting of a dyclonine salt, a prilocaine salt, a tetracaine salt, a bupivacaine salt, a mepivacaine salt, a lidocaine salt, a procaine salt, an etidocaine salt and a dibucaine salt.

60. The method of claim 57, wherein the bioadhesive is karaya gum.

61. The method of claim 59, wherein the salt is a hydrochloride.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 92/01730

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 A 61 K 9/70 A 61 L 15/44

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	A 61 K A 61 L

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
X	DD,A, 217989 (ERNST MORITZ ARNDT UNIVERSITÄT GREIFSWALD) 30 January 1985, see the whole document	9
A	EP,A,0250187 (JOHNSON & JOHNSON PRODUCTS INC.) 23 December 1987, see page 3, line 1 - page 4, line 41; pages 7-9, examples 2-4; pages 11,12, examples 6,7	1-61
A	EP,A,0363224 (BLOCK DRUG CO. INC.) 11 April 1990, see pages 7,8, examples 1,2	1-61
A	WO,A,8910740 (INNOVATA BIOMED LTD) 16 November 1989	1-61

-/-

° Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
16-07-1992	11. 08. 92
International Searching Authority: EUROPEAN PATENT OFFICE	Signature of Authorized Officer: Mme Dagmar FRANK

Form PCT/ISA/210 (second sheet) (January 1985)

DRL - EXHIBIT 1007
DRL2392

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	LU,A, 52460 (ASTRA PHARMACEUTICAL PRODUCTS) 25 June 1968, see the whole document, in particular page 5, lines 17-23; page 18, example 7	1-61

INTERNAT. NAL SEARCH REPORT

International application No.
PCT/US 92/ 01730

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: please see remark
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 26-40 and 54-61 are directed to a method of treatment of the human/ animal the search has been carried out and based on the alleged effects of the composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9201730 SA 58216

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 04/08/92
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Patent document cited in search report	Publication date	Patent family member(s)		Publication date
DD-A- 217989		None		
EP-A- 0250187	23-12-87	US-A-	4713243	15-12-87
		AU-A-	7415587	17-12-87
		JP-A-	63019152	26-01-88
		US-E-	RE33093	17-10-89
EP-A- 0363224	11-04-90	AU-A-	4265689	12-04-90
		CA-A-	2000277	07-04-90
		JP-A-	2196717	03-08-90
WO-A- 8910740	16-11-89	None		
LU-A- 52460	25-06-68	BE-A-	690383	29-05-67
		DE-A-	1617282	06-02-75
		FR-M-	6733	24-02-69
		GB-A-	1108837	
		NL-A-	6616878	31-05-67

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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

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(54) Title: WATER-SOLUBLE PRESSURE-SENSITIVE MUCOADHESIVE AND DEVICES PROVIDED THEREWITH FOR EMPLACEMENT IN A MUCOSA-LINED BODY CAVITY

(57) Abstract

Water-soluble pressure-sensitive adhesives include a water-soluble polymer that is made tacky at room temperature by addition of a water-soluble plasticizer that is miscible with the polymer. Suitable polymers are solid at room temperature; and have a hydrophilicity as measured by water uptake greater than about 25 %; they are liquid at room temperature and have a boiling point higher than about 80 °C. The adhesives according to the invention may conveniently be provided in dry film form. Preferred water-soluble pressure-sensitive adhesives of the invention adhere both to mucosal surfaces and to a variety of materials that may constitute a part of a device or prosthesis to be held in a body cavity that has a mucosal lining. Also, a laminated device for the controlled release of a substance within a mucosa-lined body cavity includes the substance dissolved or dispersed in either or both of a water-soluble pressure-sensitive adhesive layer and optionally one or more water-soluble polymer layers. Also, devices for administering a substance over an extended time for relief of sore throat or cough, or for administering a breath freshening agent, particularly a mint odorant, include a water soluble polymer film layer containing the active ingredient, and a water soluble pressure sensitive mucoadhesive layer.

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WATER-SOLUBLE PRESSURE-SENSITIVE MUCOADHESIVE AND DEVICES PROVIDED THEREWITH FOR EMPLACEMENT IN A MUCOSA-LINED BODY CAVITY

Background

Technical Field

This invention relates to mucoadhesives and to mucoadhering devices. Additionally and particularly this invention relates to compositions that adhere both to mucosal surfaces and to a variety of materials that may constitute a part of a device or prosthesis to be held in a body cavity, such as the oral cavity or the vagina or the rectum, that has a mucosal lining. Additionally this invention relates to mucoadhering devices useful for controlled release of substances within a body cavity that has a mucosal lining, such as for example the oral cavity, and particularly to such devices that are provided with adhesives suitable for fixation of the device within the oral cavity. Additionally and particularly this invention relates to administering breath-freshening agents, and particularly mint odorants, into the oral cavity of a person over extended time periods, for freshening the person's breath. And additionally this invention relates to administering agents into a person's oral cavity over extended times for relief of sore throat pain and cough.

Background Art

For a number of practical purposes, it can be useful to affix a device within a mucosa-lined body cavity, such as the oral cavity, the vaginal

cavity, or the rectal cavity. Devices that may usefully be positioned within a mucous-lined body cavity include, for example, denture prostheses and devices for controlled release of medicaments.

In one approach for such purposes, the device can be affixed to a mucosal surface of the body cavity by means of an adhesive. Various bioadhesives have been proposed for use in establishing adhesive contact with mucosal surfaces.

For example, U.S. Patent No. 4,713,243 describes an extruded film for use in controlled release of medicaments, including a water-soluble or swellable polymer matrix capable of adhering to a wet mucous surface, made up of 40 - 95 % hydroxy propyl cellulose, 5 - 60 % poly(ethylene oxide), optionally up to 10 % of a water-insoluble polymer (ethyl cellulose, propyl cellulose, polyethylene or polypropylene) and 2 - 10 % of a plasticizer introduced to facilitate processing, and containing the medicament. There is no disclosure in the '243 patent that this composition can adhere to materials that may be used in oral prosthesis or other devices, or that it is pressure-sensitive.

Adhesives for affixing dental prostheses in the mouth are conventionally in the form of pastes or creams. These are messy and inconvenient to use, and generally adhere poorly or not at all after extended periods.

U.S. Patent No. 4,529,748 describes a dental prosthesis adhesive in powder form, in which the particles are made from carboxy methyl cellulose, poly(ethylene oxide), poly(acrylic acid), and karaya gum. Some portion of the particles are coated with a cellulose or acrylate polymer film that dissolves slowly in saliva.

U.S. Patent No. 4,948,580 describes a bioadhesive composition for delivery of anti-bacterials, including a copolymer of ("PVME/MA"), and gelatin, dispersed in an ointment base.

International Patent Publication No. WO 91 16041 (Oct. 31, 1991) describes a pharmaceutical composition, to be held under the tongue, in the

form of a thin starch wafer capable of molding to the contours of the sub-lingual cavity, thereby allowing for absorption of medicaments contained within the wafer through the sub-lingual mucosa.

Conventionally, medications for treatment for relief of sore throat and cough are provided in a form such as a lozenge to be held in the mouth of the person being treated, or in the form of a mouthwash or spray. These forms of delivery work generally by shedding the medication into the saliva, which bathes the tissues of the oral cavity and throat as it passes posteriorly toward the esophagus. Such forms remain in the oral cavity only for short periods of time, generally in the range up to about 10 or 20 minutes, and they cannot provide for delivery of the medication to the oral cavity over extended times. In these forms the treatment must be readministered at short time intervals to be effective. The rate at which the medication is delivered from a lozenge can depend upon how actively the user agitates it, that is, how vigorously the user sucks on the lozenge, and whether the user breaks it with the teeth.

Moreover, the presence of a lozenge in the user's mouth can be annoying or distracting, and may interfere with speech or with ingestion of fluids. Holding the lozenge in the mouth—that is, avoiding either swallowing it or spitting it out—requires conscious effort, and inadvertent loss can be embarrassing.

U.S. Patent No. 4,927,634 (May 22, 1990) describes a incorporation of Dyclonine HCl and phenol into base vehicles such as lozenges, drops or troches. U.S. Patent No. 4,503,070 (March 5, 1985) describes administering zinc gluconate to the oral mucosa in the form of a troche or lozenge to reduce the duration of common cold symptoms.

U.S. 4,139,627 (Feb. 13, 1979) describes including a pharmaceutically acceptable acid in a process for making a lozenge containing Dyclonine HCl; the acid acts as a stabilizing agent during processing to prevent degradation of the Dyclonine HCl.

Nearly everyone at least occasionally has malodorous breath. Bad breath may be caused by consumption of strongly flavored food or drink or by use of tobacco, for example, or it may be caused by poor oral hygiene. It may be a symptom of, or may result from, a disease or metabolic condition. The condition may be temporary or chronic, and may be mild, so as to be merely somewhat unpleasant, or may be so severe as to interfere with ordinary social interaction.

Because bad breath (often termed "halitosis", particularly when the condition is severe) is so common a source of embarrassment, considerable attention has been directed to trying to prevent or mask it. In some instances, the condition may not be prevented except by correction of an underlying disease or metabolic disorder, or by improvement in oral hygiene. Some instances of halitosis are so extreme that they cannot be masked. Many cases of ordinary bad breath can be masked by use of an odorant in the mouth and throat that contributes a pleasant smell to the exhalant breath of the person. In many cultures, various mint odorants are commonly accepted on the breath.

Odorants, such as mint odorants, are conventionally administered to the mouth in the form of a spray or mouthwash. Sprays and mouthwashes provide only very temporary mask, as they are quickly washed away by ordinary salivary secretions.

Also conventionally, odorants are administered in a lozenge, or in chewing gum. Lozenges can provide for somewhat more extended administration than sprays or mouthwashes, as the odorant is continuously shed as the lozenge dissolves in the saliva. Chewing gums can also provide for somewhat more extended administration, although the odorant may after some fairly short time be delivered at such a slow rate as not to be effective. As note above, the presence of a lozenge or chewing gum in the person's mouth can be annoying or distracting, and may interfere with speech or with ingestion of fluids. Other persons can be distracted or annoyed by a

person's chewing gum, and in some social circumstances chewing gum is not accepted.

Summary of the Invention

We have discovered water-soluble pressure-sensitive mucoadhesives that can be used for affixing devices within a mucosa-lined body cavity. The water-soluble pressure-sensitive adhesives of the invention can be used in construction of devices for emplacement within a body cavity that has a mucosal lining, as for example on a mucosal surface within the body cavity. Some of the water-soluble pressure-sensitive mucoadhesives according to the invention additionally adhere to a variety of materials, such as polymers, that are conventionally employed in the construction of devices, such as dental prostheses, which are held in the mouth.

Thus the mucoadhesive compositions according to the invention can be used to affix any device within the body cavity, such as, for example, a dental plate. For placement within the oral cavity, for example, the adhesive preferably is made from materials generally regarded as safe ("GRAS-certified"), or national formulary ("NF-certified"), and therefore safe for oral use or for ingestion.

The pressure-sensitive adhesives of the invention are fully water-soluble, and are thus fully soluble in secretions present in mucous-lined body cavities. Consequently, the adhesive eventually dissolves completely within the body cavity in which it is placed, and the dissolved or dispersed matter is flushed away with the fluid secretions of the cavity or, in the case of use in the oral cavity, passes on to the alimentary canal. Pressure-sensitive adhesives according to the invention require no moistening prior to contact with the mucosal or the polymer surface.

The adhesives are additionally particularly useful in construction of laminated devices for controlled delivery of substances within a mucosa-lined body cavity. The invention therefore provides devices having an adhesive surface suitable for affixing to a mucous surface of a mucosa-lined

body cavity such as the mouth or throat, the vagina, or the rectum, or that is suitable for affixing to the dental surface or to the surface of various forms of prosthesis that may be used in the body cavity, such as for example dentures. Devices according to the invention are provided in various configurations, each configuration providing for controlled delivery of one or more substances from a single device according to one of a variety of schedules. Selected devices according to the invention can provide, for example, delayed onset delivery, pulsed delivery, and sequential delivery of two or more substances.

In some configurations, the adhesive itself serves as a reservoir for the substance to be delivered, and releases the substance into the body cavity as the adhesive dissolves. In some configurations a laminate construction includes at least one polymer layer in addition to the adhesive layer. Each such configuration releases one or more substances according to a desired timed delivery regime. In various configurations, for example, onset of release may be delayed following placement of the device within the body cavity; or, for example, a substance may be released at different rates over time, or in pulses with intervening periods in which substantially no release occurs; or, for example, two or more substances may be sequentially released, with or without an intervening period in which substantially no substance is released. The pattern of release is established according to the invention by the sequential arrangement of laminae containing the substance(s) and, in some configurations, laminae not containing the substance(s) or containing fewer than all the substances. The release rate for a substance from a particular layer is determined principally by the rate at which the layer dissolves or disperses in the fluid milieu of the body cavity, together with the concentration of the substance in the layer. Release from a particular more basally situated layer is delayed by overlying layer(s), and the duration of the delay in delivery from such a particular layer is determined principally by the time required for the overlying layer(s) to disperse.

To a limited extent, whether or not a particular layer dissolves or disperses in the fluid milieu of the body cavity, a substance may in time move diffusionally out from the layer, so that the concentration of the substance within the layer falls. Such diffusional movement may result in release of the substance into the body cavity or, where the layer is the mucoadhesive layer, release of the substance transmucosally through the contacting mucosal surface. Or, where the particular layer is covered by an overlying layer, the substance may diffuse into and through the overlying layer. Where such diffusional release is undesirable, it may be limited by rendering the overlying layer substantially impermeable to the substance, so that release from the overlain layer is occluded until such time as the overlying layer has dissolved or dispersed. Suitably occluding layers can be constructed of a water-soluble polymer composition containing as an additive a nonorganic filler such as silica gel, or a fatty acid filler such as magnesium stearate, or a wax such as a paraffin, for example. For extended delayed onset, for example, a slow-dissolving substantially substance-impermeable top layer can be constructed of a hydrophobic material such as hydroxypropyl cellulose, thereby achieving a temporary occlusive (partially occlusive, at least) effect. Such a modification may be made by a change in the polymer constituents of the top layer, or by introduction of additives into the layer itself.

The adhesive can be mucoadhesive, or it can adhere to the surface of the teeth or to a variety of materials, such as polymers, that can be used in the construction of devices that are emplaced within the mucosa-lined body cavity (such as, for example, poly(methyl methacrylate), commonly used in dental prosthesis in the oral cavity). Some adhesives according to the invention are mucoadhesive and adehere to polymer surfaces such as PMMA. The adhesive can be a moistenable adhesive or, alternatively and in some instances preferably, it can be a pressure-sensitive adhesive.

In some embodiments of laminated devices of the invention all the layers are water-soluble (or, for example, are digestible), and they therefore

dissolve or disperse entirely in the fluids secreted within the body cavity. In such embodiments the adhesive layer and the additional polymer layer(s) dissolve and are carried away at or following the time when the substance(s) have diffused away from the device. Preferred materials for the polymer layers as well as for the adhesive layers are for some applications therefore GRAS-certified or NF-certified, so that they are fully acceptable for oral use and for ingestion by humans.

We have further discovered that active substances, useful for relief of sore throat or of cough, can be delivered into the oral cavity over extended times by including the active substance within a water soluble pressure sensitive mucoadhesive device, and applying the mucoadhesive device to a mucosal surface within the oral cavity.

Such a device for temporary relief of sore throat or cough may be a layered composite, including a polymer layer that contains the active substance, and a mucoadhesive layer that serves to affix the active-containing layer to a mucosal surface such as the palate, the gum, or the cheek. Because the materials of the layers are water soluble, and therefore fully soluble in secretions present in mucous-lined body cavities, the device eventually dissolves completely within the oral cavity, and passes on to the alimentary canal. As the material of the active-containing layer dissolves in the fluid secretions, within the oral cavity, the active disperses in the fluid secretions and is distributed throughout the oral cavity and on to the throat.

In many applications delivery of an active substance into a mucosa-lined body cavity desirably is provided over an extended time. We have developed polymer compositions that dissolve slowly within the fluid secretions of the oral cavity, and that can include an active substance and can be deployed in a suitably thin layer within the oral cavity to deliver the active substance over extended times in excess of 1 hour. A desired rate of dissolution for a particular device configuration can be selected by choice of materials and proportions of materials in the active-containing polymer

composition. Generally, the dissolution rate, together with the thickness of the active-containing polymer layer, determines the extent of the delivery time for the active substance.

The rate of delivery of the active substance over the delivery time can be selected by choosing an appropriate amount of the active substance in the active-containing layer as well as by choosing an appropriate polymer composition. Polymer compositions according to the invention are capable of delivery of active substances over extended times.

Preferred water soluble adhesives may be permeable to particular active substances; that is, while the active substance is released into the oral cavity as the active-containing polymer layer dissolves, it may additionally pass by diffusion into and through the adhesive layer, and then into and through the mucosal surface onto which the adhesive layer is affixed. Where delivery of the active substance to the mucosa underlying the device is not desired, an additional water-soluble layer, poorly permeable to the active substance, may be interposed between the active-containing layer and the adhesive layer, to substantially prevent movement of the active substance into the adhesive layer.

Any of a variety of active substances may be delivered using delivery devices constructed according to the invention. For relief of sore throat pain, for example, substances such as benzocaine, lidocaine, dyclonine, and the like, which are available over the counter in syrup or tablet form, may be used. For relief of cough, for example, substances such as dextromethorphan HBr, noscpine, codeine phosphate, menthol, and the like, may be used. Further, both a sore throat medication and a cough suppressant can be combined within and delivered from a single device according to the invention.

The invention provides for continuous delivery of the medication over an extended time, providing for relief of sore throat pain for longer times, in the range up to about 1 to 4 hours, than can be provided by conventional means. Location of the disc on the upper palate helps localize the

medication nearer to the site of soreness upon swallowing during normal salivary flow.

We have further discovered that odorants suitable for masking bad breath, and particularly mint odorants, can be administered into the oral cavity over extended times by including the odorant within a suitable water soluble pressure sensitive mucoadhesive device, and applying the mucoadhesive device to a mucosal surface within the oral cavity.

The breath freshening device may be a layered composite, including a water soluble polymer layer that contains the mint odorant, and a water soluble mucoadhesive layer that serves to affix the odorant-containing layer to a mucosal surface such as the palate, the gum, or the cheek. Because the materials of the layers are water soluble, and therefore fully soluble in secretions present in mucous-lined body cavities, the device eventually dissolves completely within the oral cavity, and the dissolved material passes on to the alimentary canal. As the material of the odorant-containing layer dissolves in the fluid secretions, within the oral cavity, the odorant disperses in the fluid secretions and is distributed throughout the oral cavity.

We have developed polymer compositions that dissolve slowly within the fluid secretions of the oral cavity, and that can include an odorant and can be deployed in a suitably thin layer within the oral cavity to deliver the odorant over extended times in excess of 1 hour. A desired rate of dissolution for a particular device configuration can be selected by choice of materials and proportions of materials in the odorant-containing polymer composition. Generally, the dissolution rate, together with the thickness of the odorant-containing polymer layer, determines the extent of the delivery time for the odorant.

The rate of delivery of the odorant over the delivery time can be selected by choosing an appropriate amount of the odorant in the odorant-containing layer. Polymer compositions according to the invention are capable of delivering odorants over extended times at high enough

concentrations to contribute a continuous pleasant smell to the exhalant breath sufficient to mask bad breath odor.

Preferred water soluble adhesives may be permeable to certain mint odorant components; that is, certain of the mint odorant components may by diffusion pass into and through the adhesive layer, to the mucosal surface onto which the adhesive layer is affixed. Because some mint odorant components may be irritating to the mucosa or may cause an unpleasant local numbing effect on the mucosa when present in higher amounts, it may be desirable to avoid delivery of the odorant to the underlying mucosa. This can be accomplished according to the invention by interposing an additional water-soluble layer, poorly permeable to the odorant components, between the odorant-containing layer and the adhesive layer, to substantially prevent movement of the odorant components into the adhesive layer.

Any of a variety of odorants may be delivered according to the invention, and any of various mint odorants, as described below, may be particularly desirable.

Because the device according to the invention remains affixed to a surface of the oral cavity during use, no conscious effort by the user is required to hold the device in place, and the likelihood that it may be swallowed or spit out of the mouth during use is diminished. As the device has a thin profile, and conforms smoothly to the surface of the oral cavity, it is not mechanically annoying and does not interfere with speech or with ingestion of foods or fluids.

Disclosure of the Invention

Water-Soluble Pressure-Sensitive Adhesives

In one general aspect, the invention features a water-soluble pressure-sensitive adhesive including a water-soluble polymer that is made tacky (that is, it is rendered pressure-sensitive) at room temperature by addition of a water-soluble plasticizer that is miscible with the polymer. Suitable

polymers are characterized as being solid at room temperature (that is, as having a glass transition temperature T(g), or melting point T(m), higher than about 25 °C, and more preferably higher than about 30 °C, and lower than about 120 °C, and more preferably lower than about 100 °C); and having a hydrophilicity as measured by water uptake greater than about 25 %. Suitable plasticizers are characterized as being liquid at room temperature and having a boiling point higher than about 80 °C.

Suitable polymers include polysaccharides such as for example cellulose-type materials and natural gums, polypeptides, and water-soluble synthetic polymers. Particular examples of such suitable polymers which are GRAS certified include poly(vinyl pyrrolidone) ("PVP"), poly(vinyl alcohol) ("PVA"), hydroxy propyl cellulose ("HPC"), poly(ethylene oxide) ("PEO"), poly(acrylic acid) ("PAA"), polyacrylates such as Carbopol 934 (B.F. Goodrich), starch and starch derivatives, polysaccharides, sodium carboxymethyl cellulose ("Na-CMC"), xanthan gum, karaya gum, and gelatin, among others. Suitable plasticizers include, for example and particularly for oral-mucosal contact and other use in the oral cavity, glycerin, sorbitol, any of the glycols, polysorbate 80, triethyl citrate, acetyl triethyl citrate, and tributyl citrate.

In some embodiments for oral mucosal contact and for skin contact, a water-soluble pressure-sensitive adhesive according to the invention includes PVP (about 95 - 40 weight %) and, optionally, HPC (up to about 50 weight %) as a polymer; and glycerin as a plasticizer (about 5 - 35 weight %). Optionally, any balance (up to about 30 weight %) can be made up by water. By way of illustration, such compositions adhere instantaneously (within less than five seconds) to oral mucosal surfaces and to oral cavity prostheses or other devices of the poly(methyl methacrylate) ("PMMA") type, as well as to human skin.

In other embodiments for oral mucosal contact and for skin contact, a water-soluble pressure-sensitive adhesive according to the invention includes as a polymer HPC (about 0 - 50 weight %) and, optionally, (up to about 50

weight %) one or more of PVP, PVA, PEO, starch, polysucrose or other polysaccharide, xanthan gum, or karaya gum; and glycerin as a plasticizer (about 11 - 60 weight % and, preferably about 30 - 50 weight % for PVP- or HPC-containing adhesive compositions). In these formulations, the HPC preferably has a molecular weight between about 60 k and about 1,000 k, and more preferably between about 100 k and about 300 k.

In another general aspect, the invention features a water-soluble pressure-sensitive adhesive film made up of a water-soluble polymer that is made tacky (that is, it is rendered pressure-sensitive) at room temperature by addition of a water-soluble plasticizer that is miscible with the polymer.

In preferred embodiments the thickness of the film is in the range of about 5 - 20 mils, and is shaped to fit and to conform generally to a mucosal surface-contacting portion of a dental prosthesis such as a dental plate. Preferred water-soluble pressure-sensitive adhesive films according to the invention are very flexible, and are therefore capable of conforming to and adhering to contoured surfaces such as the gum or the roof of the mouth. Such a film can be used as a denture adhesive, that can adhere to oral mucosal surfaces and to dental prosthesis for an extended period, typically of more than about 5 hours. The film can be used as part of a system for delivery of substances through the oral mucosa (as a buccal transmucosal patch), or for delivery of substances into the oral cavity itself.

Device Having a Water-Soluble Pressure-Sensitive Adhesive for Emplacement in a Mucosa-Lined Body Cavity

In another general aspect, the invention features a laminated device for controlled release of one or more substances within a mucosa-lined body cavity, having an adhesive layer by means of which the device can be affixed within the body cavity.

In some embodiments the mucoadhesive layer is water-soluble, constructed in some embodiments of a water-soluble moistenable mucoadhesive, and in some embodiments of a water-soluble pressure-sensitive mucoadhesive; in some embodiments the adhesive adheres to a

variety of materials, such as polymers, that can be used in construction of devices for emplacement on a
mucosal surface or within a body cavity that has a mucosal lining; or it is mucoadhesive and additionally adheres to such materials. Preferably the water-soluble pressure-sensitive adhesive requires no moistening prior to contact with the mucosal or the polymer surface. For placement within the oral cavity, for example, the adhesive preferably is made from materials generally regarded as safe ("GRAS-certified"), or national formulary ("NF-certified"), and therefore safe for oral use or for ingestion.

Preferred water-soluble pressure-sensitive adhesives for use in the adhesive layer of the invention are those according to the invention, as disclosed above under the heading "Water-Soluble Pressure-Sensitive Adhesives", and as described in further detail hereafter. Accordingly they include a water-soluble polymer that is rendered tacky (that is, it is rendered pressure-sensitive) at room temperature by addition of a water-soluble plasticizer that is miscible with the polymer.

In some embodiments for oral mucosal contact, a water-soluble pressure-sensitive adhesive according to the invention includes PVP (about 95 - 65 weight %) and, optionally, HPC (up to about 50 weight %) as a polymer; and glycerin as a plasticizer (about 5 - 35 weight %). Optionally, any balance (up to about 30 weight %) can be made up by water. By way of illustration, such compositions adhere well to oral mucosal surfaces and to oral cavity prostheses or other devices of the poly(methyl methacrylate) ("PMMA") type.

In other embodiments for oral mucosal contact a water-soluble pressure-sensitive adhesive according to the invention includes as a polymer HPC (about 100 - 50 weight %) and, optionally, (up to about 50 weight %) one or more of PVP, PVA, PEO, starch, polysucrose or other polysaccharide, xanthan gum, or karaya gum; and glycerin as a plasticizer (about 5 - 35 weight %). In these formulations, the HPC preferably has a molecular weight between about 60 k and about 1,000 k, and more

preferably between about 100 k and about 300 k. The water-soluble pressure-sensitive adhesive layer may take the form of a film which preferably is about 5-10 mils thick. Preferred water-soluble pressure-sensitive adhesive films according to the invention are very flexible, and are therefore capable of conforming to and adhering to contoured surfaces such as the gum or the roof of the mouth.

In preferred embodiments the device includes at least one water-soluble polymer layer in addition to the water-soluble pressure-sensitive adhesive layer. This water soluble polymer layer is a hydrophobic material that will not dissolve in cold water (below about 40 °C) and has little or no tendency to hydrate with water. The material may further be hot water dispersible and may have non-tacky surface properties upon moistening. Examples of suitable GRAS-certified materials include but are not limited to monoglycerides, triglycerides, waxes such as paraffin, fatty acids, fatty alcohols and mixtures thereof. In a particular embodiment, sorbitan monostearate (SPAN 60) with hydroxypropyl cellulose (HPC LF) is useful.

The pressure-sensitive adhesive layer and, in some embodiments, one or more of the polymer layers in the device according to the invention are fully water-soluble, and are thus fully soluble in secretions present in mucous-lined body cavities. Consequently, the pressure-sensitive adhesive layer and the water-soluble polymer layers eventually dissolve completely within the body cavity in which the device is placed, and the material of the dissolved layers is flushed away with the fluid secretions of the cavity or, in the case of use in the oral cavity, passes on to the alimentary canal.

According to the invention, the adhesive serves to keep the device in place within the body cavity, and release of the substance or substances is controlled by the particular arrangement of layers.

Device for Controlled Release of Substance within a Mucosa-Lined Body Cavity

In a further general aspect, the invention features a device for emplacement within a mucosa-lined body cavity of a subject, the device

including a portion made of a water-soluble pressure sensitive adhesive composition. A surface of the water-soluble pressure sensitive adhesive portion forms a basal surface of the device which, when the device is in use, is affixed to a surface of the body cavity.

The adhesive compositions providing an adhesive surface of the device of the invention are pressure-sensitive; that is, the adhesive surface of the device requires no wetting prior to contacting it with the body cavity surface to which it is to be affixed.

The adhesive compositions are fully water-soluble, and are thus fully soluble in secretions present in mucous-lined body cavities. Consequently, the adhesive eventually dissolves completely within the body cavity in which the device is placed, and is flushed away with the fluid secretions of the cavity or, in the case of use in the oral cavity, passes on to the alimentary canal. For placement within the oral cavity, for example, the adhesive preferably is made from materials generally regarded as safe ("GRAS-certified"), or national formulary ("NF-certified"), and therefore safe for oral use or for ingestion.

Preferred water-soluble pressure-sensitive adhesives for use in the adhesive layer of the invention are those according to the invention, as disclosed above under the heading "Water-Soluble Pressure-Sensitive Adhesives", and as described in further detail hereafter. Accordingly they include a water-soluble polymer that is rendered tacky (that is, it is rendered pressure-sensitive) at room temperature by addition of a water-soluble plasticizer that is miscible with the polymer.

In some embodiments the device is emplaced within the body cavity by contacting the adhesive surface with a mucosal surface within the body cavity or with a surface of a prosthesis that is employed within the body cavity, and for such embodiments the water-soluble pressure sensitive adhesive composition preferably includes PVP (about 95 - 40 weight %) and, optionally, HPC (up to about 50 weight %) as a polymer; and glycerin as a plasticizer (about 5 - 35 weight %). Optionally, any balance (up to

about 30 weight %) can be made up by water. By way of illustration, such compositions adhere instantaneously (within less than five seconds) to mucosal surfaces as well as to surfaces of prostheses or other devices of the poly(methyl methacrylate) ("PMMA") type.

In other embodiments, a water-soluble pressure-sensitive adhesive according to the invention includes as a polymer HPC (about 0 - 50 weight %) and, optionally, (up to about 50 weight %) one or more of PVP, PVA, PEO, starch, polysucrose or other polysaccharide, xanthan gum, or karaya gum; and glycerin as a plasticizer (about 11 - 60 weight % and, preferably about 30 - 50 weight % for PVP- or HPC-containing adhesive compositions). In these formulations, the HPC preferably has a molecular weight between about 60 k and about 1,000 k, and more preferably between about 100 k and about 300 k. In some embodiments the device is a device for delivery of one or more substances into the body cavity or across the mucosa. Typically the device has a laminated structure, and the water-soluble pressure sensitive portion is a basal layer of the device. Conveniently, the water-soluble pressure sensitive adhesive portion of such a device is constructed as a film made up of an adhesive composition as described above. In preferred embodiments the film has a thickness in the range about 5 - 20 mils, and is shaped to fit and to conform generally to the surface to which the device is intended to be attached for use. Preferred water-soluble pressure-sensitive adhesive films according to the invention are very flexible, and are therefore capable of conforming to and adhering to contoured surfaces such as the gum or the roof of the mouth.

In some embodiments the device when in place within the body cavity provides a protective barrier for the area of the mucosal surface to which it is affixed which is covered by the device. The barrier may protect the underlying mucosal surface from mechanical abrasion or erosion, for example, or, for example, it may serve to protectively isolate the underlying mucosal surface from some substance in the fluid of the milieu of the body cavity.

Where the device is a laminated device for delivery of an active agent, and includes an upper active-containing layer laminated to an adhesive layer, or where the device provides a protective barrier, and includes an upper barrier layer laminated to an adhesive layer, the upper layer is preferably constructed of a hydrophobic polymer material that will not dissolve in cold water (below about 40 °C) and has little or no tendency to hydrate with water. The material may further be hot water dispersible and may have non-tacky surface properties upon moistening. Examples of suitable GRAS-certified materials include but are not limited to monoglycerides, triglycerides, waxes such as paraffin, fatty acids, fatty alcohols and mixtures thereof.

The rate of release of the active substance within the oral cavity depends to at least some extent upon the rate of dissolution or dispersion of the polymer of the active layer *in situ*, which in turn varies substantially according to the molecular weight of the principal polymer component: a given polymer type dissolves or disperses more slowly at higher molecular weights than at lower molecular weights. In some embodiments the active-containing layer includes a polymer such as hydroxypropyl cellulose, and may additionally include a plasticizer such as glycerin. In a particular embodiment, hydroxypropyl cellulose (HPC Klucel LF), having a molecular weight of 80,000, with glycerin as a plasticizer, is useful.

Long-Lasting Mucoadhesive Device for Temporary Relief of Sore Throat and Cough

In yet another general aspect, the invention features a layered composite mucoadhesive device for delivery of an active substance into the oral cavity, having an active-containing layer that includes the active substance dispersed or dissolved in a water soluble polymer, and a water soluble adhesive layer.

In some embodiments the active-containing water soluble polymer layer is a hydrophobic material that will not dissolve in cold water (below about 40 °C) and has little or no tendency to hydrate with water. The

material may further be hot water dispersible and may have non-tacky surface properties upon moistening. As noted above examples of suitable GRAS-certified materials include but are not limited to monoglycerides, triglycerides, waxes such as paraffin, fatty acids, fatty alcohols and mixtures thereof.

Also as noted above, the rate of release of the active substance within the oral cavity depends to at least some extent upon the rate of dissolution or dispersion of the polymer of the active layer *in situ*, which in turn varies substantially according to the molecular weight of the principal polymer component; a desired release rate can be specified by choice of the polymer or polymer combination.

In some embodiments the adhesive for use in the adhesive layer of the invention is a water-soluble pressure-sensitive adhesive according to the invention, as disclosed above under the heading "Water-Soluble Pressure-Sensitive Adhesives", and as described in further detail hereafter. Accordingly such adhesives include a water-soluble polymer that is rendered tacky (that is, it is rendered pressure-sensitive) at room temperature by addition of a water-soluble plasticizer that is miscible with the polymer.

Additional ingredients, such as, for example, deodorants or reodorants or flavorants, may be delivered along with the active substance as the active-containing layer disperses within the oral cavity. Such additional ingredients include, for example, sweeteners such as aspartame, and breath fresheners such as menthol.

In another general aspect the invention features a method for administering a substance over an extended time period for relief of sore throat or cough. The method involves dissolving or dispersing the substance in a laminated water soluble device that has a water soluble pressure sensitive adhesive layer. The device is affixed to the mucosal surface of the oral cavity.

Long-Lasting Mucoadhesive Device for Administration of Breath-Freshening Agent

In still another general aspect, the invention features a laminated composite device for administering an odorant into the oral cavity over an extended time. The device has at least two layers, including a basal layer constructed of a water soluble pressure sensitive mucoadhesive polymer composition; and an odorant-containing water soluble polymer layer.

In some embodiments the basal adhesive layer is mucoadhesive and additionally adheres to a variety of materials, such as polymers, that can be used in construction of devices for emplacement on an oral mucosal surface or within the oral cavity. The basal adhesive layer preferably is constructed of a water soluble pressure sensitive adhesive that requires no moistening prior to contact with the mucosal or the polymer surface. The adhesive preferably is made from materials generally regarded as safe ("GRAS-certified"), or national formulary ("NF-certified"), and therefore safe for oral use or for ingestion.

Preferred water-soluble pressure-sensitive adhesives for use in the adhesive layer of the invention are those disclosed above under the heading "Water-Soluble Pressure-Sensitive Adhesives", and described in further detail hereafter. Accordingly such adhesives include a water-soluble polymer that is rendered tacky (that is, it is rendered pressure-sensitive) at room temperature by addition of a water-soluble plasticizer that is miscible with the polymer.

In some embodiments the odorant containing layer includes a polymer such as a hydroxypropyl cellulose, and in a particular embodiment may additionally include a plasticizer such as glycerin. The rate of release of the odorant within the oral cavity can be specified by selection of particular polymer or polymer combinations, as noted generally above under the heading "Device for Controlled Release of Substance within a Mucosa-Lined Body Cavity". In a particular embodiment, a hydroxypropyl cellulose (HPC Klucel GF), having a molecular weight of 300,000, is useful.

The water soluble odorant containing layer may take the form of a film which preferably is about 20 - 30 mils thick. Suitable slow-dissolving polymers such as HPC are typically not sufficiently flexible to conform with the irregularly curved surfaces of the oral cavity or of oral or dental prostheses, and addition of a plasticizer to the polymer or polymer mixture of films would be required for these applications. Suitable plasticizers can include glycerin, for example.

In some embodiments the odorant is an essential oil of a plant material, or a refined fraction of an essential oil, or a combination of the chief aromatic constituents of an essential oil. Preferably the odorant is a mint odorant. We have discovered that, surprisingly, the essential oils that are commonly used as flavorings, particularly oil of wintergreen, oil of peppermint, and oil of spearmint, are themselves effective as plasticizers. For breath freshener devices for delivering a mint odorant, therefore, the odorant containing layer therefore can consist of the polymer and the mint odorant (and, optionally, a sweetener and a preservative), without any requirement for a plasticizer other than the mint odorant.

Accordingly, in another aspect the invention features a laminated composite device for administering a mint odorant into the oral cavity over an extended time, comprising a basal layer constructed of a water soluble pressure sensitive mucoadhesive composition and an upper layer containing a water soluble polymer, such as a HPC, and a mint oil.

Extended delivery of odorant can be obtained according to the invention from devices whose composite thickness is 35 mils or less. The devices according to the invention are very flexible, and are therefore capable of conforming to and adhering to contoured surfaces such as the gum or the roof of the mouth. Breath freshening devices according to the invention can deliver a mint odorant such as a peppermint continuously over a period of up to two hours or longer from a single device, and can provide breath freshening for even greater periods of time.

Description of Preferred Embodiments

Preferred embodiments of the invention will now be described, beginning with a brief description of the drawings.

Brief Description of the Drawings

Fig. 1 is a sketch in sectional view showing a device of the invention configured to provide delivery of one or more substances at two different rates.

Fig. 2 is a sketch in sectional view showing a device of the invention configured to provide delayed-onset delivery of one or more substances.

Fig. 3 is a sketch in sectional view showing a device of the invention configured to provide delivery of one or more substances in a sequence of pulses.

Fig. 4 is a sketch in sectional view showing a device of the invention configured to provide delayed-onset delivery of one or more substances while minimizing diffusion of the substance(s) at the edges of the device.

Figs. 5 through 7 are rough hypothetical plots showing quantity of an active substance released by devices of the invention configured on the plans shown in Figs. 1 through 3, respectively.

Fig. 8 is a sketch in transverse sectional view showing a bilaminate device according to the invention.

Fig. 9 is a sketch in transverse sectional view showing a trilaminate device according to the invention.

Fig. 10 is a plot of data showing the cumulative release of Dyclonine HCl into water from a mucoadhesive disc according to the invention, and from a Sucrets® lozenge.

Fig. 11 is a plot of data comparing release of benzocaine into distilled water from mucoadhesive discs according to the invention, having different molecular weight polymers in the active-containing layer.

Fig. 12 is a sketch in sectional view showing another embodiment of a device according to the invention.

Fig. 13 is a sketch in sectional view showing another embodiment of a device according to the invention.

Fig. 14 is a graph comparing tack characteristics, on a PMMA surface, of dry and of moistened adhesive films according to the invention with tack characteristics of conventional films.

Fig. 15 is a graph comparing adhesion characteristics, on a PMMA surface, of dry and of moistened adhesive films according to the invention with adhesion characteristics of conventional films.

Fig. 16 is a graph comparing elastic moduli of HPC films, illustrating the plasticizing effect of mint odorants.

Fig. 17 is a graph comparing menthol release over time from a breath freshening device according to the invention and from a conventional commercially marketed "breath mint" (Certs®).

As will be appreciated, the drawings are not made to scale, and, in particular, no attempt has been made to represent relative thicknesses of the layers proportionately, and the thicknesses of the various layers are exaggerated for clarity of presentation.

Modes of Carrying out the invention

Water-Soluble Pressure-Sensitive Adhesives

1. Preparation of a water-soluble pressure-sensitive adhesive composition made up of PVP and glycerin.

A solution of poly(vinyl pyrrolidone) ("PVP": Kollidon®, obtained from BASF) and glycerin was first prepared in isopropyl alcohol ("IPA"), in the following proportion by weight: 15 parts PVP, 6 parts glycerin, and 79 parts IPA. The solution was coated on a polyester release liner and allowed to dry at room temperature for 15 hours to permit evaporation of the IPA. The resulting dry film is both pressure-sensitive and water-soluble.

Measurements of tack were made using a TA.XT2 Texture Analyzer (Texture Technologies Corp.) together with an XT.RA Dimension software

package (Stable Micro Systems, Ltd.), as follows. A sample of the film on a release liner is mounted upon a block, and a probe is moved at a fixed speed against the adhesive surface of the film, distorting the film to a fixed penetration depth, where the probe is permitted to dwell for a fixed time. The probe is then withdrawn from the film, at a fixed speed, and the peak force required to detach the probe from the film surface is measured as a measure of tack.

Measured tack of samples of a PVP-glycerin film prepared as described above and having 5 mils thickness was 1820 g/cm^2, using a probe diameter of 0.80 cm, a penetration depth of 0.1 mm, a penetration rate of 1.0 mm/sec, a dwell time of 10 sec, and a withdrawal rate of 5.0 mm/sec. Typical tack values for adhesives used in transdermal devices, for example, are about 1000 - 2000 g/cm^2.

Measurements of water solubility were made by submersion of a sample of the film in water at 21 °C, stirring the water, and determining the time required for apparent complete dissolution of the film.

The total measured dissolution time of samples of a PVP-glycerin film prepared as described above and having 5 mils thickness was about 10 minutes. 2. Preparation of a water-soluble pressure-sensitive adhesive composition made up of HPC, PVP and glycerin.

Hydroxy propyl cellulose ("HPC"), PVP and glycerin were first blended in the proportion, by weight, of 4 parts HPC, 2 parts PVP, and 2 parts glycerin. The resulting mixture was pressed in a heated Carver laboratory press at 200 °F to a thickness about 35 mils. The resulting film was flexible, translucent and tacky at room temperature.

3. Preparation of dental prosthesis adhesive film.

A water-soluble pressure-sensitive adhesive film made as described above can be die-cut in a shape that conforms to that portion of the dental prosthesis that closely fits the mucosal surface of the mouth, such as the part of the dental plate that fits against the palate. The shaped film pieces can be packaged dry. For use, the dry film is pressed onto the appropriate surface

of the dental prosthesis so that it adheres. Then the dental prosthesis with the adhesive affixed is inserted into the correct position in the mouth and pressed against the mucosal surface until adhesion is achieved.

The following Example is intended to illustrate but not to limit the invention.

Example I

Breath Freshening Device

A dissolvable mucoadhesive device capable of releasing a flavor into the oral cavity was constructed as follows: A solution was made up by co-dissolving 15.4 grams of polyvinyl pyrrolidone PVP (K90) and 6.0 grams of glycerin in 80 grams of isopropanol (IPA). The resulting solution was coated at a thickness of 30 mils onto a polyester release liner and allowed to dry for 15 hours at room temperature. The resulting dry film was tacky at room temperature and had a final thickness of about 5 mils. A second solution containing 43 grams of IPA, 42 grams of water, 15 grams of HPC EF, 2.5 grams of peppermint oil and 3.0 grams of Nutrasweet™ brand sweetener containing aspartame was prepared by mixing all the components until fully dissolved. The solution was then coated at a thickness of 50 mils onto a polyester release liner. The film was allowed to dry at room temperature for 15 hours to a final thickness of about 5 mils.

The two dry films were laminated together. Discs having a diameter of about 1.2 cm were cut from the laminate. The discs were tested *in vivo* by adhering a single disc to the upper palate of three volunteers. The discs adhered well to the mucosal surface and upon hydration with saliva immediately began releasing peppermint oil and aspartame as noticed by taste. The total time of dissolution in the mouth was about 10 minutes, during which time a pleasant, refreshing mint flavor was perceived.

Device Having a Water-Soluble Pressure-Sensitive Adhesive for Emplacement in a Mucosa-Lined Body Cavity

1. Water-soluble pressure-sensitive adhesive layer.

The preferred water-soluble pressure-sensitive adhesive layer of the device according to the invention provides the foundation upon which the device operates. There follows first a description, by way of examples, of protocols for making exemplary water-soluble pressure-sensitive adhesives and films suitable for use in the adhesive layer.

a. Preparation of a water-soluble pressure-sensitive adhesive composition made up of PVP and glycerin.

A solution of poly(vinyl pyrrolidone) ("PVP": Kollidon®, obtained from BASF) and glycerin was first prepared in isopropyl alcohol ("IPA"), in the following proportion by weight: 15 parts PVP, 6 parts glycerin, and 79 parts IPA. The solution was coated on a polyester release liner and allowed to dry at room temperature for 15 hours to permit evaporation of the IPA. The resulting dry film is both pressure-sensitive and water-soluble.

Measurements of tack were made using a TA.XT2 Texture Analyzer (Texture Technologies Corp.) together with an XT.RA Dimension software package (Stable Micro Systems, Ltd.), as follows. A sample of the film is first mounted onto a block, and a probe is moved at a fixed speed against the adhesive surface of the film, distorting the film to a fixed penetration depth, where the probe is permitted to dwell for a fixed time. The probe is then withdrawn from the film, at a fixed speed, and the peak force required to detach the probe from the film surface is measured as a measure of tack.

Measured tack of samples of a PVP-glycerin film prepared as described above and having 5 mils thickness was 1820 g/cm^2, using a probe diameter of 0.80 cm, a penetration depth of 0.1 mm, a penetration rate of 1.0 mm/sec, a dwell time of 10 sec, and a withdrawal rate of 5.0 mm/sec. Typical tack values for adhesives used in transdermal devices, for example, are about 1000 - 2000 g/cm^2.

Measurements of water solubility were made by immersing a sample in water at 21 °C, stirring the water, and determining the time required for apparent complete dissolution of the film.

The total measured dissolution time of samples of a PVP-glycerin film prepared as described above and having 5 mils thickness was about 10 minutes.

b. Preparation of a water-soluble pressure-sensitive adhesive composition made up of HPC, PVP and glycerin.

Hydroxy propyl cellulose ("HPC"), PVP and glycerin were first blended in the proportion, by weight, of 4 parts HPC, 2 parts PVP, and 2 parts glycerin. The resulting mixture was pressed in a heated Carver laboratory press at 200 °F to a thickness about 35 mils. The resulting film was flexible, translucent and tacky at room temperature.

2. Device configurations.

a. Device having two substance-containing layers:

Referring to Fig. 1, there is shown by way of example a device **10** having a basal adhesive layer **12** which in use adheres to mucosal surface **M** and an upper polymer layer **14**, in which a substance or substances to be delivered are contained in both layers. As the upper layer is bathed by the fluids in the body cavity (for example by saliva and ingested fluids in the mouth), dissolution of the upper layer begins first and is substantially complete when dissolution of the basal layer begins. Where a different substance is contained in each layer, the substances are released sequentially. The two layers can be made to have different dissolution rates or swelling rates, resulting in one release rate for the substance or substances in the basal adhesive layer, and another release rate for the substance or substances in the upper polymer layer. If, for instance, the dissolution rate of the upper layer is slower than that of the lower layer, the resulting release regime is of a slow release of the substance in the upper layer, followed by a relatively rapid release of the substance in the basal layer. Or, alternatively, the two layers can have approximately the same dissolution

rates, but be loaded with the substance at different concentrations, resulting in a higher rate of delivery from that layer having the substance present in higher concentration.

Fig. 5 shows a rough diagrammatic plot of the release of active over time from a device made on the plan in Fig. 1. As will be appreciated, the different rates need not be linear, nor need the break between the rates be abrupt as shown.

Such a configuration can be useful in a breath freshener for oral use, by way of example, in which the basal layer can have a relatively slow dissolution rate and can be loaded with an antimicrobial, while the upper layer can have a relatively fast dissolution rate and can be loaded with a flavor or a reodorant. Such can result in a rapid release of flavorant or reodorant after emplacement in the mouth, followed by a slower release of the antimicrobial. Or, both layers can be loaded with a microbial, resulting release in an early burst followed by a more sustained delivery.

In one embodiment of this configuration, the basal layer is made of a polymer that becomes sticky on moistening, such as, *e.g.*, HPC or PAA.

In a modification of this configuration, the two layers described above can constitute middle and upper layers, respectively, of a three-layer device that is provided with a basal layer that is a water-soluble pressure-sensitive adhesive, so that the device need not be moistened prior to placement within the body cavity. As is described above, suitable compositions for such an adhesive layer include PVP as a polymer (95 - 65 weight %) and glycerine as plasticizer (5 - 35 weight %).

b. Device providing delayed-onset delivery:

Referring now to Fig. 2, there is shown a device **20** having a basal adhesive layer **22** which in use adheres to the mucosal surface **M**, a middle substance-containing water-soluble layer **26**, and an upper layer **28**, not containing the substance, that dissolves relatively slowly in the fluid environment of the body cavity. As in the device shown in Fig. 1, the adhesive layer is a water-soluble adhesive, which may be a mucoadhesive

that becomes tacky when moistened. More preferably, the basal adhesive layer is a water-soluble pressure-sensitive adhesive as described above; and in some embodiments the middle layer is eliminated and the substance to be delivered in loaded into the adhesive layer. However, where loading is so high (upwards of 25 % by weight, for example) that it would compromise the adhesive capacity of the adhesive layer, a system having the substance to be delivered loaded in a middle layer can be preferred.

Fig. 6 shows a rough plot of the amount of active released over time from a device made on the plan of Fig. 2. Here, as in Fig. 5, the rate need not be linear, nor need the onset be abrupt as shown.

Such a delayed-onset release configuration can be useful, by way of example, in a breath freshener that can be emplaced in the mouth before retiring for sleep, and which provides for release several hours later, so that the breath is fresh upon waking.

c. Device providing pulsed delivery:

A more complex release pattern can be achieved using several layers, in which altering layers contain the active, as shown by way of example in Fig. 3. The basal adhesive layer **34** of device **32** can be made, as in the devices of Figs. 1 and 2, either as a moistenable adhesive, or as a water-soluble pressure-sensitive adhesive. A moistenable adhesive may be preferred for reasons of greater stability. Basal layer **34** adheres to mucosal surface **M** when the device is in use and contains a substance to be delivered. Layers **36, 38** contain a substance to be delivered, while alternating layers **35, 37** are slowly dissolving layers not containing the substance.

Fig. 7 shows a rough plot of the amount of active released over time from a device made on the plan of Fig. 3. Here, as in Figs. 5 and 6, the rates for each delivery phase need not be linear, nor need the onset be abrupt as shown.

Such a configuration can be useful, for example, in an oral after-meals breath freshener, which provides for release of a flavor or reodorant

or deodorant at intervals corresponding with post-mealtimes, with no release during mealtimes or at other times.

Such a configuration can be useful, to cite another example, for pulsed delivery of actives that can be toxic if administered continuously. Such actives include, by way of example, anti-bacterials such as Cetyl Pyridinium Chloride ("CPC"); pulsed release can give adequate antibacterial protection without raising toxicity concerns.

d. Device having suppressed marginal release.

In any of the devices described above, dissolution at the edges or margins of the device, as well as from the upper surface, can be expected to result in release of the substance or substances within the layers whose edges are exposed. Loss of the desired release pattern can result, particularly where, as in Fig. 2, delayed onset is desired, or where, as in Fig. 3, pulsed release is desired. To minimize loss from the margins, a peripheral adhesive can be provided, as shown in Fig. 4, by way of example of a delayed onset release device having a marginal adhesive. The device **40** includes a moistenable mucoadhesive layer **44** containing the substance or substances to be delivered, which in use adheres to the mucosal surface **M**, and which is overlain by a water-soluble pressure-sensitive adhesive layer **46** whose edges extend beyond the edges of the mucoadhesive layer **44** on all sides and there adhere to the mucosal surface, forming a seal to prevent escape of the substance from the edges of the mucoadhesive layer **44** until the water-soluble pressure-sensitive adhesive layer has dissolved. The water-soluble pressure-sensitive adhesive layer is in turn covered by a slowly dissolving layer **48** not containing the substance. The slowly dissolving layer **48** provides a delay before the water-soluble pressure-sensitive adhesive begins to dissolve, which in turn prevents release of the substance until the upper surface of the substance-containing mucoadhesive layer is exposed.

Examples of substances that can be delivered within the oral cavity include: reodorants such as peppermint oil and other flavors, deodorants

such as for example the odor-preventive antimicrobial CPC, anti-bacterials such as chlorhexidine, sore-throat medicants such as Hexylresorcinol/Phenol derivatives/Menthol, cough suppressants such as Dextrathomorphan Hydochloride, agents to prevent mouth dryness, benzocaine for treatment of rhinitis, *etc.*

3. Particular devices.

Example II

Two-layer device having a water-soluble pressure-sensitive adhesive layer

A two-layer device according to the invention was made according to the following protocol. First the necessary components (polymers, additives, *etc.*) for each layer were dissolved or dispersed in an appropriate solvent. For an upper layer, the casting solution in one prototype consisted of 41 parts isopropyl alcohol ("IPA"), 40 parts water, 14 parts hydroxypropyl cellulose ("HPC") EF (MW ~ 80,000), 2.4 parts peppermint oil and 2.8 parts Aspartame. The casting solution for the basal layer consisted of 79 parts IPA, 15 parts poly(vinyl pyrrolidone) ("PVP") (Kollidon 90), and 6 parts glycerin. Each of these two casting solutions was coated onto a polyester release liner, to provide a substratum for forming the layer, at the desired thicknesses of 50 mils for the upper layer and 25 mils for the basal layer. The layers were then allowed to dry on the respective release liners overnight (at least 15 hours) at room temperature inside a hood). The dry films were then carefully hand-laminated together to provide a two-layer system consisting of a non-tacky upper layer containing the substances to be released, and an adjacent tacky pressure-sensitive-adhesive soluble basal layer.

Alternatively, manufacture of the pressure sensitive adhesive device can be carried out by extruding a blend of the components for each layer through a slit die to form a thin film. The upper and basal films can then be laminated together through rollers, with the tacky layer protected by a release liner from contact with the rollers.

Alternately, the substances to be delivered (*e.g.*, peppermint oil or other printable material or materials) can be printed onto an extruded pure HPC EF or other similar extruded film, as described in Miranda *et al.* U.S. Patent No. 4,915,950, which is hereby incorporated by reference.

Example III

Two-layer device having a moistenable mucoadhesive layer, and capable of delivering at two different constant rates

An alternative two-layer device according to the invention was made as follows. The upper layer was made by first co-dissolving HPC HF and CPC in IPA in the following proportions: 10 parts HPC EF, 0.135 parts CPC, and 90 parts IPA. The solution was then coated at a thickness of 15 mils onto a polyester release liner, and allowed to dry at room temperature overnight (at least 15 hours). This film formed an upper layer having a dry thickness of 1.5 mils. The basal layer was made by first co-dissolving HPC EF, CPC and IPA in the following proportions: 2 parts HPC HF, 0.0054 parts CPC, and 98 parts IPA. The solution was then coated at a thickness of 50 mils onto a polyester release liner, and dried in an oven at 70 °C for 6 hours. The dry film was then collected and ground to a coarse powder using a mortar and pestle. This powder was then pressed in a heated Carver laboratory press to form a film having a thickness about 2 mils. Then the upper (EF) and basal (HF) films were laminated together and then bonded by compressing in a heated (275 °F) Carver press.

Example IV

Multilayer device providing pulsed release

A multilayer device was made by first co-dissolving poly(vinyl propylene) ("PVP") (K 90), glycerine, methylene blue and IPA in the following proportions: 7.2 parts PVP (90), 2.8 parts glycerine, 90 parts IPA and 0.030 parts methylene blue. The solution was coated onto a polyester release liner at a thickness about 25 mils wet, and then dried at room temperature for 15 hours. The resulting dry film constituted the active

layer material. A second film was prepared by pressing HPC EF powder to a thickness of about 4 mils, using the heated Carver press.

The PVP/glycerin/methylene blue film and the HPC EF film were then arranged in alternating fashion to produce a laminate of six layers, three containing and three not containing the substance to be delivered. The PVP/glycerin/methylene blue layers served as an adhesive to bond the laminate composite, and served as a reservoir for the substance (methylene blue, in this illustrative example) to be released from each layer as it dissolved. The HPC EF layers provided for periods of time between releases, providing the pulsed release profile.

Example V

Delayed-Onset device

A delayed-onset device was made by first blending hydroxypropyl cellulose (HPC LF) and sorbitan monostearate (SPAN 60) as dry powders in a 1:1 ratio by weight. This blend was pressed using a heated Carver press at

200 °F to a thickness of 15 mils. The resulting polymer film was flexible having a waxy, hydrophobic surface.

An adhesive film was made by blending the following components:

HPC MF	1.0 gram
Kollidon PVP (K90)	2.0 grams
Glycerin	2.0 grams

After blending at room temperature, the resulting mixture was pressed in a heated Carver press at 200 °F to a thickness of 10 mils. This adhesive layer was used to adhere the HPC LF:SPAN 60 film to the top layer of the 25 min. breath disc described above in Example II.

The multilayer disc was tested over-night by adhering the disc to the upper palate just prior to going to sleep for the night. There was no noticeable mint flavor initially and during the several minutes thereafter before actually falling asleep. Approximately 5.5 hours later, however, the

disc released a burst of peppermint oil into the mouth strong enough to stimulate and awaken the wearer.

Device for Controlled Release of Substance within a Mucosa-Lined Body Cavity

Any of a variety of devices, in any configuration and for any intended use when emplaced within a body cavity of a subject, are within the scope of the claims. The invention is illustrated below by way of example only; the examples are not intended as limiting the scope of applicants' contribution to the art, and other types and arrangements of devices are within the scope of the invention.

Example VI

Laminated Composite Device for Delivery of Antimicrobial

By way of example of a device according to the invention that can be affixed to a mucosal surface of a body cavity to provide delivery of an active substance into the body cavity, Fig. 12 shows generally at **70** a device having a basal water-soluble pressure-sensitive adhesive layer **72**, and an overlying polymer layer **74** containing the active substance **78**. The device is shown removably affixed by the adhesive surface to a release liner **76**.

The adhesive layer can be constructed as follows. An HPC polymer is thoroughly mixed with a poly vinylpyrrolidone ("PVP") polymer, with glycerol as a plasticizer, with a food colorant, and with a preservative (BHA), and the resulting mixture is formed and pressed to a thickness of 5 mils. For this particular example, the components were mixed in the following proportions.

PVP (K90)	47.0 %
Glycerin	37.0
Klucel HPC GF	16.0
FD & C #40	0.024
BHA	0.0020

This resulting adhesive film was then laminated to the active containing film, described below, to form a bilaminate composite 30 mils thick. Disks having diameter 1/2 inch were then die cut from the bilaminate composite.

Disks formed as described above, 1/2 inch in diameter and 30 mils thick have an active substance-containing layer weighing approximately 100 milligrams.

The active containing layer can be constructed as follows. Using 85 grams of ethyl alcohol as the solvent, 13.5 grams of hydrohypropyl cellulose (HPC EF) was dissolved with stirring with 1.5 g CPC. The mixture was blended until uniform, at which time the thickened solution was cast as a film onto a release liner and left in a hood overnight to allow the solvent to evaporate, forming a dried film. The dried film was pressed using a heated Carver press to form an active containing layer of 25 mils thickness.

The tack and work of adhesion of the adhesive surface of the device as described in this example, as an indication of its adhesive properties, was measured for three samples as follows.

Sample 1 peak: -0.561 kg; area:-0.0177 kg

Sample 2 peak: -0.420 kg; area:-0.0097 kg

Sample 3 peak: -1.306 kg; area:-0.0352 kg

Example VII

Protective Barrier Device

Additionally by way of example of a device according to the invention that can be affixed to a mucosal surface of a body cavity to provide a protective barrier for the underlying mucosal surface, Fig. 13 shows generally at **80** a device having a basal water-soluble pressure-

sensitive adhesive layer **82**, and an overlying protective layer **84** constructed of a relatively abrasion-resistant water soluble polymer. The device is shown removably affixed by the adhesive surface to a release liner **86**.

In this example, the adhesive layer can have the composition, and can be constructed, as described generally above and particularly, for example, as described for the adhesive layer of Example VI.

The overlying protective layer can be constructed, for example, of a water soluble polymer as would be suitable for an active containing layer for delivery into the body cavity; and the protective layer can be constructed as described generally and particularly above. Particularly suitable polymers include for example HPC HF, polyvinyl alcohol ("PVA"), and hydroxymethyl cellulose.

A device made according to this example can be used, for example, as a temporary covering for an area of injury to the mucosal surface, such as an area of cheek of lip that has been abraded or cut. Or, the device can provide an abrasion preventive for areas of mouth tissue that are subject to abrasion by, for example, orthodontural devices.

Long-Lasting Mucoadhesive Device for Temporary Relief of Sore Throat and Cough

1. Construction of the device

Preparation of a mucoadhesive disc for containing a sore throat medication.

A medication-containing mucoadhesive laminated disc according to the invention can be made by forming and then laminating an adhesive film and an active substance-containing polymer film generally as follows.

a. The adhesive layer. A water-soluble adhesive layer can be formed from an adhesive polymer film, according to the following general protocol. First, the polymer (or polymers) and the plasticizer are thoroughly mixed, using where necessary a suitable solvent such as ethyl alcohol. Where a solvent is used, the resulting mixture is then coated on a release liner, and the solvent is allowed to evaporate to produce a dry film.

Dry film samples are then collected and pressed to the desired final film thickness. Where no solvent is used, the mixture can be pressed to a film of the desired thickness.

b. The active substance-containing layer. First, the polymers and one or more desired active agents and one or more desired flavorants are dissolved, for example by stirring, in an appropriate solvent. Then the resulting thickened solution is formed into a thin (wet) film, for example by casting onto a release liner, and then the solvent is permitted to evaporate to a dry film. Then the dry film is pressed to a desired thickness and is affixed, for example by pressing, onto an adhesive layer prepared as described above.

Hydroxypropyl cellulose (HPC) can be a particularly suitable polymer for construction of the active-containing layer. HPC dissolves completely in aqueous fluids such as the fluids of the oral cavity, and within a selected range of molecular weights, HPC dissolves (or disperses) in the oral cavity sufficiently slowly to provide substantially continuous delivery of the active substance over an extended period. HPC is flexible, so that it conforms well to irregular curved surfaces of the oral cavity; HPC is not tacky when moistened, and has a pleasant texture in the mouth. It is thus comfortable and unobtrusive for the user. HPC blends well with a variety of active substances.

Glycerol, which may be added as a plasticizer in the active-containing layer, may additionally (or alternatively) act to inhibit crystallization of some active substances that might otherwise occur at the loading concentrations employed (for example, menthol).

c. Laminated devices are then cut from the laminated film by, for example, die-cutting, to the desired size and shape. Typically, circular or oval shapes may be preferred. The devices can be stored on a release liner affixed to the adhesive surface, and removed from the liner as needed by the user.

A laminated device according to the invention may be bilaminate, having an adhesive layer and an active-containing layer, as shown for example in transverse sectional view in Fig. 8. Or, the device may be trilaminate, having a third water soluble layer, poorly permeable to the active substance, interposed between the adhesive layer and the active-containing layer, as shown for example in transverse sectional view in Fig 9. This layer may be made of a material such as for example polvinyl acetate ("PVAc") or ethyl cellulose, or such, for example, one of the Eudragit family of polymethacrylic copolymers commercially available from Rohm (*e.g.*, Eudragit S100, L100, E100, L100-55). The Eudragit polymethacrylic copolymers are characterized by being variously soluble at various pH; Eudragit S100 has a suitably low solubility at the typical pH of the normal human saliva. The interposed third layer may where desired be made more flexible by addition of a plasticiser such as, for example, glycerine, in amount up to, for example, about 20 %.

Referring now to Fig. 8, a bilaminate device **50** includes a polymer layer **52** containing the active substance **54**, laminated onto an adhesive layer **56**. The device is shown removably affixed to a release liner **58**.

Referring to Fig. 9, a trilaminate device **60** includes a third polymer layer **72**, poorly permeable to the active substance, laminated between polymer layer **62** containing the active substance **64**, laminated onto an adhesive layer **66**. The device is shown removably affixed to a release liner **68**.

2. Use of the device

As the need for relief of sore throat or cough arises, the user simply peels a laminated device away from the release liner, and affixes it to a surface within the oral cavity. It can be preferred to affix the device to the mucosal surface at the roof of the mouth, as that provides for direct flow of the active substance toward the rear of the mouth and the throat.

The following examples, are intended for illustration only, and are not intended to limit the scope of the invention.

Example VIII

Disc for Delivery of Cineole

The active containing layer was constructed as follows. Using 80 grams of ethyl alcohol as the solvent, the following materials were dissolved with stirring in order of appearance:

Glycerin	1.0 grams
Cineole	1.0 grams
Aspartame	0.3 grams
Menthol	1.7 grams
HPC Klucel LF	16 grams

The mixture was blended until uniform, at which time the thickened solution was coated to a thickness of 50 mils wet onto a release liner and left in a hood overnight to allow the solvent to evaporate, forming a dried film. The dried film was pressed using a Carver press under 20,000 p.s.i. at 200 °F for 1 - 2 min., to form an active containing layer of 25 mils thickness.

The adhesive layer was constructed as follows. An HPC polymer was thoroughly mixed with a poly vinylpyrrolidone ("PVP") polymer, with glycerol as a plasticizer, with a food colorant, and with a preservative (BHA), and the resulting mixture was formed and pressed to a thickness of 5 mils. For this particular example, the components were mixed in the following proportions.

PVP (K90)	47.0 %
Glycerin	37.0
Klucel HPC GF	16.0
FD & C #40	0.024
BHA	0.0020

This resulting adhesive film was then laminated to the active containing film, described above, to form a bilaminate composite 30 mils thick. Disks having diameter 1/2 inch were then die cut from the bilaminate composite.

Disks formed as described above, 1/2 inch in diameter and 30 mils thick have an active substance-containing layer weighing approximately 100 milligrams. Such a layer (and the disc) therefore contains 8.5 milligrams of menthol and 5 milligrams of cineole.

Example IX

Disc for Delivery of Dyclonine HCl

The active containing layer was formed as follows. Using 80 grams of ethyl alcohol as the solvent, the following materials were dissolved with stirring in order of appearance:

Glycerin	2.0 grams
Dyclonine HCl	0.6 grams
Menthol	1.0 grams
Aspartame	0.3 grams
HPC Klucel LF	16.1 grams

The mixture was blended until uniform, at which time the thickened solution was coated to a thickness of 50 mils wet onto a release liner and left in the hood overnight to allow the solvent to evaporate, forming a dried film.

The dried film was pressed using a Carver press under 20,000 p.s.i. at 200 °F for 1 - 2 min., to 25 mils thickness. This pressed film was then laminated to an adhesive film, 5 mils thick, made as described in Example 1, to form a bilaminate composite. Disks having diameter 1/2 inch were then die cut from the bilaminate composite.

Disks formed as described above, 1/2 inch in diameter and 30 mils thick have an active substance-containing layer weighing approximately 100 milligrams. Such a layer (and the disc) therefore contains 5 mg of menthol and 3 mg of Dyclonine HCl.

Example X

Comparison of release of Dyclonine HCl from a mucoadhesive disc and from a Sucrets® lozenge: disc affixed to glass.

The release profile of Dyclonine HCl into water from a prototype mucoadhesive disc according to the invention and from Sucrets® lozenge were compared as follows.

A Sucrets® lozenge containing 3.0 mg Dyclonine HCl was placed in a Pyrex® flask. A laminated disc made as described in Example 2 above, and containing 3.0 mg Dyclonine HCl, was removed from the release liner and affixed to the inner surface of a second Pyrex® flask by pressing the adhesive surface onto the flask wall. 100 ml deionized water at 25 °C were added to the flasks and the contents of the flasks were stirred priodically.

Thereafter sample aliquots of the aqueous phase were removed from each flask at intervals, and analyzed using UV spectroscopy to determine the amount of Dyclonine HCl released.

The resulting release profiles for both the prototype mucoadhesive disc and the Sucrets lozenge are shown in Fig. 10. Fig. 10 shows the cumulative release of Dyclonine HCl into the water. Although both dosage forms initially contained equivalent amounts of Dyclonine HCl (3.0 mg), the disc gives an appreciably extended and more uniform delivery of the Dyclonine HCl.

Example XI

Release of Dyclonine HCl from a mucoadhesive disc into a mucous surface to which the disc is affixed.

In this Example, a prototype mucoadhesive disc containing Dyclonine HCl according to the invention was affixed to mucous tissue and the quantity of Dyclonine HCl released into the mucous tissue over an extended time was determined as follows.

A laminated disc was made generally as described in Example IX above, except that it was die cut to 3/8 inch diameter so that it contained 1.11 mg Dyclonine HCl. The disc was removed from the release liner and affixed to a piece of palate tissue (porcine palate) by pressing the adhesive

surface of the disc onto a surface of the palate tissue. Then the palate tissue with the disc affixed was immersed in deionized water at 25 °C in a flask the contents of the flask were stirred prior to removing the sample.

After 2 hours, the disc was removed from the palate tissue and the disc was returned to the flask and allowed to dissolve completely (with stirring). Then the amount of Dyclonine HCl in the water was measured. The Dyclonine HCl not accounted for was taken to be an amount that had been delivered to the palate tissue. That is, the difference between the amount of Dyclonine HCl initially present in the disc and the amount that was released into the water is the amount released into the mucous tissue. The results are shown in Table I.

Table I

Dyclonine HCl initially in the disc	1.11 mg
Dyclonine HCl released to water	1.04 mg
Dyclonine HCl not accounted for	.07 mg

As Table I shows, after the disc had been affixed to the mucous tissue and suspended in water for 2 hours, only 0.07 mg of Dyclonine HCl (5.8 % of the total amount initially contained in the disc) was unaccounted for in the water, and presumably had diffused into the palate tissue.

Example XII

Inhibition of release of Dyclonine HCl from a trilaminate mucoadhesive disc into a mucous surface to which the disc is affixed.

In this Example, a prototype mucoadhesive disc containing Dyclonine HCl according to the invention was constructed with a third layer interposed between the adhesive layer and the active substance-containing layer, for limiting the rate of movement of the active substance into and through the adhesive layer. The trilaminate disc was affixed to mucous tissue and the quantity of Dyclonine HCl released into the mucous tissue over an extended time was determined as described in Example XI.

A laminated disc was made generally as described in Example IX above, except that a thin film (5 mil thickness) of a polymethacrylic copolymer (Eudragit S100) was laminated between the adhesive later and the active substance-containing layer, and the disc was die cut to 3/8 inch diameter so that it contained 1.02 mg Dyclonine HCl. The trilaminate disc was removed from the release liner and affixed to porcine palate tissue, and the release to the palate tissue was determined as described in Example XI. The results are shown in Table II.

Table II

Dyclonine HCl initially in the disc	1.02 mg
Dyclonine HCl released to water	0.98 mg
Dyclonine HCl not accounted for	.04 mg

As Table II shows, after the disc had been affixed to the mucous tissue and suspended in water for 2 hours, only 0.04 mg of Dyclonine HCl (3.9 % of the total amount initially contained in the disc) was unaccounted for in the water, and presumably had diffused into the palate tissue. The interposition of the limiting layer between the Dyclonine HCl-containing layer and the adhesive layer reduced the amount of Dyclonine HCl diffused into the palate tissue from 5.8% to 3.9%.

Example XIII

Comparison of release of Dyclonine HCl through a semipermeable membrane from a trilaminate mucoadhesive disc and from a bilaminate mucoadhesive disc to which the disc is affixed.

In this Example, bilaminate and trilaminate mucoadhesive discs containing Dyclonine HCl according to the invention were constructed generally as described in examples XI and XII. The discs were affixed to a semipermeable membrane, and the quantity of Dyclonine HCl released through the membrane over an extended time was determined as described in Example 4. Briefly, the disc (1/2 inch diameter) was placed in a horizontal Franz cell (7.5 ml capacity) separated by a mesh barrier (70 μm Teflon), by

affixing an adhesive surface of the disc onto the mesh barrier. Both sides of the cell were filled with nano-filtered water; water in the "donor" side of the cell bathed the surface of the active layer, and water in the "receiver" side of the cell bathed the mesh barrier. The results are shown in Table III.

Table III

	Sample	Dyclonine Release
Bilaminate disc	1	9.65 %
Bilaminate disc	2	10.91 %
Bilaminate disc	3	8.82 %
	Mean	9.79 ± 1.05 %
Trilaminate disc	1	1.45 %
Trilaminate disc	2	1.43 %
Trilaminate disc	3	0.30 %
	Mean, Samples 1 & 2	1.44 ± 0.014 %

As Table III shows, the total quantity of Dyclonine passing from the active-containing layer into and through the adhesive layer and then through the semipermeable membrane was greatly reduced by interposition of the occlusive layer between the adhesive layer and the active-containing layer. Particularly, in three experiments for each disc type (bilaminate and trilaminate) shows an average decrease in the release of Dyclonine HCl into the receiver side, from 9.79 ± 1.05 % to 1.44 ± 0.014 %, after a period of two hours.

Example XIV

Release of benzocaine into distilled water from a mucoadhesive disc according to the invention: effect of different molecular weight of polymer in the benzocaine-containing layer.

In this Example, bilaminate mucoadhesive discs containing benzocaine were constructed generally as described in Example IX, substituting benzocaine for Dyclonine. Discs were made using HPC both at the same molecular weight as described in Example 2 (80 k), and at a higher molecular weight (300 k), and the release into distilled water was tested as described in Example X. The results are shown in Fig. 11. These results show a decrease in release rate of benzocaine with increasing molecular weight of HPC in the active-containing layer.

Example XV

Transport of Dyclonine HCl and of benzocaine through pig mucosa.

In this example, bilaminate mucoadhesive discs, containing as an active substance benzocaine or Dyclonine HCl, were affixed to porcine buccal mucosa and mounted on Franz diffusion cells as described in Example XIII. Average amounts of active substance was measured using HPLC, and percents were expressed as a percent of the total initially in the disc.

Particularly, the donor side of the cell was filled with pH 6 buffer and the receiver side was filled with phosphate buffered saline ("PBS"). Samples were taken from the receiver side every thirty minutes for three hours, and the samples were analyzed by HPLC. The average amount and the average percent of active substance appearing in the receiver side after three hours are shown in Table IV.

Table IV

	Average Amount Delivered ($\mu g/cm^2$)	Average % Transported
15 % Benzocaine	284.63	3.29
15 % Dyclonine HCl	282.77	3.94

The average amount delivered reflects the cumulative amount of drug transported through the mucosa over the three hour period. The average percent delivered represents the cumulative amount of drug transported, in terms of percent of drug contained in the device at the outset. The data show that very low values of benzocaine or Dyclonine HCl were transported through the tissue, and demonstrate that such devices, placed within a mucosa-lined body cavity, such as the oral cavity, can be expected to deliver relatively little of such active substances through the mucosa during the period that the active substance is administered into the body cavity itself.

Example XVI

Transport of Dyclonine HCl and of benzocaine through human stratum corneum.

In this example, bilaminate mucoadhesive discs, containing as an active substance benzocaine or Dyclonine HCl, were affixed to human stratum corneum and mounted on Franz diffusion cells. The donor side of the cell was filled with pH 6 buffer and the receiver side was filled with PBS. Samples were taken from the receiver side and analyzed using HPLC, and the average amount and percentage of active substance appearing in the receiver cell were determined. The average amount and the average percent of active substance appearing in the receiver side are shown in Table V.

For both benzocaine and Dyclonine HCl the amount of active substance delivered through the human stratum corneum (Example XVI) is lower than the amount of active substance delivered through the pig buccal mucosa (Example XV). For administration of Dyclonine HCl or benzocaine

into the oral cavity of a human subject, so that the active substance is carried by the saliva to the irritated tissues of the mouth and throat, it is desirable to limit the amount of active substance delivered through the oral mucosal surface to which the device is affixed. Preferably a device for delivery of active substances for relief of cough and sore throat is affixed to the palate. The transfer coefficient for human palate tissue is lower than that for pig buccal mucosa and higher than that for human stratum corneum, and Examples XV and XVI thus provide an approximate range within which the extent to which delivery of active substances across the underlying human palate mucosa can be expected to fall. For a device according to the invention, affixed to the palate, the great majority of benzocaine or Dyclonine HCl can be expected to be delivered into the oral cavity.

Table V

	Average Amount Delivered ($\mu g/cm^2$)	Average % Transported
15 % Benzocaine	255.56	2.42
15 % Dyclonine HCl	14.60	0.18

Interposition of a third layer, relatively impermeable to the active agent, between the active agent-containing layer and the adhesive layer, as described for example in Example XII, can reduce further the quantity of active agent passing through the mucosa. As the results in Examples XV and XVI show, however, a bilaminate system can be suitable for delivery.

Long-Lasting Mucoadhesive Device for Administration of Breath-Freshening Agent

Generally, the breath freshening device according to the invention is constructed as a laminated composite including a basal adhesive layer constructed of a water soluble pressure sensitive mucoadhesive composition; and an odorant containing layer constructed of a water soluble polymer

mixed with the odorant. Optionally the device may include a third layer, interposed between the adhesive layer and the odorant containing layer, constructed of a water soluble polymer that is substantially impermeable or is poorly permeable to the constituents of the odorant.

The device may be made by forming the respective layers as films and then laminating the films, and finally cutting (as, for example, by die cutting) the device from the laminate.

The films may be made from polymer mixtures by any of a variety of techniques known in the polymer film-forming art, including casting, calendaring, coating, and extrusion. Batch processing techniques may be employed, but for large scale production, continuous processing can be preferred. Die extrusion through a slit is a particularly suitable continuous processing technique for making the films for use in the devices according to the invention.

Lamination may be carried out by contacting the films and applying pressure. Laminated films may be made in small quantities by use of a press, but for continuous processing the films can be pressed together using one or more rollers. Heat may be applied to the films as they are brought together, for example by heating the press or by heating the roller or rollers.

Referring again now to Fig. 8, a bilaminate device configuration according to the invention suitable for a breath freshening device is shown generally at **50**. The device includes a basal adhesive layer **56** constructed of a water soluble pressure sensitive mucoadhesive composition, and an upper odorant containing layer **52** constructed of a water soluble polymer mixed with the odorant **54**.

A trilaminate device configuration suitable for a breath freshening device is shown generally at **60** in Fig. 9. The trilaminate device includes a basal adhesive layer **56** constructed of a water soluble pressure sensitive mucoadhesive composition, and an upper odorant containing layer **52** constructed of a water soluble polymer mixed with the odorant **54**, generally

as in the bilaminate device shown in Fig. 8. The trilaminate device additionally includes a third layer **62**, interposed between layer **52** and layer **56**, constructed of a water soluble polymer that is substantially impermeable or poorly permeable to the constituents of the odorant.

The devices as shown in the Figs. are provided with a release liner **58**, which is peeled away from the device just prior to use.

The content of the layers is described in greater detail below.

1. The adhesive layer.

Suitable GRAS certified polymers for use in the water soluble pressure sensitive mucoadhesives include poly(vinyl pyrrolidone) ("PVP"), poly(vinyl alcohol) ("PVA"), hydroxy propyl cellulose ("HPC"), poly(ethylene oxide) ("PEO"), poly(acrylic acid) ("PAA"), polyacrylates such as Carbopol 934, starch and starch derivatives, polysaccharides, sodium carboxymethyl cellulose ("Na-CMC"), xanthan gum, karaya gum, and gelatin, among others. Suitable plasticizers include, for example and particularly for oral-mucosal contact and other use in the oral cavity, glycerin, sorbitol, any of the glycols, polysorbate 80, triethyl citrate, acetyl triethyl citrate, and tributyl citrate.

In particular embodiments the water soluble pressure sensitive mucoadhesive includes as a polymer PVP (about 30 - 60 weight %), HPC (about 10 - 30 weight %); and glycerin as a plasticizer (about 10 - 60 weight %). In these formulations, the molecular weight of the PVP is in the range about 30,000 - 1,000,000; and the molecular weight of the HPC is in the range about 60,000 - 1,000,000. Such compositions adhere quickly on contact and without moistening to oral mucosal surfaces and to oral cavity prostheses or other devices of the poly(methyl methacrylate) ("PMMA") type, and continue to adhere well to such surfaces for extended times in the milieu of the oral cavity.

The water soluble pressure sensitive adhesive layer may take the form of a film which preferably is about 5-10 mils thick.

Preferably the adhesive layer additionally includes a preservative, such as for example BHA or BHT, in a suitable small quantity. The adhesive additionally may include a certified colorant.

2. The odorant-containing layer.

Suitable GRAS certified polymers for use in the odorant containing layer include, particularly, hydroxypropyl cellulose ("HPC").

The term "odorant", as used herein, refers to a substance or combination of substances which, when present in the fluids of a subject's oral cavity, impart a pleasing smell to the person's exhalant breath. A breath freshening substance may work in part by addition of a desirable odor to the breath, and in part as a "reodorant", that is, by masking an unpleasant odor in the subject's breath, and the term "odorant" herein includes such reodorant effects.

As is well recognized in the flavorist's art, the appreciation of flavor is a complex response, principally, to the senses of aroma and taste. *See generally, e.g.,* G. Reiniccius, ed. (1994), *Source Book of Flavors*, 2d Ed., Chapman & Hall (herein, the "*Source Book of Flavors*"). The various tastes (sweet, salt, sour, bitter) are due to nonvolatile components of the flavor, while the aroma or odor is due to volatile components. The chemical makeup of a flavor, and particularly of the volatile components of a flavor, may be exceedingly complex, with a number of volatile components contributing significantly to the distinctive aroma. On the other hand, certain chemical compounds are by themselves when smelled reminiscent of a particular flavor, even where the flavor that is recalled is in fact complex. Such character impact compounds include, for example, Menthol (having the character impact of peppermint); L-Carvone (spearmint); Methyl salicylate (wintergreen); and Citral (lemon).

A straightforward way to provide desired odorant in the odorant-containing layer of a breath freshening device according to the invention is to add to the polymer of the layer an essential oil (*i.e.,* a volatile oil) of a plant material. The *Source Book of Flavors* describes essential oils that are

in common use in the flavoring industry, including descriptions of methods for their industrial production and an account of their chemistry.

Any of a variety of breath freshening odorants may be delivered to the oral cavity by adding into the polymer of the odorant-containing layer a flavoring that includes the odorant. In at least some cultures, mint-like odorants are acceptable and even desireable on the breath, and accordingly the odorant containing layer of a suitable breath freshening device can include a mint flavoring, as described more fully below.

Preferably the odorant containing layer additionally includes a preservative, such as for example BHA or BHT in a suitable small quantity. Optionally the odorant containing layer additionally includes a sweetener, most preferably a non-sugar sweetener, such as aspartame in a suitable small quantity.

3. Mint odorants.

Mint odorants can be provided by essential oils derived by extraction and distillation from leaves and/or flowering parts of any of various plants. The composition of such distillates depends, among other things, upon the species and variety of plant, as well as its geographical origin, and upon the method of extraction and degree of distillation. A variety of mint flavorings are described, for example in the *Source Book of Flavors*. They include, particularly for example, oil of peppermint, the chief aromatic constituents of which are menthol, menthone, and menthyl acetate; oil of spearmint, the chief aromatic constituent of which is L-Carvone; and oil of wintergreen, the chief aromatic constituent of which is Methyl salicylate.

4. Device fabrication.

As pointed out generally above, the layers can be produced using techniques known in the art of polymer film fabrication, by conventional batch process or by continuous process, as for example by conventional die extrusion through a slit. Typically, for example, batch processing can be carried out as follows. The components making up each layer (*e.g.*, the

adhesive layer, or the odorant containing layer, or an intermediate layer) are blended together either with a suitable solvent to aid in mixing or, as may be more preferable, without a solvent. The blending may be carried out at an elevated temperature (particularly where no solvent is employed), to aid in homogeneous mixing of the components. The blended components of each layer are thereafter pressed to a film having the desired final layer thickness using a heated Carver press. The resulting films are then laminated, for example by contacting them and applying pressure.

Generally, for example, a conventional continuous die extrusion process entails feeding the components of the layer to an extruder, such as a twin screw extruder. The extruder melt blends the components of the layer and then forces the blended mixture continuously through a slit whose thickness is selected to provide the desired thickness in the resulting film. The individual films may be rolled for temporary storage before lamination, or the lamination may be carried out immediately following extrusion. The films are containuously laminated by bringing the films into contact and pressing them together over a roller or between rollers, which may as appropriate be heated to facilitate the lamination process.

Individual devices are then cut from the completed laminate, for example by punching or die cutting, and stored for use.

The examples that follow are presented by way of illustration only, and are not meant as limiting the invention.

Example XVII

Construction of Device for Delivery of Peppermint

This example illustrates the construction of a device for delivery of a refined (reduced) oil of peppermint. The oil of peppermint used in this example is a "Reduced Oil of Peppermint FCC/NF "Rose Mitcham" ", which is commercially available from the A.M. Todd Company of Kalamazoo, MI. It contains the following mint flavor components:

menthofuran (GLC)	02.6 %
menthol	57.0
menthone	24.8
menthyl acetate	07.4

As provided from the commercial source, this reduced oil of peppermint has a specific gravity .903, an optical rotation -28.2, and a refractive index 1.4600. It is soluble in three volumes of 70 % ethanol.

1. Construction of the odorant containing layer.

In this example, the odorant containing layer is constructed by thoroughly mixing the peppermint oil (as described above), a non-sugar sweetener (Aspartame), and a preservative (BHA) with a hydroxypropyl cellulose ("HPC") polymer, and then extruding the odorant containing polymer mixture through a slit to form a film. Preferably a twin screw extruder is employed, and the components are continuously fed into the extruder, in which the blending is effected. In this particular example, the odorant containing layer has these ingredients in the following proportions.

Klucel HPC GF	83.5 %
Peppermint oil	15.0
Aspartame	1.50
BHA	0.0083

2. Construction of the adhesive layer.

In this example, the adhesive layer is constructed by thoroughly mixing an HPC polymer with a poly vinylpyrrolidone ("PVP") polymer, with glycerol as a plasticizer, with a food colorant, and with a preservative (BHA), and then extruding the adhesive polymer mixture through a slit to form a film. In this particular example, the adhesive layer has these ingredients in the following proportions.

PVP (K90)	47.0 %
Glycerin	37.0
Klucel HPC GF	16.0
FD & C #40	0.024
BHA	0.0020

The formed adhesive film and odorant containing film are then laminated by passing the films together between rollers under pressure, and the individual devices are die cut from the resulting laminated composite.

Example XVIII

Tack and Adhesion Properties of the Adhesive Layer

The properties of tack and adhesion of the water soluble pressure sensitive mucoadhesive employed in the breath freshening device of the invention were tested as follows.

An adhesive film was made generally as described in Example XVII.

Tack and work of adhesion were measured using a Texture Technologies TXA.XT2 Texture Analyzer in which a PMMA probe was used in place of the usual SS probe. A 5 mil thick adhesive film made as described in Example XVII was tested under the following conditions.

Probe speed (penetration):	1.0 mm/sec
Penetration depth:	0.10 mm
Dwell time:	10 sec
Probe speed (withdrawal)	5.0 mm/sec
Probe diameter:	0.80 cm

All measurements were made at room tepmerature (20 - 25 °C).

The resulting trace of the force during withdrawal versus time allowed for a determination for each sample of both the tack (the peak maximum, in Kg) as well as the work of adhesion (area under the peak curve, in Kg-sec). Films were tested dry as well as after moistening by

spraying the dry film surface with a fine mist of distilled water, followed by a resting time of 60 seconds to allow for hydration of the sample.

In this example, the above test protocol was applied to films according to the invention (indicated as "BFD" in the Figs.), and to constructed with the following compositions.

"279-190": 60 % PEO 301; 30 % HPC MF; 5 % PE; 3 % PG; 2 % PEG 400 (described in Schiraldi U.S. 4,731,243).

"279-191": 55.3 % NaPAA; 37.5 % HPC HF; 6.3 % Glycerin (described in Chang U.S. 4,373,036).

"310-30B#2": 40 % HPC HF; 35.5 % PVP 90 F; 20 % HPC LF; 2 % Mentha Oil; 2 % Menthol; 0.5 % Fennel Oil (described in Hisahige JP 63-209797).

"310-44" 44.5 % PVP 90 F; 30 % HPC LF; 10 % HPC HF; 10 % PEG 400; 2.5 % Menthol; 2.0 % Mentha Oil; 1.0 % Fennel Oil (described in Hisahige JP 63-209797).

The results are shown in Figs. 14 and 15. In these tests the adhesive film according to the invention is significantly more adhesive toward the PMMA probe in the dry state (*i.e.*, before moistening) than did four other formulations tested. Following moistening the adhesive film according to the invention was comparably adhesive or was more adhesive toward the PMMA probe than were the other tested formulations.

Example XIX

Flexibility of Odorant Containing Layer

As noted above, water soluble polymers such a hydroxypropyl cellulose that dissolve suitably slowly in the milieu of the oral cavity may not themselves be sufficiently flexible for use in an odorant containing layer in a device according to the invention. Conventionally, the layer would be rendered more flexible by addition of a suitable plasticizer such as glycerol. We have discovered that the essential oils of Spearmint, or Peppermint, and

of Wintergreen can provide substantial and sufficient plasticizing effect when mixed with HPC in quantities suitable for extended delivery of mint odorant to the oral cavity at breath freshening rates.

In this example, the elastic moduli (as a measure of flexibility) are compared for film preparations of HPC containing no additional components, and of film preparations containing 15 weight % of oil of peppermint, oil of spearmint, oil of wintergreen, and oil of lemon. This conventional measurement entails measuring the tensile force per unit cross sectional area (stress) of a sample of the film during elongation of the sample at a fixed rate (strain). The elastic modulus is derived from the stress/strain curve. In this example, the test was carried out on bone-shaped film samples 5 mils thick and 0.25 inch wide, gage length 1.0 inch, at an elongation rate of 0.2 inch/min. All samples were tested at room temperature (20 - 25 °C).

The results are shown in Fig. 16. As the Fig. shows, addition of any of the mint odorants to the HPC composition results in a substantially and sufficiently flexible film, while addition of lemon oil does not sufficiently lower the elastic modulus of the film. Thus, where a mint odorant is used, no additional plasticizer is required in the odorant containing layer.

Example XX

Delivery of Peppermint over Extended Times

In this example, the capacity for delivering a breath-freshening substance into an aqueous medium was compared in devices according to the invention and in a "breath mint" that is commercially marketed under the name "Certs®". A flavor containing film was constructed, generally as described in Example XVII. Portions of the film 1/2 inch in diameter and 25 mils thick, each containing 8.6 mg menthol were immersed in distilled water, and breath mint tablets each containing 4.3 mg menthol were immersed in distilled water in separate flasks, and the flasks were continuously shaken. Samples were withdrawn from the flasks after elapsed

times of 15 min., 30 min., 45 min., 60 min., and 120 min., and the quantity of menthol was analyzed by gas chromatography.

The results are shown in Fig. 17. On average, the breath freshening device of the invention had by the first (fifteen minute) sample interval released about 0.7 mg menthol, and thereafter the device delivered menthol at a continuous steady rate throughout the sampling period; at the two hour sampling interval, approximately 2.0 mg of the original 8.6 mg of menthol had been released from the device, and rate of delivery was continuing at slightly less than 0.25 mg per hour. By contrast, each breath mint had on average by the first sampling interval released nearly half its total quantity of menthol, and had nearly exhausted their delivery capacity at the second (thirty minute) sampling interval.

In a person's mouth, the saliva is swallowed more or less continuously, and once a conventional breath mint has been completely dissolved, the breath freshening effect wanes quickly as the residual odorant is flushed away. As the example shows, the invention can provide for a sustained and steady supply of the breath freshening odorant to the saliva flow, resulting in an extended breath freshening effect.

Example XXI

Evaluation of Breath-Freshening Effect

In this example, the breath freshening effectiveness of devices according to the invention, constructed generally as described in Example XVII above, were informally evaluated by volunteers. The volunteers reported that the device was convenient to use, was non-obtrusive, did not materially interfere with speech, and left a pleasant taste and odor in the mouth.

Other Embodiments

Other embodiments are within the following claims.

For example, the water-soluble pressure-sensitive adhesives according to the invention can be used to affix transdermal devices to human skin.

Because the materials in the adhesive are GRAS certified, they can result in an adhesive product having very low skin irritation and reaction.

The water-soluble pressure-sensitive adhesives of the invention can act as a reservoir for diffusional delivery of a substance into the mucosa-lined body cavity (such as the oral cavity or gastrointestinal tract, or the vaginal cavity), or for delivery of a substance transmucosally through the area of adhesive contact. Preferably for such applications, the adhesive is provided in film form, and is loaded with a suitable quantity of the substance to be delivered. For use in transmucosal delivery, one surface of the adhesive film makes adhesive contact with the mucosal surface; preferably the other surface of the adhesive film is covered with a substance-occlusive backing layer made of a material that is poorly soluble in water or in the fluid secretions of the body cavity in which the film is used. Examples of substance-occlusive poorly soluble materials that are safe for oral use include poly(dimethyl siloxane), poly(tetrafluoro ethylene), cellulose acetate, and copolymers of neutral methacrylic acid esters with one or both of methacrylic acid and diethylaminoethyl methacrylate.

In a dental prosthesis adhesive film application, for example, the adhesive can be loaded with a flavoring or a mouth deodorant to act as a breath freshener, or with an antibacterial. Suitable flavorings, mouth deodorants, and antibacterials are known in the oral hygiene art. As the adhesive slowly dissolves, the agent is gradually released into the oral cavity.

Or, in a dental prosthesis adhesive film application, the adhesive can be loaded with a substance to be delivered transmucosally; in this configuration, the dental prosthesis works as an occlusive backing.

The water-soluble pressure-sensitive adhesives of the invention can be employed as an adhesive layer in a laminated device for diffusional delivery of an agent within a mucosa-lined body cavity. Such laminated devices can take any of a variety of forms, and may have just one layer in addition to

the adhesive (such as the substance-occlusive poorly soluble layer described above, for example), or many additional layers.

Water-soluble pressure-sensitive adhesive films according to the invention can be made by other processes than described above. Where a press is used to form the film, for example, different temperatures may be used, according to the particular polymer composition.

Alternatively, the molten polymer may be extruded through a slit die to form a film of the desired thickness; or it can be extruded or cast as a single film between release surfaces. In the latter case, the product can be cut to a shape appropriate to the particular application, and the release liners can be peeled away just prior to use.

Other embodiments are within the following claims, and variations on the embodiments shown by way of example above have been made and can be altered as may be desired. For example, with reference to Examples 1 and 2, aspartame can be left out and a flavor imparting a different taste or odor can be added instead. Also, the loading of actives dyclonine HCl, menthol, and cineole can be controlled by either varying the concentration or changing the thickness of the disc. Other active substances useful for relief of sore throat pain or cough can be delivered according to the invention.

Claims

1. A water-soluble pressure-sensitive adhesive comprising a water-soluble polymer and a water-soluble plasticizer, said polymer having a T(g) or a T(m) greater than about 25 °C and having a hydrophilicity greater than about 25 %, said plasticizer being miscible with said polymer at room temperature and being liquid at room temperature and having a boiling point higher than
80 °C.

2. The water-soluble pressure sensitive adhesive of claim 1 wherein said polymer has a T(g) or a T(m) greater than about 30 °C.

3. The water-soluble pressure-sensitive adhesive of claim 1, said polymer comprising poly(vinyl pyrrolidone) and said plasticizer comprising glycerol.

4. The water-soluble pressure-sensitive adhesive of claim 3, said polymer further comprising hydroxy propyl cellulose.

5. The water-soluble pressure-sensitive adhesive of claim 3, comprising 95 - 40 weight % poly(vinyl pyrrolidone), 0 - 50 weight % hydroxy propyl cellulose, and 11 - 60 weight % glycerol.

6. The water-soluble pressure-sensitive adhesive of claim 5, said glycerol being present in the range 30 - 50 weight %.

7. The water-soluble pressure-sensitive adhesive of claim 1, in film form.

8. A dental prosthesis adhesive, comprising the water-soluble pressure-sensitive adhesive film of claim 7, shaped to conform to a portion of the mucosal surface-contacting surface of the dental prosthesis.

9. A laminated device for the controlled release of a substance within a mucosa-lined body cavity, said device comprising:

a water-soluble adhesive layer; and

a water-soluble polymer layer;

wherein the substance is dissolved or dispersed in either or both of said adhesive or polymer layers.

10. The device of claim 9 wherein delivery of the substance is characterized by a delayed onset.

11. The device of claim 10 wherein the polymer layer is substantially impermeable to the substance and does not contain the substance.

12. The laminated device of claim 11, said polymer layer being insoluble in water that is below 40 °C.

13. The laminated device of claim 12, said polymer layer comprising hydroxypropyl cellulose and sorbitan monostearate.

14. The device of claim 13 wherein the substance is a breath reodorant.

15. The device of claim 9 wherein the adhesive layer comprises and an adhesive selected from the group consisting of a pressure-sensitive adhesive and a moistenable adhesive.

16. The device of claim 15 wherein the adhesive comprises a pressure-sensitive polymer adhesive having a T(g) or a T(m) greater than about 25 °C and having a hydrophilicity greater than about 25 %, said plasticizer being miscible with said polymer at room temperature and being liquid at room temperature and having a boiling point higher than 80 °C.

17. The device of claim 9 comprising one or more polymer layers and two or more substances to be delivered.

18. The device of claim 17 wherein the substances are delivered sequentially.

19. A laminated device for the controlled release of a substance within a mucosa-lined body cavity, said device comprising:

a water-soluble adhesive layer;

a first water-soluble polymer layer; and

a second water-soluble polymer layer;

wherein the substance is dissolved or dispersed in any or all of said adhesive or polymer layers.

20. The device of claim 19 wherein the adhesive layer and the second polymer layer contain the substance and wherein the first polymer layer is disposed between the adhesive layer and the second polymer layer, and wherein the device provides for pulsatile delivery of the substance.

21. The device of claim 20 wherein the pulsatile delivery is characterized by periods of no delivery of the substance.

22. The device of claim 19 further comprising a third polymer layer wherein the first and the third polymer layers contain the substance and wherein the first polymer layer is disposed between the adhesive layer and the second polymer layer and the second polymer layer is disposed between the first polymer layer and the third polymer layer and wherein the device provides for pulsatile delivery of the substance.

23. The device of claim 22 wherein the pulsatile delivery is characterized by periods of no delivery of the substance.

24. A laminated device for the controlled release of a substance within a mucosa-lined body cavity comprising the substance dissolved or dispersed in a water-soluble pressure-sensitive adhesive layer.

25. The device of claim 24 wherein the water-soluble adhesive layer comprises a pressure-sensitive polymer adhesive having a T(g) or a T(m) greater than about 25 °C and having a hydrophilicity greater than about 25 %, said plasticizer being miscible with said polymer at room temperature and being liquid at room temperature and having a boiling point higher than 80 °C.

26. A laminated composite device for delivering a substance into the oral cavity for relief of sore throat or cough, comprising a water soluble polymer film layer containing the active ingredient, and a water soluble pressure sensitive mucoadhesive layer.

27. The laminated composite of claim 26 wherein the active ingredient is a medicament for the relief of sore throat pain.

28. The laminated composite of claim 27 wherein the active ingredient is selected from the group consisting of benzocaine, lidocaine and dyclonine.

29. The laminated composite of claim 26 wherein the active ingredient is a medicament for the relief of cough.

30. The laminated composite of claim 29 wherein the active ingredient is selected from the group consisting of dextromethorphan HBR, noscpine, codeine phosphate, menthol.

31. The laminated composite of claim 27 additionally comprising a medicament for the relief of cough.

32. The laminated composite of claim 26 wherein the active-containing water soluble layer comprises a hydrophobic material that will not dissolve in water below 40°C and is hot water dispersible.

33. The laminated composite of claim 32 wherein the active-containingwater soluble layer is selected from the group of materials consisting of monoglycerides, triglycerides, waxes, fatty acids, fatty alcohols and mixtures thereof.

34. The laminated composite of claim 26 wherein the pressure sensitive adhesive is comprised of a water soluble polymer with a glass transition temperature above about 25°C and a hydrophilicity greater than about 25%, and a plasticizer that is liquid at room temperature and has a boiling point higher than about 80°C.

35. The laminated composite of claim 34 wherein the polymer is selected from the group consisting of poly(vinyl pyrrolidone), poly(vinyl alcohol), hydroxy propyl cellulose, poly(ethylene oxide), poly(acrylic acid), polyacrylates, starch and starch derivatives, polysaccharides, sodium carboxymethyl cellulose, xanthan gum, karaya gum, and gelatin or mixtures thereof.

36. The laminated composite of claim 34 wherein the plasticizer is selected from the group consisting of glycerin, sorbitol, glycol, polysorbate 80, triethyl citrate, acetyl triethyl citrate and tributyl citrate.

37. The laminated composite of claim 26 further including a third polymer layer interposed between the adhesive layer and the active-containing layer.

38. A method for administering a substance over an extended time period for relief of sore throat or cough, comprising dissolving or dispersing the substance in a laminated water soluble device having a water soluble pressure sensitive adhesive layer, and affixing the device onto a mucosal surface of the oral cavity.

39. The method of claim 38 wherein the substance is a medicament for the relief of sore throat pain.

40. The method of claim 39 wherein the medicament is selected from the group consisting of benzocaine, lidocaine and dyclonine.

41. The method of claim 38 wherein the substance is a medicament for the relief of cough.

42. The method of claim 41 wherein the medicament is selected from the group consisting of dextromethorphan HBR, noscpine, codeine phosphate.

43. The method of claim 42 additionally comprising a medicament for the relief of cough.

44. A device for emplacement within a mucosa-lined body cavity of a subject, said device including a portion made of a water-soluble pressure sensitive mucoadhesive composition, said water-soluble pressure sensitive adhesive portion having a surface that forms a basal pressure-sensitive adhesive surface of said device.

45. The device of claim 44, being a device for delivery of a substance to the subject.

46. The delivery device of claim 45, said device being constructed to deliver a substance into the body cavity in which the device is emplaced.

47. The delivery device of claim 45, said device being constructed to deliver a substance across a mucosal surface to which the basal pressure-sensitive adhesive surface of the device is affixed.

48. The device of claim 44, being a laminated device structure, wherein the water-soluble pressure sensitive portion comprises a basal layer of the device.

49. A laminated device for administering a mint aroma into the oral cavity over an extended time, said device including a basal layer comprising a water soluble pressure sensitive mucoadhesive polymer composition, and an upper layer comprising a water soluble polymer composition and a mint flavoring.

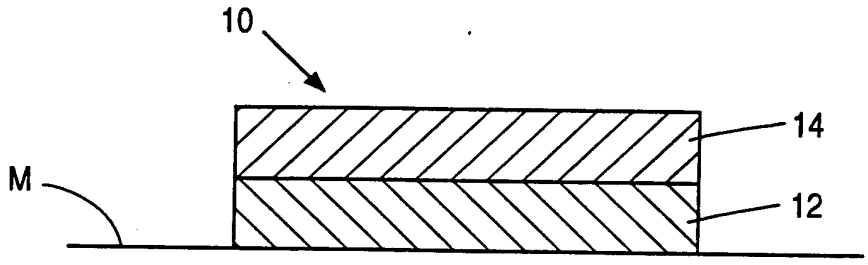

FIG. 1

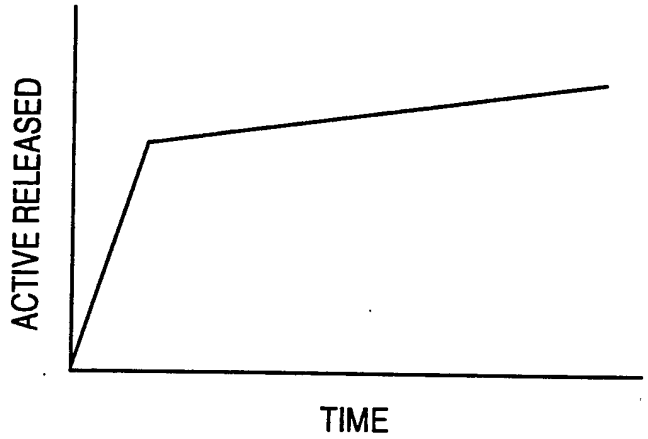

FIG. 5

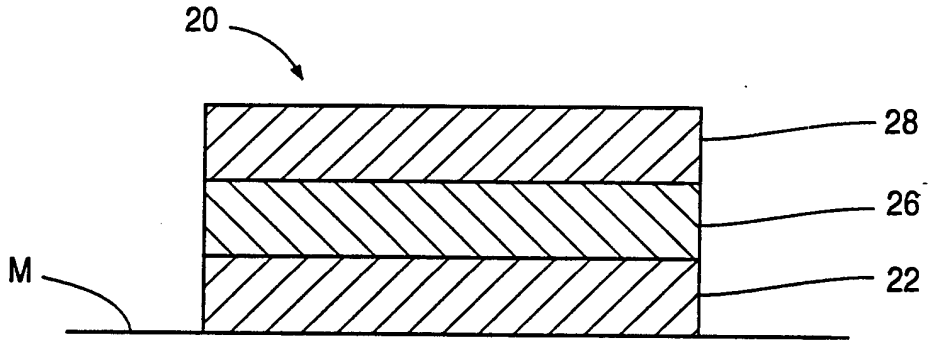

FIG. 2

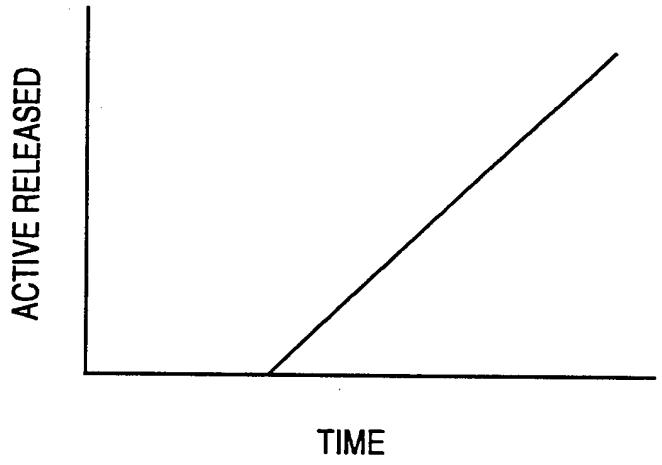

FIG. 6

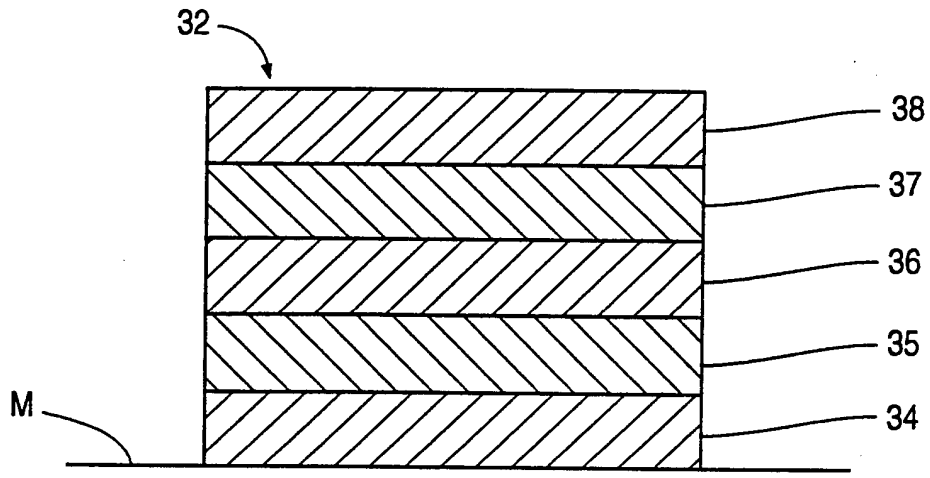

FIG. 3

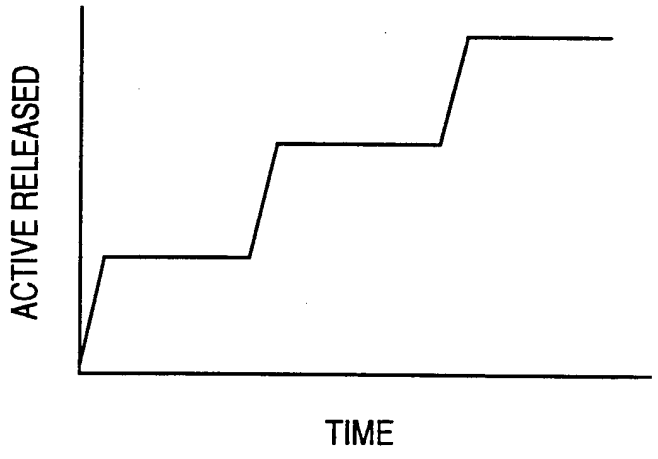

FIG. 7

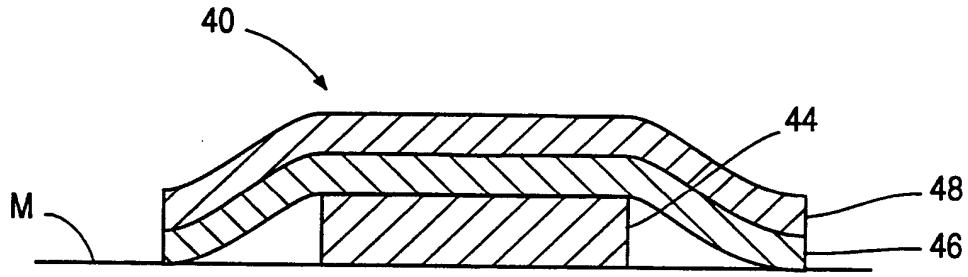

FIG. 4

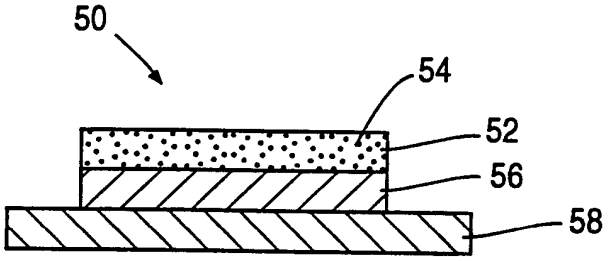

FIG. 8

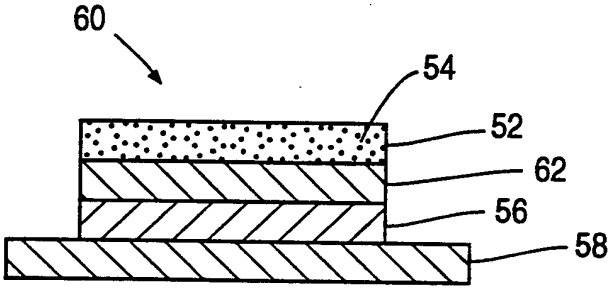

FIG. 9

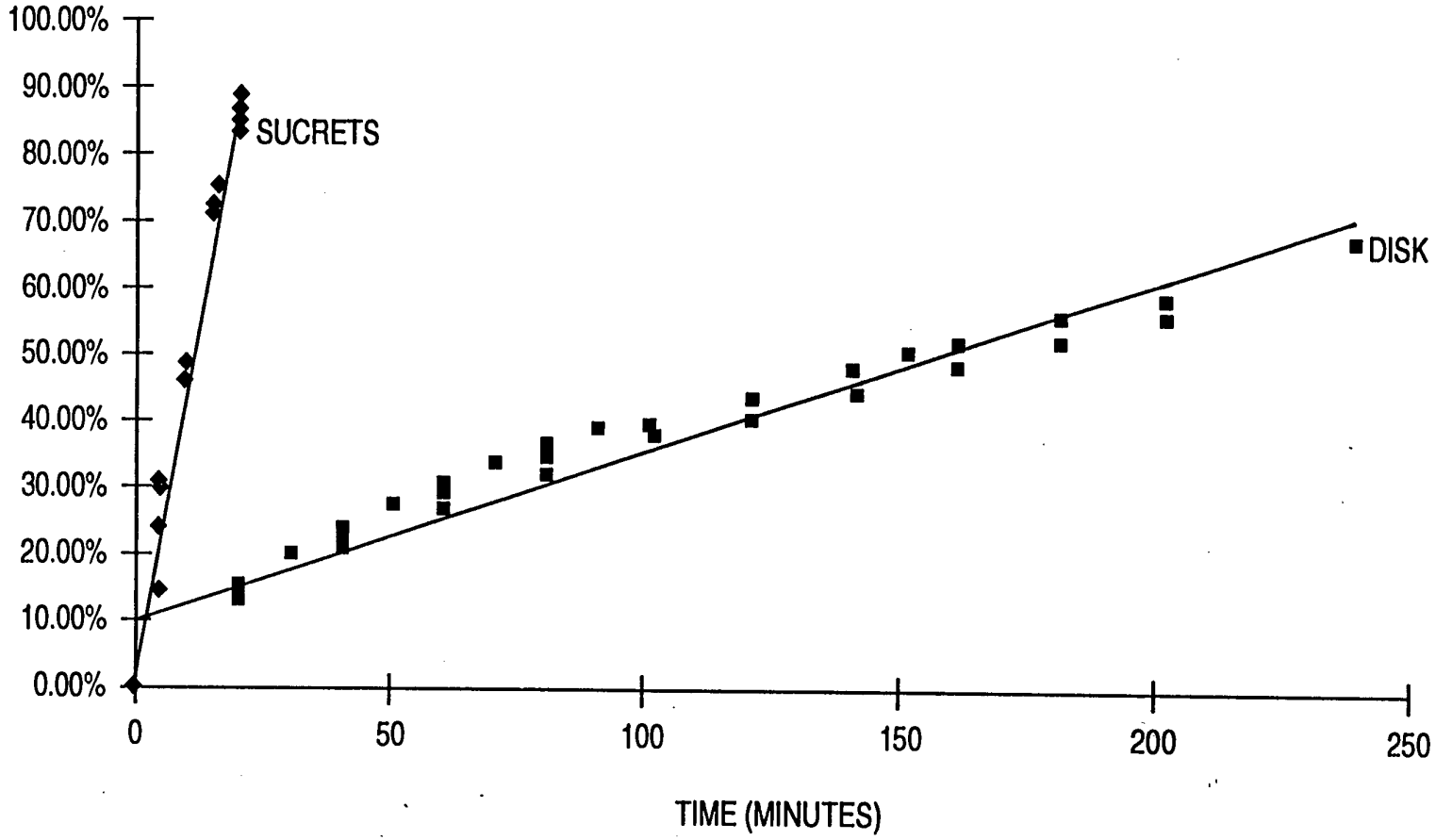

FIG. 10

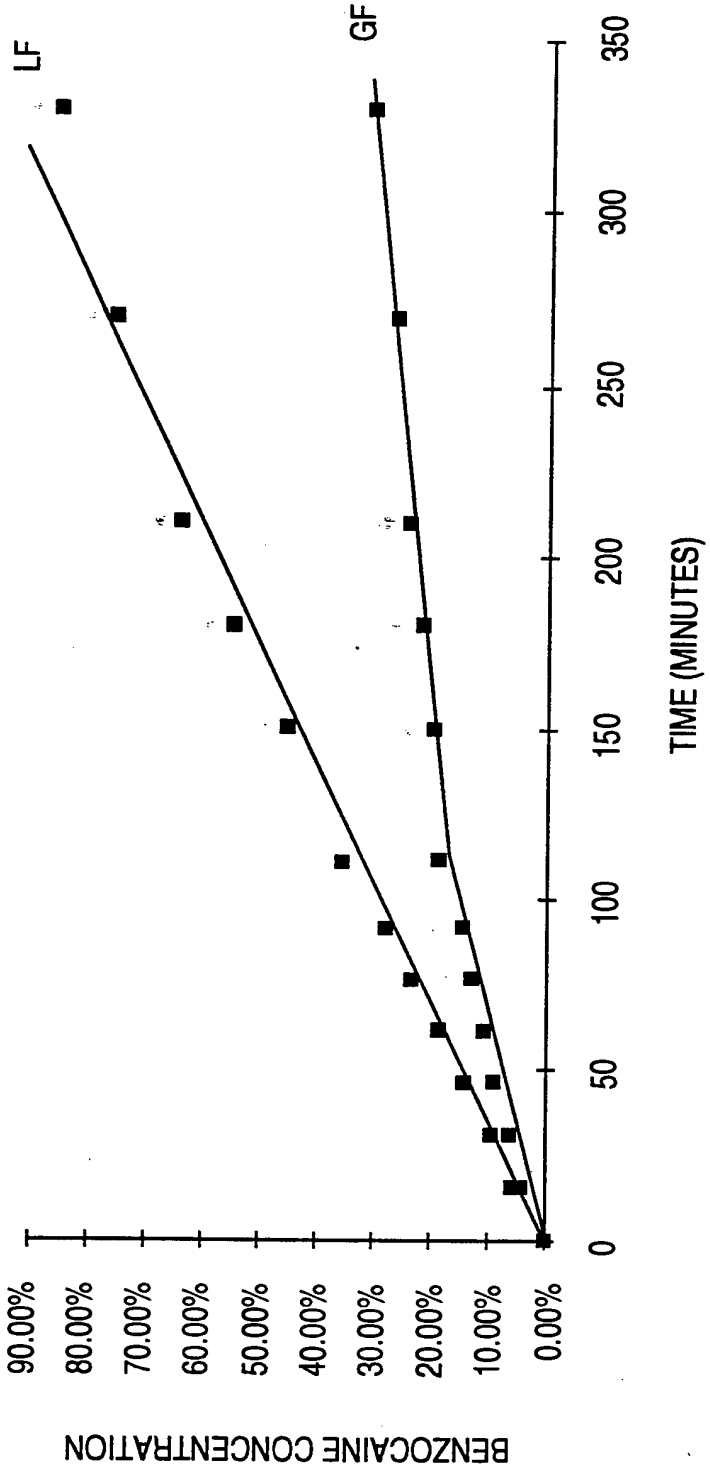

FIG. 11

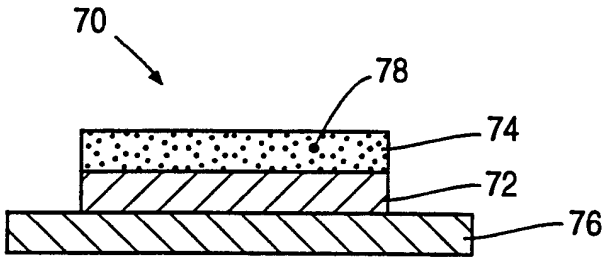

FIG. 12

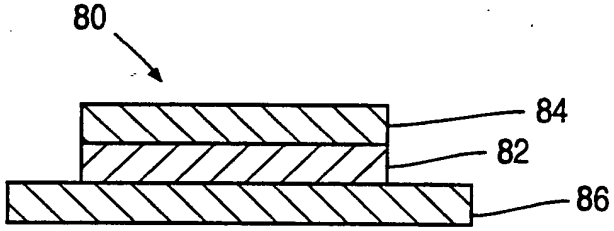

FIG. 13

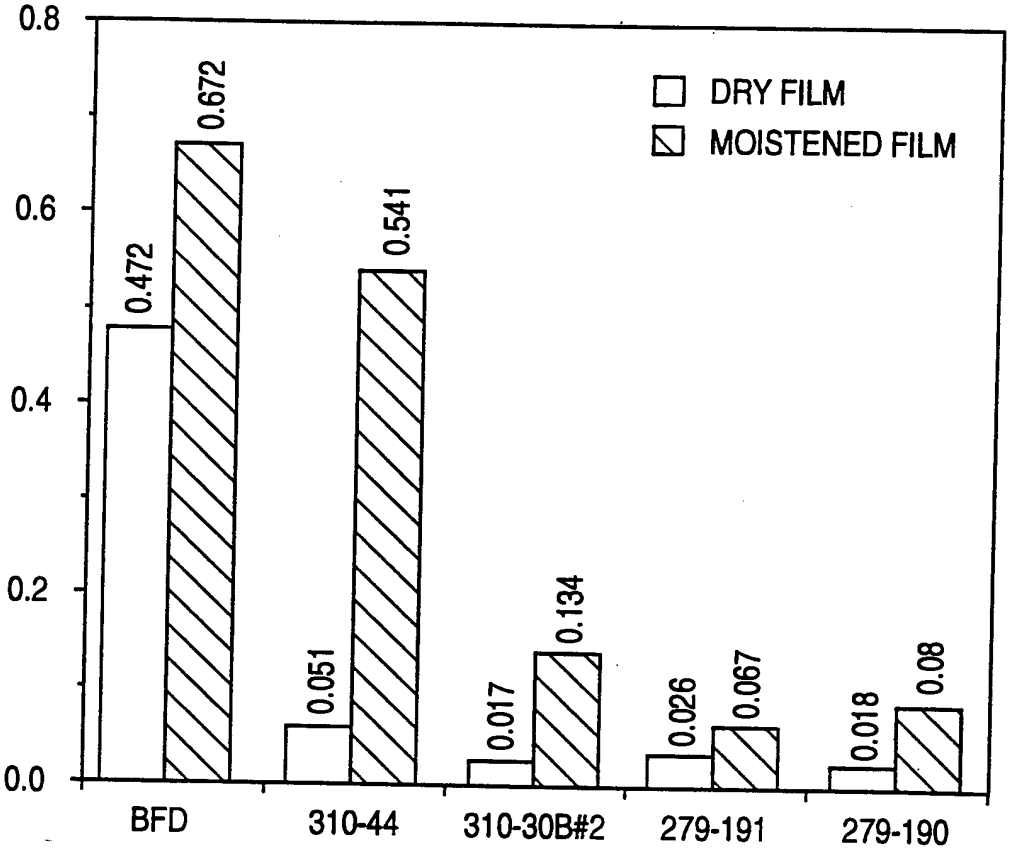

FIG. 14

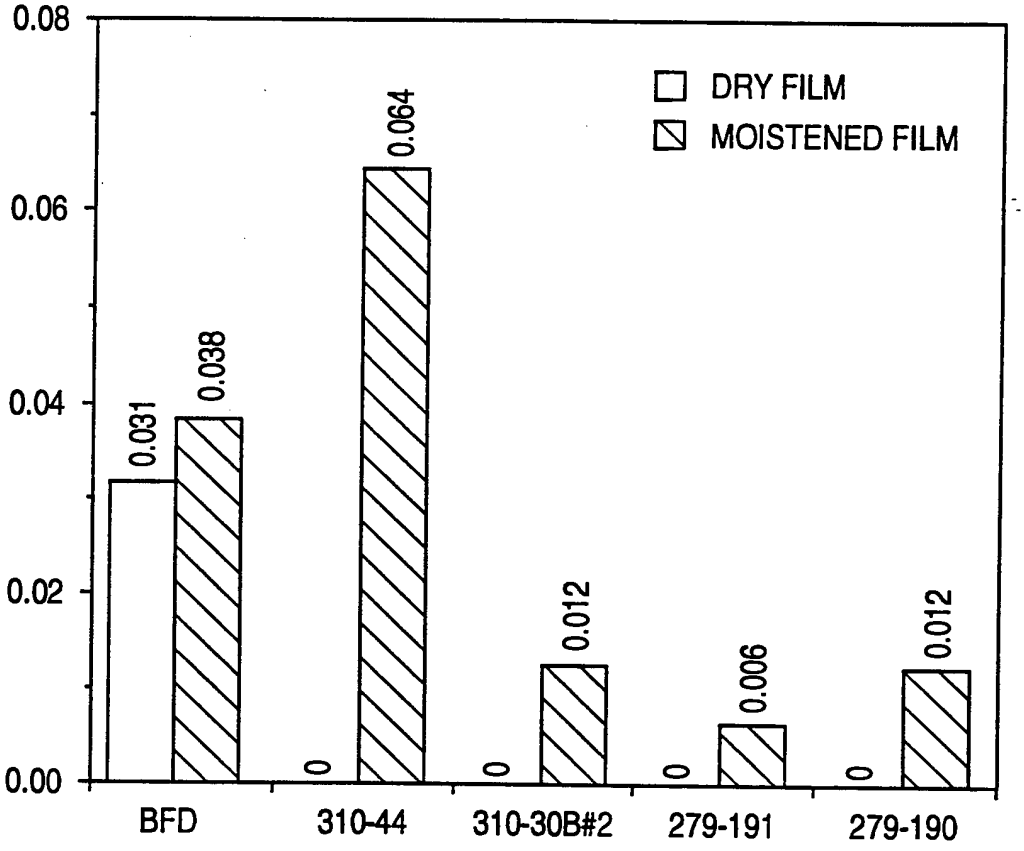

FIG. 15

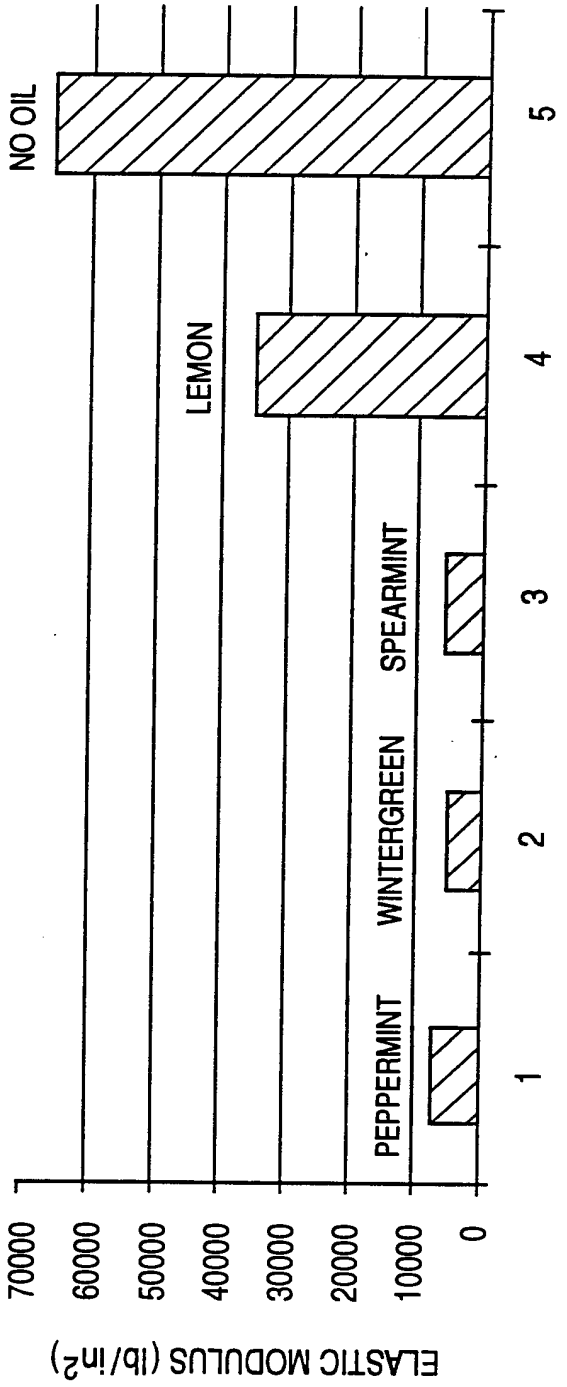

FIG. 16

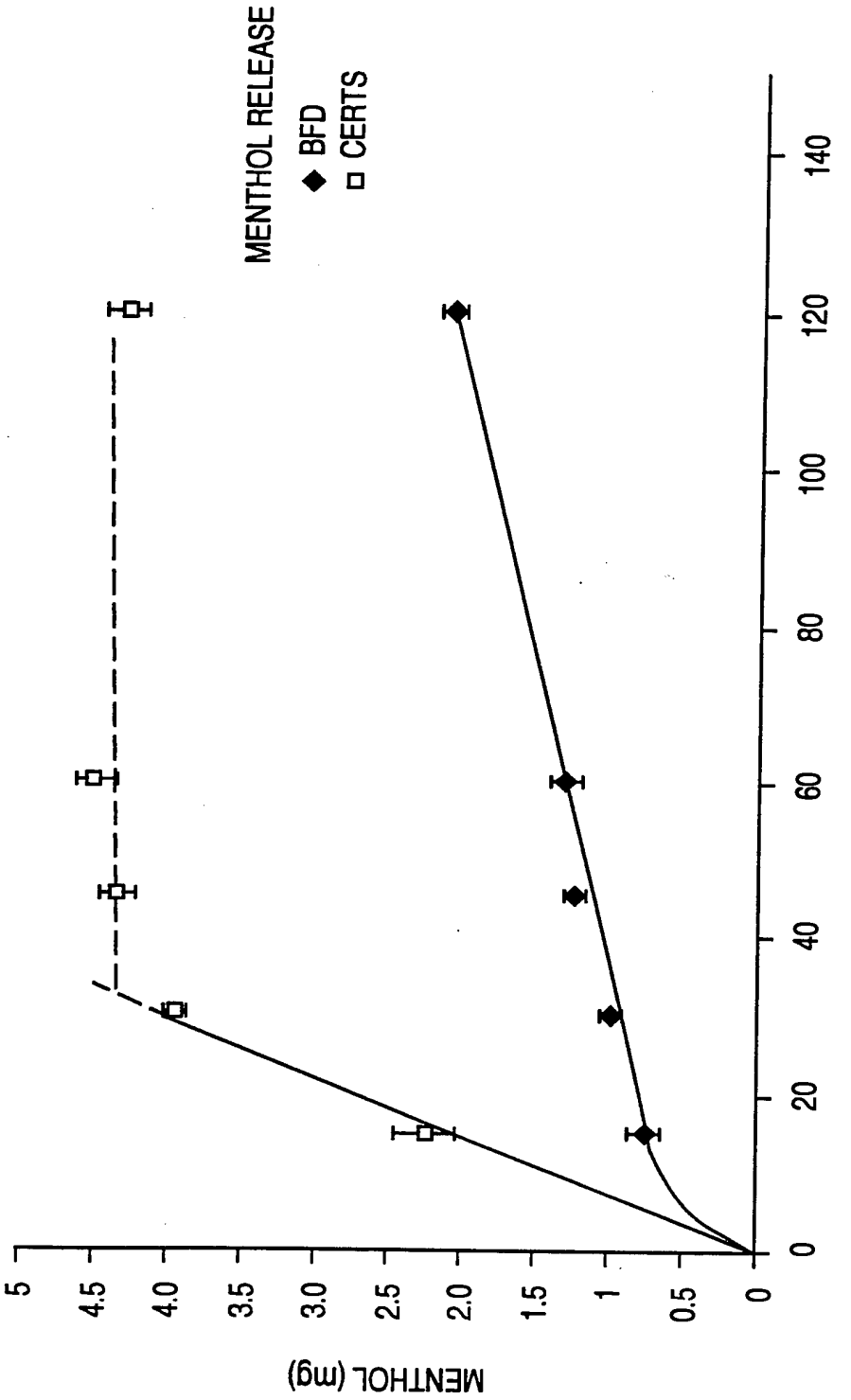

FIG. 17

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :		(11) International Publication Number: **WO 95/05416**
C08L 1/26, C08K 5/10, 5/11, 15/00 **A61K 6/00, A61F 13/00**	**A3**	(43) International Publication Date: 23 February 1995 (23.02.95)

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(74) Agents: KENNEDY, Bill et al.; Morrison & Foerster, 755 Page Mill Road, Palo Alto, CA 94034-1018 (US).

(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD).

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(54) Title: WATER-SOLUBLE PRESSURE-SENSITIVE MUCOADHESIVE

(57) Abstract

Water-soluble pressure-sensitive adhesives include a water-soluble polymer that is made tacky at room temperature by addition of a water-soluble plasticizer that is miscible with the polymer. Suitable polymers are solid at room temperature; and have a hydrophilicity as measured by water uptake greater than about 25 %; they are liquid at room temperature and have a boiling point higher than about 80 °C. The adhesives according to the invention may conveniently be provided in dry film form. Preferred water-soluble pressure-sensitive adhesives of the invention adhere both to mucosal surfaces and to a variety of materials that may constitute a part of a device or prosthesis to be held in a body cavity that has a mucosal lining. Also, a laminated device for the controlled release of a substance within a mucosa-lined body cavity includes the substance dissolved or dispersed in either or both of a water-soluble pressure-sensitive adhesive layer and optionally one or more water-soluble polymer layers. Also, devices for administering a substance over an extended time for relief of sore throat or cough, or for administering a breath freshening agent, particularly a mint odorant, include a water soluble polymer film layer containing the active ingredient, and a water soluble pressure sensitive mucoadhesive layer.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/09305

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C08L 1/26; C08K 5/10, 5/11, 15/00; A61K 6/00; A61F 13/00
US CL :523/111,120; 524/43,312; 424/435; 428/40, 355
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 523/111,120; 524/43, 312; 424/435, 449; 428/40,355

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS: POLYVINYL PYROLIDONE, GLYCEROL, PRESSURE SENTITIVE ADHESIVE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 4,529,748 (WIENECKE) 16 July 1985, see entire document.	1,2,7-8
Y	US, A, 4,713,243 (SCHIRALDI ET AL) 15 December 1987, column 2, lines 30-60 and column 3, line 10 to column 4, line 38.	1,2,7
Y	US, A, 5,166,233 (KUROYA ET AL) 24 November 1992, see entire document.	1,2,7
Y	US, A, 4,373,036 (CHANG ET AL) 08 February 1983, see entire document.	1,2,7
Y	US, A, 5,158,825 (ALTWIRTH) 27 October 1992,column 1, lines 45-68 and column 2, lines 19-55.	1,2,7

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

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"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 03 OCTOBER 1994	Date of mailing of the international search report 13 FEB 1995
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer PAUL MICHL Telephone No. (703) 308-2351

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/09305

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 4,910,247 (HALDAR) 20 March 1990, column 3, line 20 to column 4, line 29.	1-4
A	US, A, 5,064,717 (SUZUKI ET AL) 12 November 1991, column 3, lines 33-54 and column 10, lines 21-33.	1-8
X	US, A, 4,292,299 (SUZUKI) 29 September 1981, columns 2-5.	9-18,24-49
---		---
Y		19-23
Y	JP, A, 62-59513 (KYUKYU YAKUHIN KOGYO) 28 February 1990, pages 2-12.	19-23

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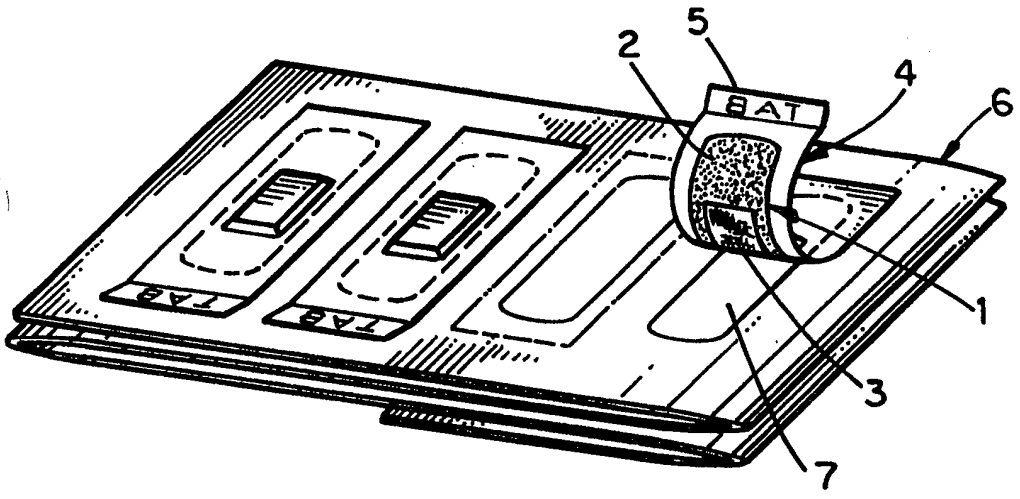
(71)(72) Applicant and Inventor: FRANK, Richard, D. [US/US]; 11909 South Lake Drive, Houston, TX 77077 (US).

(74) Agent: CAGLE, Stephen, H.; Arnold, White & Durkee, P.O. Box 4433, Houston, TX 77210 (US).

Published
With international search report.

(54) Title: PAKAGING AND DISPENSING DEVICE FOR STERILE ARTICLES



(57) Abstract

The present invention provides an encased article combination that includes a support member (100, 6, 53, 71), a cover member (104, 4, 50, 72), and an encased article (101, 1, 52, 70). The encased article is in the form of adhesive bandages (1), chemical applicator pads (52), and doses of medicine (70). In particular, the invention in part allows access to and use of such items with a single hand.

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PACKAGING AND DISPENSING DEVICE FOR STERILE ARTICLES

This invention relates to a dispensing device for sterile articles such as adhesive bandage strips, chemical applicator pads, and medication. More particularly, this invention permits one-handed access, removal, and application or use of adhesive bandages, chemical substances, or medication.

While adhesive-backed articles such as adhesive bandage strips are known in the art, they are commonly sealed in sterile, individual wrappings and packaged within paper or metal boxes. Examples include the well-known "Band-Aid®" brand bandage strips. While popular, these products suffer certain disadvantages such as the fact that the bandages themselves can be difficult to remove from the wrappings and difficult to apply to the desired location. The user generally must remove the bandage from the wrapping, remove the nonstick layers from the

adhesive portion of the bandage and then attempt to apply the bandage to the desired location in its sanitary and sterile condition without the bandage curling or adhering to itself.

Previous attempts to improve upon this concept include U.S. Patent No. 4,993,586 to Taulbee, et al., which discloses a bandage dispenser device in which a continuous strip is grasped with one hand and a bandage is removed with the other hand. This is accomplished by the use of a continuous strip with a first and second layer. Bandages are placed on sterile mounting pads affixed to the first layer. The bandages and the first layer are then enclosed by a second layer and stacked or rolled within a container. In use, the sheet is pulled through a splicer attached to the container that cuts the first and second layers. The second layer is then lifted and removed. The first layer is then grasped with one hand and a bandage is removed with the other.

U.S. Patent No. 5,133,477 to Etheredge, et al. also discloses a bandage dispensing device employing the use of a continuous strip. The strip has a nonstick coating upon which one end of a bandage is affixed. The other end of the bandage and the cotton gauze area of the bandage are covered with a release sheet. In use, the continuous sheet is grasped with one hand the bandage is grasped and removed with the other hand. The bandage is then applied to the desired location by affixing the exposed half to the skin. Once applied, this end of the bandage is held in place while the release sheet is removed from the bandage and the other end of the bandage is applied to the skin.

Despite these and other prior art devices, there remains a need for a packaging and dispensing device for adhesive-coated articles, such as adhesive bandage strips, by which the article may be grasped with one hand from the front of dispenser and then applied, also one-handedly, to the desired location without the article curling or adhering to itself. Both Taulbee and Etheredge require the use of two hands to remove and apply a bandage strip, and neither addresses the

problem of the bandage strip curling or adhering to itself. Further, the device disclosed by Taulbee would entail considerable manufacturing costs due to the splicer structure. Similarly, there is still a need for a packaging and dispensing device that allows convenient, and in some cases, one-handed access to sanitary applicators and doses of medication.

While the prior art has improved upon access to sanitary articles, there is a need for both improved access to the article and improved applicability of the article. As an example, a lab technician who is drawing blood from a patient could use the improved access to such articles to apply an adhesive bandage strip with one hand while maintaining pressure on the puncture with the other.

Similarly, there remains a need for a device used for the application of chemical substances such as alcohol, makeup, sunscreen and other lotions, antiseptics and medicaments to the skin of the human body in a sterile and sanitary fashion with the use of a single hand. Additionally, there is also a need for convenient, and in some cases, one-handed access to doses of medicine.

The encased article combination of this invention includes a support member, a cover member and an encased article. The encased articles may be packaged either individually, as an assemblage of articles, or as an assemblage of articles in a dispensing device. In one embodiment of this invention the encased article is an adhesive coated article such as a conventional adhesive bandage or other form of wound dressing. In other embodiments of this invention the article is an applicator for chemicals, such as medicines, cosmetics, ointments, salves and the like. In yet another embodiment of this invention pills, capsules, or capelets, or other forms of medicinal dosage units are enclosed for dispensing.

The support member of this invention may take the form of a continuous sheet, coated or uncoated, or a series of molded housings for the articles to be

dispensed. In the most preferred embodiments the support member is flexible so that it can be loaded into a dispensing device in folded or rolled form.

The cover member of this invention is typically adhered to the support member to form the encasement for the article. In certain preferred embodiments the cover member has either one or two adhesive coatings for releasable adherence to the support member and to the encased article. In another preferred embodiment the cover member includes means for gripping the cover member for removal to enable one-handed application or use of the encased device.

In the practice of this invention it is important that the assembly of the support member, the cover member and the encased article form bonds of appropriate adhesive strengths to ensure correct release characteristics. A first adhesive bond is typically formed between the support member and the adhesive surface of the encased article. Such a first bond is typically found in the adhesive bandage encasement embodiment of this invention. A second adhesive bond is formed between the support member and the cover member. A third adhesive bond is formed between the cover member and the encased article. It is important that the third adhesive bond (between the cover member and the encased article) be adhesively stronger than either the first or second adhesive bond. This relationship of the first, second, and third adhesive bonds is important to the practice of this invention. Likewise, it is important that the third adhesive bond be weaker than the bond between the adhesive surface of the encased article and the surface to which it is ultimately applied (recipient surface).

Generally, the present invention comprises an apparatus for packaging and dispensing a sterile article such as an adhesive bandage, a swab-type or sponge-like applicator that may be pretreated with the substance to be applied, or a dose of medicine.

In the present invention, adhesive-coated items are encased within self-contained, sanitary packaging. The adhesive-coated item, such as an adhesive bandage usually has two substantially flat sides. The bottom (or adhesive) side or surface, which is the side applied to the skin in the case of standard adhesive bandages, is coated at least in part with a first adhesive and typically has a sanitary pad affixed thereto.

The adhesive-coated article such as an adhesive bandage is packaged by sandwiching the item between a dispensing support structure, layer, or sheet and a cover layer or strip. The adhesive-coated article is removably adhered to the support sheet by the first adhesive, which forms a first bond with the support sheet. The length and width dimensions of the support sheet exceed those of the adhesive-coated article. Alternatively, sterile, nonstick mounting pads may be affixed to the support sheet and an adhesive-coated article such as an adhesive bandage may instead be removably adhered to each of the mounting pads. If the support sheet is made of suitable material, then nonstick mounting pads are not necessary.

The packaging or encasement is further accomplished by forming or removably adhering a cover structure or layer, which also exceeds the dimensions of the adhesive-coated article, both to the top surface of the adhesive-coated article and to an additional peripheral area of the support sheet surrounding the article. A second adhesive may be used to removably adhere the cover layer to the top surface of the adhesive-coated article by forming a second bond therebetween. The second adhesive forms an additional bond between the peripheral area of the cover strip extending beyond the edges of the adhesive-coated article and the corresponding peripheral area of the support sheet. The second bond, that formed between the adhesive-coated article and the cover strip, is of greater strength than the first bond, that between the adhesive-coated article and the support sheet, so that when the cover strip is removed, usually by grasping a tab portion of the cover strip or any other suitable gripping means attached to the cover strip, the

adhesive-coated article is detached from the support sheet, while the top surface of the adhesive-coated article remains removably attached to the cover strip.

The adhesive-coated article can then be transported to and applied to the receiving surface, such as the human skin, with single handed use of the cover strip. Once the bottom surface of the adhesive-coated article, containing the first adhesive, is applied to the receiving surface, the first adhesive forms a strong bond between the receiving surface and the bottom surface of the article such that the strength of this bond with the receiving surface exceeds that of the bond between the cover layer and the top surface of the article so that subsequent pulling force exerted upon the cover layer will cause the cover layer to become detached from the top surface of the article, thereby leaving the article suitably applied to the receiving surface.

In another form, the present invention comprises an apparatus for packaging and dispensing a swab-type or sponge-like applicator, which is packaged by sandwiching it between a support structure, layer, or sheet and a cover structure, layer, or strip. In this application, the swab-type or sponge-like applicator, such as a piece of gauze, cotton, cloth, sponge, or other material is attached to a cover strip having length and width dimensions that exceed those of the applicator. The cover strip is attached to the applicator with an adhesive or some other suitable means of attachment. A peripheral area of the cover strip surrounding the applicator is coated with an adhesive which forms a temporary bond between the peripheral area of the cover strip extending beyond the edges of the applicator and the corresponding peripheral area of the support sheet. When the cover strip is pulled, the applicator is removed with the cover sheet, thereby exposing the applicator so that it may be moved to the receiving surface. The applicator can be pretreated with antiseptics, lotions, sunscreens, makeup or any medicament or other chemical to be applied, but does not necessarily have to be pretreated.

In yet another form, the present invention comprises an apparatus for packaging and dispensing doses of medicine such as capsules, capelets, pills, or other units of medicine. In this embodiment, capsules, for example, are packaged in trays which function as the support member and which contain troughs for holding the capsules. The capsules are further packaged with the use of a cover sheet which is removably adhered to at least the peripheral area of the trays. The package may or may not include an additional, protective, thin burstable film between the cover sheet and the capsules. The inner dimensions of the troughs may or may not be slightly smaller than the outer dimensions of the capsules in at least one dimension. If the troughs are slightly smaller than the capsules, then the user must exert force on the troughs to eject the capsules once the troughs have been removed from the cover layer with the use of a tab or other suitable gripping means attached to or formed as part of the tray. If the troughs are of the same or equal size as the capsules, then a portion of the underside of the cover layer may be coated with a temporary adhesive that removably adheres the capsules to the cover layer and removes the capsules from the troughs when the cover layer is removed.

Embodiments of this invention include the individual packaging and dispensing of individual or multiple adhesive bandages of virtually any shape, or applicators as well as the packaging and dispensing of multiple bandages, applicators, or doses of medicine positioned on individual or continuous sheets or rolls or in trays packed within a dispenser.

The dispenser itself may be a desktop or wall-mounted refillable container constructed of metal, plastic or paper. The dispenser has an opening or a window to provide access to sterile, individually wrapped adhesive bandages or applicators affixed to single or continuous sheets or rolls, or doses of medicine in trays formed from single or continuous sheets or rolls. A continuous support sheet of bandages or applicators may be layered or rolled in the bottom of the dispenser and fed across the dispenser window so that the leading end of the sheet either

exits through one end of the dispenser or is attached to a spool. As the bandage strips or applicators are removed via the access window and used, the support sheet may be pulled through the aperture or the spool may be turned, thus exposing additional bandages or applicators in the dispenser window. If medicine is dispensed then single sheets or multiple layers of single sheets of trays of medicine may be loaded into the dispenser and the trays may be accessed through the access window for use.

An aperture may be in addition to or instead of the access window. The aperture allows single or multiple packaged bandages, applicators or packets of medicine to be dispensed from one side of the dispenser for immediate or subsequent use. In a dispenser containing both an access window and an aperture, the aperture also allows the packaging material remaining from bandages, applicators, or pills accessed through the access window to be removed and discarded.

Thus, it is an object of the present invention to provide an improved package and dispenser for sterile articles such as adhesive bandages, chemical applicators, and doses of medicine.

It is also an object of present invention to provide a device that allows the user to apply a common sterile adhesive bandage or chemical substance using only one hand in the process of removing the bandage or substance applicator from the dispenser and applying it to the desired location.

It is a further object of this invention to provide an apparatus for application of a bandage strip to its desired location with the use of a single hand without the bandage strip curling or adhering to itself.

Yet another object of this invention is to provide an apparatus for the application of a chemical substance to a surface with the use of a single hand.

It is still a further object of the invention to provide a convenient dispenser which displays several adhesive bandages or substance applicators for immediate use, eliminates the handling of individually wrapped bandages or substance applicators, and reduces the amount of immediately discarded wrapping material.

Other objectives, features and advantages of the present invention will become apparent upon reading the following specification, when taken in conjunction with the drawings and the claims.

FIG. 1 is an exploded side view conceptually showing the layers and adhesives of an adhesive-coated article encased according to the present invention.

FIG. 2 is an exploded side view conceptually showing the layers and adhesives of an adhesive coated article encased according to the present invention.

FIG. 3 is a side view conceptually showing the layers and adhesives of an adhesive coated article encased according to the present invention.

FIG. 4 is an exploded side view conceptually showing the layers and adhesives of a sterile article encased according to the present invention.

FIG. 5 is a side view conceptually showing the layers and adhesives of a sterile article encased according to the present invention.

FIG. 6 is a perspective view showing an adhesive bandage strip removably adhered to a cover strip containing a pull tab.

FIG. 7 is a perspective view showing the positioning of adhesive bandage strips and non-continuous cover strips on a continuous support layer.

FIG. 8 is a perspective view showing the positioning of adhesive bandage strips and continuous cover strips on a continuous support layer.

FIG. 9 is an exploded perspective view of a single adhesive bandage strip encased according to the present invention.

FIG. 10 is a perspective view showing the typical application of an adhesive bandage strip with a cover strip to a recipient's skin.

FIG. 11 is an exploded perspective view of one embodiment of a dispenser for adhesive bandages packaged on a continuous support member.

FIG. 12 is a side cut away view showing the dispenser of FIG. 11 packed with a fan folded continuous member of adhesive bandage strips.

FIG. 13 is a perspective view of the dispenser of FIG. 11.

FIG. 14 is a perspective cut away view of one embodiment of a dispenser for adhesive bandages packaged on continuous support member.

FIG. 15 is a perspective view of a portion of a dispenser for adhesive bandages packaged on a continuous support member.

FIG. 16 is a cut away perspective view of a wall mounted dispenser containing a spool for dispensing adhesive-coated bandages packaged on a roll according to the present invention.

FIG. 17 is a cut away perspective view of a wall mounted dispenser containing a roll of adhesive coated bandages on a roll packaged according to the present invention.

FIG. 18 is an exploded perspective view showing an applicator packaged according to the present invention.

FIG. 19 is an exploded perspective view showing a plurality of applicators packaged on a single support member according to the present invention.

FIG. 20 is a perspective view showing one embodiment of a dispenser for a plurality of applicators packaged on a single support member according to the present invention.

FIG. 21 is a perspective view of one embodiment of a dispenser for dispensing the applicators shown in FIG. 19.

FIG. 22 is an exploded perspective view of one embodiment of capsules packaged according to the present invention.

FIG. 23 is an exploded perspective view of another embodiment of capsules packaged according to the present invention.

FIG. 24 is a bottom perspective view of the packaged capsules shown in FIG. 23.

FIG. 25 is a perspective view of a user ejecting capsules packaged according to the present invention.

FIG. 26 is a cut away perspective view of one embodiment of a dispenser for dispensing
medicine packaged according to the present invention.

FIG. 27 is an exploded cut away perspective view of another embodiment of a dispenser for dispensing medicine packaged according to the present invention.

FIG. 1 is an exploded side view conceptually showing the layers and adhesives of an adhesive-coated article encased according to the present invention. FIG. 1 shows adhesive-coated article 101 having first adhesive surface 102 encased between support member 100 and cover member 104. A first adhesive bond removably adheres the first adhesive surface 102 and support member 100 by first adhesive coating 103 disposed on first adhesive surface 102. Cover member 104 is removably adhered to support member 100 by the second adhesive coating 105 disposed therebetween and which forms a second adhesive bond therebetween.

FIG. 2 is an exploded side view conceptually showing the layers and adhesives of another embodiment of an adhesive-coated article encased according to the present invention. Adhesive-coated article 101 having first adhesive surface 102 is encased between support member 100 and cover member 104. A first adhesive bond removably adheres the first adhesive surface 102 and support member 100 by first adhesive coating 103 disposed on first adhesive surface 102. Cover member 104 is removably adhered to support member 100 by second adhesive coating 105 disposed therebetween and which forms a second adhesive bond therebetween. Cover member 104 is also removably adhered to the adhesive-coated article 101 by third adhesive coating 106 which forms a third adhesive bond therebetween which is stronger than the second adhesive bond.

FIG. 3 further shows the encased adhesive-coated article of FIG. 2 with the addition of contact between the appropriate layers and adhesives, and also shows the addition of means for gripping 107 to facilitate removal of cover member 104.

FIG. 6 shows an application of the present invention to the packaging of an adhesive bandage strip. The adhesive bandage strip 1 is the adhesive-coated

article. The cover member in this embodiment is cover strip 4, as these terms may be used interchangeably in this configuration. The support member in this embodiment is support sheet 4. FIG. 6 shows a perspective view of an adhesive bandage strip 1 joined to a cover strip 4 with a pull tab 5. The adhesive bandage strip 1 is generally constructed of plastic, paper, or cloth material with an adhesive substance applied to the adhesive side 2 of the strip and a cotton gauze area 3 in the middle of this adhesive side 2 of the strip 1. A conventional adhesive bandage strip, such as the "Band-Aid®" brand bandage strip, may be used.

The adhesive bandage strip 1 is joined to a cover strip 4 by a temporary adhesive. Examples of the temporary adhesive substance include "DryLine™" temporary adhesive made by the Gillette Company. The cover strip 4 may be constructed of any suitable material, including paper or plastic. The temporary adhesive used to join the cover strip 4 to the adhesive bandage strip 1 forms a stronger bond between the cover strip and the bandage than the bond formed by the adhesive substance between the adhesive side 2 of the adhesive bandage strip 1 and the support sheet 6 of FIG. 7. The cover strip 4 also contains a suitable means for gripping, such as pull tab 5, for ease of removal, as explained below.

FIG. 7 is a perspective view showing the positioning of the adhesive bandage strips 1 and non-continuous cover strips 4 on a continuous support sheet 6. The continuous support sheet 6 may be constructed out of any suitable material, including paper or plastic. The support sheet 6 can be of any suitable length and can be fan folded as shown in FIG. 7, or rolled as shown in FIGS. 16 and 17.

FIG. 8 shows a perspective view of an embodiment of the invention in which adhesive bandage strips are dispensed on a fan folded continuous support sheet 6 and covered and dispensed with the use of continuous cover strips 18 formed by the perforation or cutting of a continuous cover layer 19.

In the embodiments utilizing either continuous or non-continuous cover strips, a variable number of sterile, nonstick mounting pads 7, as shown in FIG. 7, may be permanently affixed to or incorporated into the continuous support sheet 6. The sterile, nonstick mounting pads 7 are generally constructed out of paper, such as the release liner-type paper manufactured by Rhinelander Paper Company. The adhesive bandage strips 1 are positioned on the sterile, nonstick mounting pads 7 such that the adhesive side 2 of a bandage strip 1 is in contact with the sterile, nonstick mounting pads 7. Alternatively, the continuous support sheet 6 itself can be treated with a nonstick substance such that the adhesive bandage strips 1 may be placed directly on the support sheet 6.

If non-continuous cover strips 4 are used as shown in FIG. 7, then a cover strip 4 is joined to each of the adhesive bandage strips 1 as discussed above. The cover strip 4, covers the adhesive bandage strip 1 and adheres to that area of the support sheet 6 immediately surrounding the adhesive bandage strip 1, such that each adhesive bandage strip 1 is sealed within the cover strip 4 and the support sheet 1. This enclosure ensures that the adhesive bandage strips 1 remain sterile until use. The support sheet 6 may be scored or perforated between a predetermined number of packaged bandages so that individual or groups of packaged bandages may be torn off for immediate or subsequent use as shown in FIGS. 14 and 15. This also allows the user to remove and discard portions of the support sheet 6 remaining after any number of bandages has been used.

If continuous cover strips 18 are used, as shown in FIG. 8, then a continuous cover sheet 19 covers any number of adhesive bandage strips 1 and adheres to the area of the continuous support sheet 6 immediately surrounding each adhesive bandage strip 1, such that each adhesive bandage strip 1 is sealed between a portion of the continuous cover sheet 19 and the continuous support sheet 6, maintaining sterility. The continuous cover sheet 19 is cut or perforated into individual cover strips 18 so that bandages 1 can be removed and applied individually.

In this embodiment, the continuous support sheet 6 and continuous cover sheet 19 may both be scored or perforated between any number of adhesive bandages 1 as shown in FIGS. 8 and 13, thereby allowing any number of packaged bandages to be removed individually or in groups and also allowing removal of portions of the continuous support sheet 6 after any number of bandages 1 has been used.

FIG. 9 shows an exploded perspective view of an individual, packaged adhesive bandage that has been removed from a continuous support sheet of adhesive bandages having perforations between bandages and that also has cover strips cut or perforated from a continuous cover sheet.

Referring to FIG. 7, in operation, the cover strip 4 is grasped via the pull tab 5. When the pull tab 5 is pulled, the adhesive bandage strip 1 and the cover strip 4 are peeled together from the continuous support sheet 6, or from alternative, nonstick mounting pad 7 and the continuous support sheet 6. The temporary adhesive joining the bandage strip 1 and the cover strip 4 is of sufficient strength to overcome the bond between the adhesive side 2 of bandage strip 1 and sterile, nonstick mounting pad 7 or the support sheet. The adhesive bandage strip 1, still backed by cover strip 4, is then applied to the desired location on the recipient's skin.

FIG. 10 is a perspective view showing the typical application of an adhesive bandage strip 1 with a cover strip 4 to a recipient's skin. Once the adhesive bandage strip 1 is applied, because the temporary adhesive joining the adhesive bandage strip 1 and the cover strip 4 forms a bond that is weaker than the bond formed between the adhesive side 2 of bandage strip 1 and the recipient's skin, the cover strip 4 is peeled away from both the adhesive bandage strip 1 and the recipient's skin, thereby leaving the adhesive bandage strip 1 applied to the recipient's skin. The cover strip 4 may then be discarded.

FIG. 11 is an exploded perspective view showing the elements of a dispenser 10 for the packaged bandages described. The dispenser 10 consists of a top half 11 defining an access window 12, a bottom half 13, a support ledge 14, a spool 15, and a knob 16. As shown, the support ledge 14 is positioned within top half 11 directly underneath access window 12 and is supported by bottom half 13. The bottom half 13 is generally hollow so as to provide space for the packing of the continuous sheet 6. The spool 15 is generally located on one end of the lower half 13 and communicates with knob 16 on the exterior of the dispenser 10. Optionally, the dispenser 10 may also contain an aperture through which prepackaged bandages, or portions of support sheet remaining from bandages accessed through the access window 12, may pass for use or discarding.

The dispenser 10 can be manufactured out of any suitable material including metal, plastic or paper. The dispenser 10 may be refillable and may be used on a desktop or mounted to a wall.

FIG. 12 is a side cut away view showing a dispenser 10 packed with a fan folded continuous support sheet 6 of adhesive bandage strips 1. The continuous support sheet 6 is fed through and across support ledge 14 such that the adhesive bandage strips 1 are exposed through access window 12. The leading end 8 of continuous support sheet 6 is attached to spool 15 such that the continuous support sheet 6 can be advanced by rotating knob 16 as the adhesive bandage strips 1 are removed. Alternatively, the leading end 8 of continuous support sheet 6 may be fed through optional aperture 15a so that either packaged bandages can be removed for subsequent use, or portions of continuous support sheet 6 that remain after bandages have been removed via access window 12 may be removed and discarded.

FIG. 13 is a perspective view of the dispenser of FIGS. 11 and 12, showing the optional dispensing aperture.

FIG. 14 shows an alternate embodiment of a dispenser for packaged bandages or other adhesive-coated articles, in which the dispenser contains an access window 12 and a dispensing aperture 15a, but does not contain a spool and knob. The continuous support sheet 6 may be pulled through the aperture 17 so as to advance the continuous support sheet 6 after adhesive bandage strips 1 are removed through the access window 12. Alternatively, the dispenser 10 may allow bandages packaged on the continuous support sheet 6, and which were not removed while exposed in the access window 12, to pass through the aperture 17 and be removed at perforations in the continuous support sheet 6 either individually or in groups for later use.

FIG. 15 shows a perspective view of a portion of yet another embodiment of a dispenser for packaged bandages or other adhesive-coated articles. In this embodiment, multiple adhesive-coated articles are visible on access shelf 20.

FIG. 16 shows a perspective cut away view of a wall-mounted dispenser for bandages or other adhesive-coated articles packaged according to the present invention, in which the assemblage of adhesive-coated articles is rolled.

FIG. 17 shows a perspective cut away view of yet another embodiment of a dispenser for adhesive coated articles packaged according to the present invention, in which the assemblage of adhesive-coated articles is rolled. In this configuration, the dispenser contains no spool for coiling the remaining portions of the support sheet after removal of adhesive-coated articles.

While the invention has been disclosed with respect to an adhesive bandage strips, it will be appreciated that the invention is equally well suited for other shapes of adhesive bandages as well as other types of adhesive-backed articles such as bumper stickers, adhesive-backed name tags, and the like.

FIG. 4 is an exploded side view conceptually showing the layers and adhesives of a sterile article encased according to the present invention. A sterile article 133 is effectively encased for dispensing or distribution by its attachment to cover member 132. The sterile article 133 is further encased by removably adhering cover member 132 to support member 130 with first adhesive coating 131 to form an adhesive bond therebetween.

FIG. 5 is a conceptual side view of another embodiment of the present invention, showing a sterile article adhered to cover member 132 by second adhesive 134, forming a second bond therebetween. As in the embodiment of FIG. 4, the sterile article 133 is encased by removably adhering cover member 132 to support member 130 with the use of first adhesive coating 131 to form a first bond therebetween and functionally encase the sterile article 133.

FIG. 18 shows an exploded perspective view of an embodiment of the invention in which the sterile article is a chemical substance applicator 52 such as a cotton swab, a portion of gauze, sponge, cloth, or other material and is affixed to a cover 50 which serves as the cover member. The applicator 52 is further packaged by placement of the applicator 52 on a support sheet 53 which serves as the support member. The portion of the cover 50 extending beyond the periphery of the applicator 52 is coated with a temporary first adhesive which removably adheres that portion of the cover 50 to a corresponding region of the continuous support sheet 53, thereby sealing the applicator 52 in a sanitary package. The adhesive surrounding the applicator 52 used to removably adhere the periphery of the applicator 52 to the support sheet 53 may also be used to adhere the cover 50 to the applicator 52.

Multiple covers may be formed from a continuous sheet that is cut, scored, or perforated between adjacent applicators or they may formed from separate pieces of material. The covers 50 may contain a corner-type tab 54 as shown in 18, an edge-type tab 55 as shown in FIG. 19, or any other means for gripping that

facilitates the removal of the cover 50 and applicator 52 from the support sheet 53. The cover 50 may contain an additional handle or gripping device on its surface to further assist the user in removing or holding the cover 50.

The applicator 52 may be pre-treated with any chemical substance to be applied such as antiseptics, makeup, lotions, medicaments or any other suitable substance for application. Alternatively, the applicator 52 may not be pre-treated. If the applicator 52 is pre-treated, then the user will pull the tab 55, thereby removing the applicator 52 from the support sheet 53, and exposing the applicator 52 for application to the recipient surface such as human skin. If the applicator 52 is not pre-treated, then after removal from the support sheet, the applicator 52 may be used as a sanitary wipe, or the user may apply any suitable substance such as bottled alcohol, makeup, or lotion, or any other suitable substance to the applicator and then apply the applicator to a recipient surface. In this embodiment, it is contemplated that both pretreated and non-pretreated swabs will have application beyond the medical field and will provide a convenient swab or applicator for the application of any number of chemical substances in any number of commercial or household applications.

Applicators of this embodiment may be dispensed from single or continuous sheets or rolls. FIG. 19 shows an embodiment in which multiple applicators 52 are packaged on a single support sheet 53. The encased, or packaged, applicators of FIGS. 18 and 19 may be dispensed with the use of the dispensers of FIGS. 20 and 21 respectively. Alternatively, the encased articles may be dispensed with dispensers not shown in the figures, but which may be similar or identical to the dispensers of FIGS. 14 and 15 in which any such articles may be dispensed via the aperture at the end of an access shelf of the dispenser. In yet another configuration not shown, such encased sterile articles may be dispensed on rolled sheets with dispensers similar or identical to the dispensers of FIGS. 16 or 17.

FIG. 22 shows another embodiment in which the invention is used to dispense doses of medication such as capsules, capelets, pills, or other units of medicine. In this embodiment, a dosage of medicine, such as capsule 70, is packaged in dispensing tray 71 which functions as the support member and which contains holding troughs 73. In one embodiment, the size of the capsule 70 exceeds the interior size of the holding trough 73 in at least one dimension so that some pressure may be required for the removal of capsules 70 from the trough 73. The capsules 70 are further packaged with the use of a cover sheet 72 which functions as the cover member and which is coated in part on one side with an adhesive that removably adheres peripheral and central portions of the cover sheet 72 to corresponding portions of the dispensing tray 71 so as to retain the capsules 70 in a completely enclosed sanitary package. The tray 71 may contain a suitable means for gripping, such as pull tab 75 in one or more corners or along one or more edges for ease in removing the tray 71 from the cover sheet 72.

In this embodiment, filled packages may be dispensed through a dispenser such as that shown containing a spool and aperture in FIG. 27 or an aperture only as in FIG. 26. Trays 71 may be pulled with tab 75 through access window 81. Alternatively, complete, unused packages may be dispensed through an aperture 82 for immediate or subsequent use and are perforated or scored between single or multiple packages. If complete, unused packages are dispensed through an aperture, then, the user removes capsule 70 by peeling back the tray 71 with the use of tab 73 or a suitable handle or grasping device affixed to the exterior of the tray 71. The user then squeezes the trough 73 to eject the capsule 70 therefrom, as shown in FIG. 25.

In another embodiment, as shown in FIGS. 23 and 24, a thin, burstable film 74, made of paper, plastic, metal foil, or any other suitable material, is adhered to the top surface of dispensing tray 71 so as to form an intermediate layer between cover sheet 72 and dispensing tray 71. In this embodiment, the cover sheet 72 is removably adhered to the film 74. Once the cover sheet 72 is

removed, the user must then squeeze the trough 73 to force the capsule 70 to penetrate or break through the film 74 and eject the capsule 70 from the package for use.

For any of the embodiments used in dispensing medication, the dispensing trays may be formed individually or from single or continuous sheets of material. The cover sheets may be spaced or may be formed by cutting, perforating, or scoring of a continuous sheet of material. If multiple dispensing trays are formed from a single piece of material, the material may be perforated or scored between adjacent packages or at other regular or varying intervals to allow dispensing or single or multiple packages of medication.

In any of the embodiments for dispensing medication, dosage information may be printed on the surfaces of the cover sheet or dispensing tray. This allows the manufacturer or user to label particular doses. For example, with certain medications, a particular dosage must be taken on each day of the week such that the dosages for different days will differ. In this case, a particular dosage can be labelled for "Monday," "Tuesday," and so forth. These embodiments allow the user to see quickly whether the dosage for a particular day has already been dispensed. This may be particularly helpful in the case of forgetful patients.

While the invention has been disclosed with respect to particular embodiments, the applicant does not regard the invention as being limited to such embodiments or applications. It is also understood that this description is not meant to be limiting because further modifications may now suggest themselves to those skilled in the art and is intended to cover such modifications as fall within the scope of the following claims.

CLAIMS:

1. An encased adhesive-coated article combination comprising:

a. a support member;

b. an adhesive-coated article, said adhesive-coated article including a first adhesive surface, said first adhesive surface having a first adhesive coating covering at least a portion thereof, said adhesive-coated article being removably adhered to said support member by contact of said first adhesive coating, the first adhesive coating between said support member and said first adhesive surface forming a first adhesive bond; and

c. a cover member removably attached to said support member to releaseably encase said adhesive-coated article, said cover member including a second adhesive coating covering at least a portion thereof, said cover member being removably attached to said support member by contact of said second adhesive coating with said support member, the contact between said support member and said cover member forming a second adhesive bond.

2. The encased adhesive-coated article combination of claim 1, wherein said second adhesive bond is weaker than the first adhesive bond.

3. The encased adhesive-coated article combination of claim 2, wherein said support member further comprises a nonstick mounting pad.

4. The encased adhesive-coated article combination of claim 1 further comprising a means for gripping attached to said cover member.

5. The encased adhesive-coated article combination of claim 4, wherein said adhesive-coated article is an adhesive bandage.

6. An assemblage of encased adhesive-coated article combinations comprising:

a. a support member;

b. a plurality of adhesive-coated articles, each said adhesive-coated article including a first adhesive surface, said first adhesive surface having a first adhesive coating covering at least a portion thereof, said adhesive-coated article being removably adhered to said support member by contact of said first adhesive coating, the first adhesive coating between said support member and said first adhesive surface forming a first adhesive bond; and

c. a plurality of cover members, each said cover member removably attached to said support member to releaseably encase a respective adhesive-coated article, each said cover member including a second adhesive coating covering at least a portion thereof, each said cover member being removably attached to said support member by contact of said second adhesive coating with said support member, the contact between said support member and each said cover member forming a second adhesive bond.

7. The assemblage of encased adhesive-coated articles of claim 6, further comprising a plurality of means for gripping, each said means for gripping attached to a respective cover member.

8. The assemblage of encased adhesive-coated articles of claim 6 wherein the support member further comprises a plurality of nonstick mounting pads.

9. The assemblage of encased adhesive-coated articles of claim 7, wherein said adhesive-coated articles are adhesive bandages.

10. The assemblage of encased adhesive-coated articles of claim 8, wherein said adhesive-coated articles are adhesive bandages.

11. The assemblage of encased adhesive-coated articles of claim 7, wherein said support member is a sheet.

12. The assemblage of encased adhesive-coated articles of claim 11, wherein said sheet is a continuous sheet.

13. The assemblage of encased adhesive-coated articles of claim 12, wherein said assemblage is contained in a dispensing unit in a folded configuration.

14. The assemblage of encased adhesive-coated articles of claim 12, wherein said assemblage is contained in a dispensing unit in a rolled configuration.

15. The assemblage of encased adhesive-coated articles of claim 12, wherein said continuous sheet is perforated at predetermined intervals.

16. The assemblage of encased adhesive-coated articles of claim 12, wherein said continuous sheet is perforated between each adhesive-coated article and an adjacent adhesive-coated article.

17. The assemblage of encased adhesive-coated articles of claim 11, wherein said adhesive coated articles are adhesive bandages.

18. The assemblage of encased adhesive-coated articles of claim 12, wherein said adhesive coated articles are adhesive bandages.

19. The assemblage of encased adhesive-coated articles of claim 6, wherein each said cover member is dimensioned to extend beyond the peripheral edges of a respective adhesive-coated article.

20. An encased adhesive-coated article combination comprising:

a. a support member having a patterned second adhesive coating applied thereto;

b. an adhesive-coated article, said adhesive-coated article including a first adhesive surface, said first adhesive surface having a first adhesive coating covering at least a portion thereof, said adhesive-

coated article being removably adhered to said support member by said first adhesive coating, the first adhesive coating between said support member and said first adhesive coating, the first adhesive coating between said support member and the first adhesive surface forming a first adhesive bond; and

c. a cover member removably attached to said support member to releaseably encase said adhesive-coated article, said cover member including a third adhesive coating thereon, said cover member being removably attached to said support sheet by contact of said patterned second adhesive coating with said cover member, the contact between said support member and said cover member forming a second adhesive bond, said cover member further being removably attached to said adhesive-coated article by said third adhesive coating, the third adhesive coating forming a third adhesive bond between said cover member and said adhesive-coated article, said third adhesive bond being stronger than said second adhesive bond.

21. The encased adhesive-coated article combination of claim 20, wherein said second bond is weaker than said first bond.

22. The encased adhesive-coated article combination of claim 20, wherein said support member further comprises a nonstick mounting pad.

23. The encased adhesive-coated article combination of claim 20 further comprising a means for gripping attached to said cover member.

24. The encased adhesive-coated article combination of claim 23, wherein said support member further comprises a nonstick mounting pad.

25. The encased adhesive-coated article combination of claim 23, wherein said adhesive-coated article is an adhesive bandage.

26. The encased adhesive-coated article combination of claim 24, wherein said adhesive-coated article is an adhesive bandage.

27. An assemblage of encased adhesive-coated article combinations comprising:

a. a support member having a patterned second adhesive coating applied thereto;

b. a plurality of adhesive-coated articles, each said adhesive-coated article including a first adhesive surface, said first adhesive surface having a first adhesive coating covering at least a portion thereof, each said adhesive-coated article being removably adhered to said support member by said first adhesive coating, the first adhesive coating between said support member and said first adhesive coating, the first adhesive coating between said support member and each said first adhesive surface forming a first adhesive bond; and

c. a plurality of cover members, each said cover member being removably attached to said support member to releaseably encase a respective adhesive-coated article, each said cover member including a third adhesive coating thereon, each said cover member being removably attached to said support sheet by contact of said second

adhesive coating with said support member, the contact between said support member and each said cover members forming a second adhesive bond, each said cover member further being removably attached to a respective adhesive-coated article by a third adhesive coating, the third adhesive coating forming a third adhesive bond between said each said cover member and a respective adhesive-coated article, said third adhesive bond being stronger than said second adhesive bond.

28. The assemblage of encased adhesive-coated articles of claim 27, further comprising a plurality of means for gripping, each said means for gripping attached to a respective cover member.

29. The assemblage of encased adhesive-coated articles of claim 27, wherein said support member further comprises a plurality of nonstick mounting pads.

30. The assemblage of encased adhesive-coated articles of claim 28, wherein said adhesive-coated articles are adhesive bandages.

31. The assemblage of encased adhesive coated articles of claim 30, wherein said support member further comprises a plurality of nonstick mounting pads.

32. The assemblage of encased adhesive-coated articles of claim 28, wherein said support member is a sheet.

33. The assemblage of encased adhesive-coated articles of claim 32, wherein said sheet is a continuous sheet.

34. The assemblage of encased adhesive-coated articles of claim 33, wherein said continuous sheet is folded.

35. The assemblage of encased adhesive-coated articles of claim 33, wherein said continuous sheet is rolled.

36. The assemblage of encased adhesive-coated articles of claim 33, wherein said continuous sheet is perforated at predetermined intervals.

37. The assemblage of encased adhesive-coated articles of claim 33, wherein said continuous sheet is perforated between each adhesive-coated article and an adjacent adhesive-coated article.

38. The assemblage of encased adhesive-coated articles of claim 33, wherein said adhesive coated articles are adhesive bandages.

39. The assemblage of encased adhesive-coated articles of claim 37, wherein said adhesive coated articles are adhesive bandages.

40. The plurality of encased adhesive-coated articles of claim 27, wherein each said cover member is dimensioned to extend beyond the peripheral edges of said adhesive coated articles.

41. An encased sterile article combination comprising:

a. a support member;

b. a sterile article; and

c. a cover member removably attached to said support member to functionally encase said sterile article, said sterile article being removably adhered to said cover member.

42. The encased sterile article combination of claim 41 wherein said sterile article is a medical applicator.

43. The encased sterile article combination of claim 41 wherein said sterile article is a medical applicator that includes a dispensable medicament.

44. The encased sterile article combination of claim 41 wherein said sterile article is a unit of medicine.

45. The encased sterile article combination of claim 41 wherein said sterile article is a pill, capelet, or capsule.

46. The encased sterile article combination of claim 41 wherein said support member comprises a continuous sheet of molded housings adapted to fittably receive said sterile article.

47. The enclosed sterile article combination of claim 41 wherein said cover member further includes gripping means.

48. The encased sterile article combination of claim 41 further comprising a non-adhesive, burstable film disposed between said support member and said cover member, said film being functionally effective to protect the sterility of said sterile article after the cover member has been removed.

49. An assemblage of encased sterile article combinations wherein said assemblage is contained in a dispensing unit in a folded configuration.

50. An assemblage of encased sterile article combinations wherein said assemblage is contained in a dispensing unit in a rolled configuration.

51. An assemblage of encased sterile article combinations wherein said assemblage is contained in a dispensing unit as individual encased units.

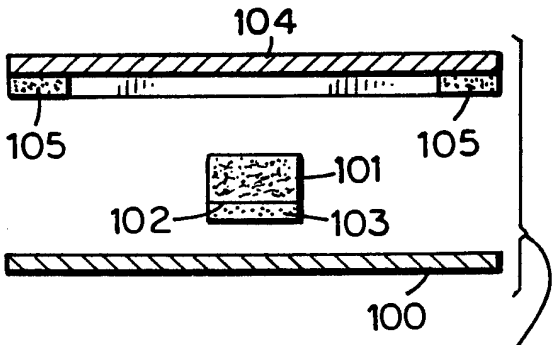


Fig. 1

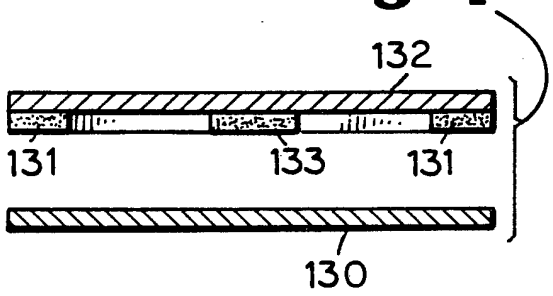


Fig. 4

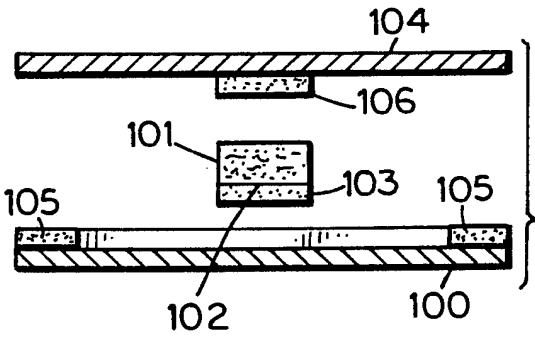


Fig. 2

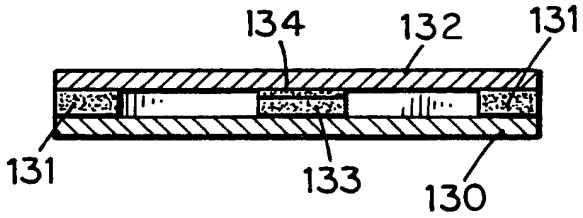


Fig. 5

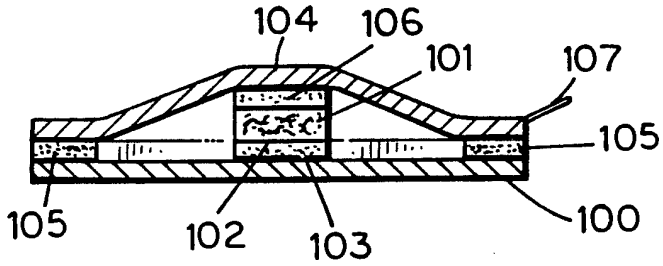


Fig. 3

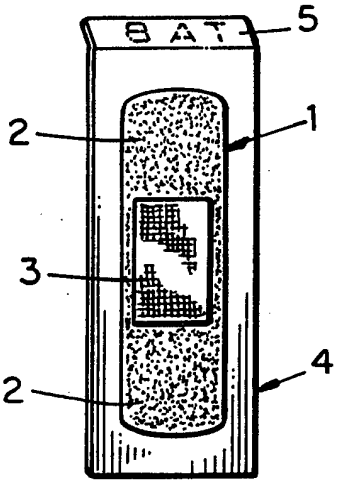


Fig. 6

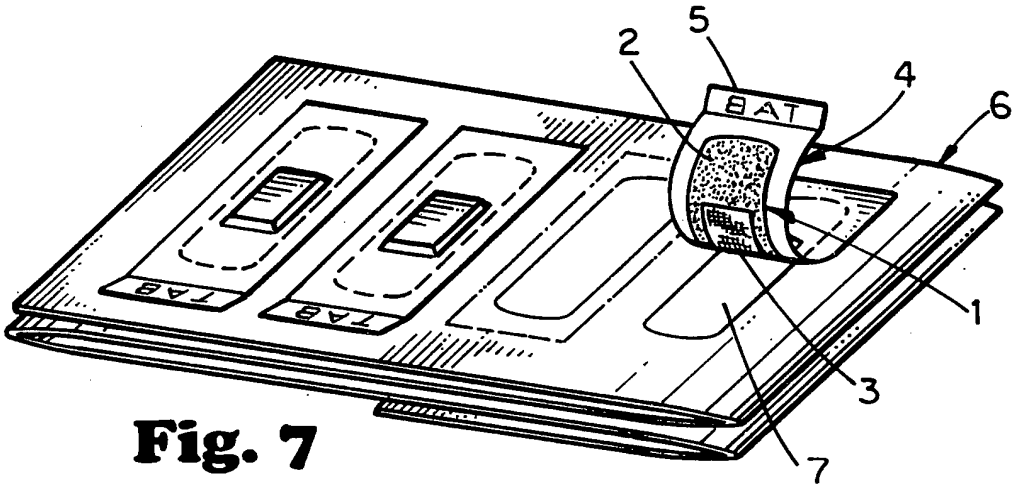


Fig. 7

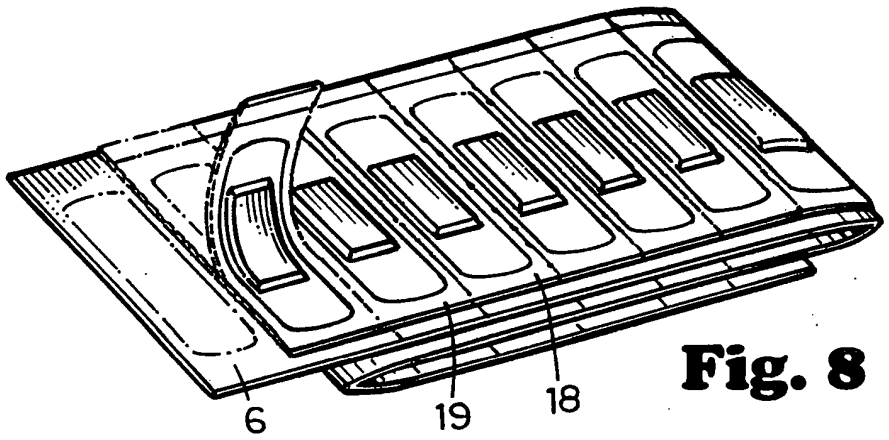


Fig. 8

Fig. 11

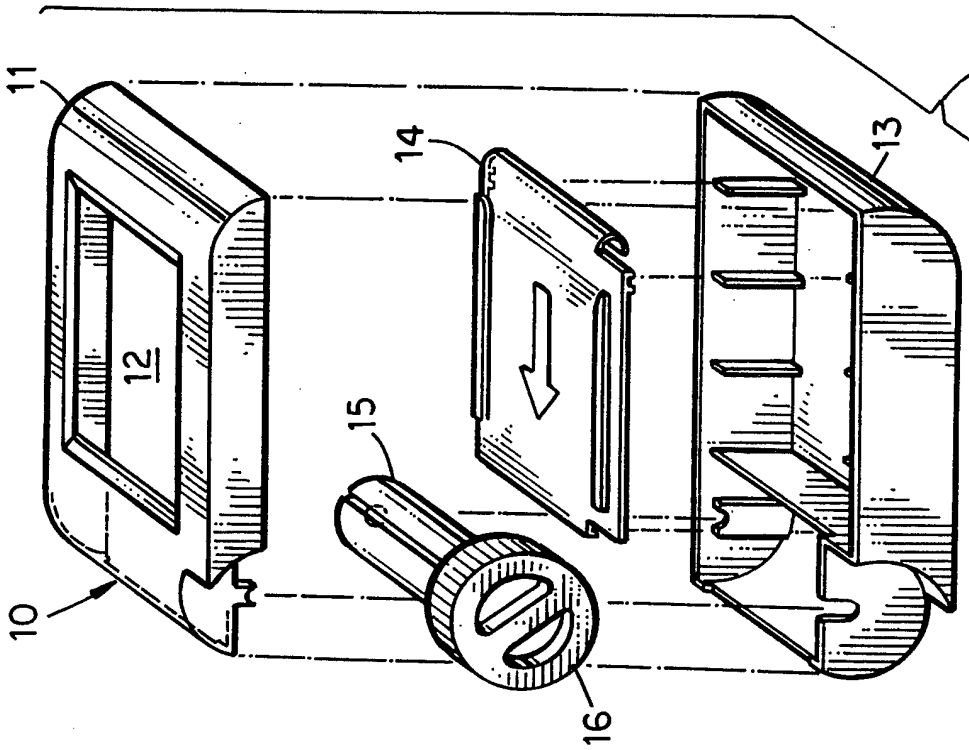


Fig. 9

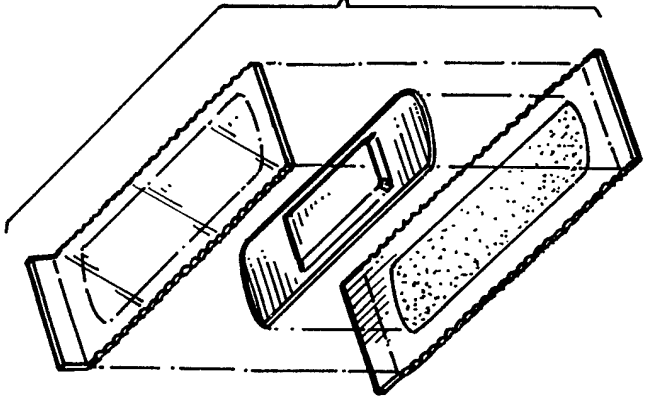
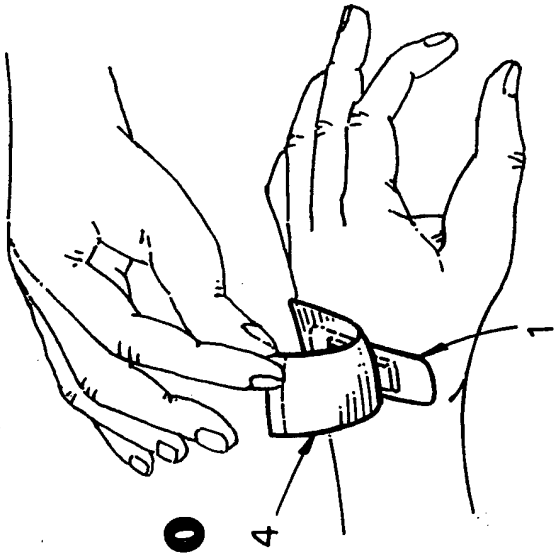


Fig. 10



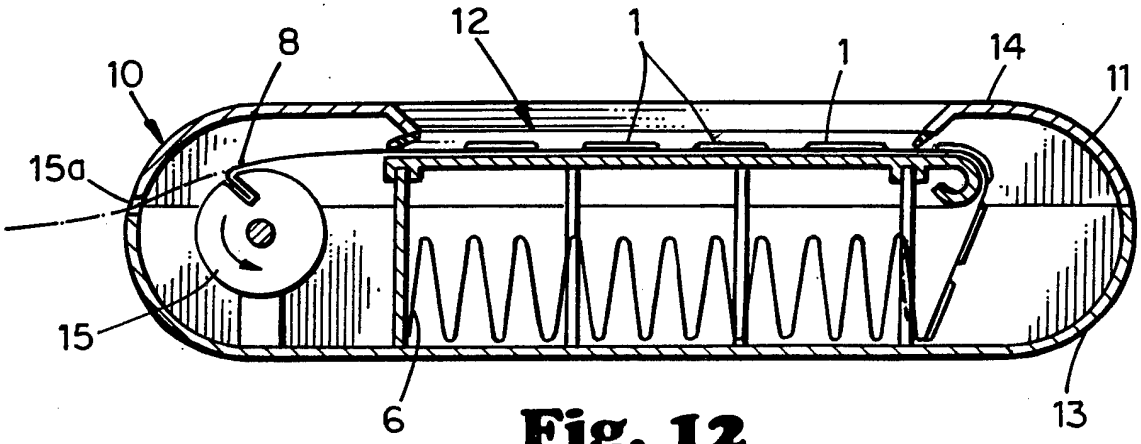


Fig. 12

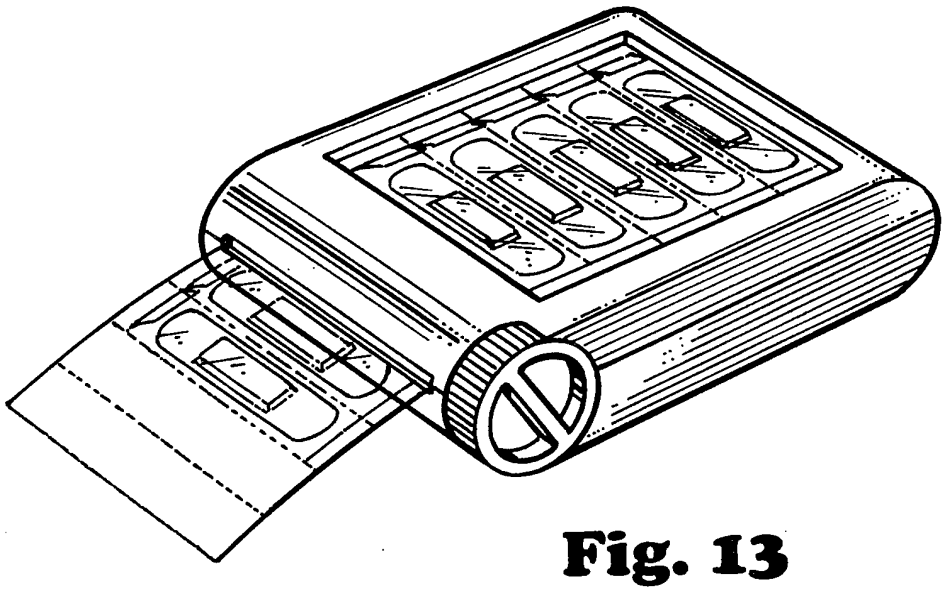


Fig. 13

Fig. 14

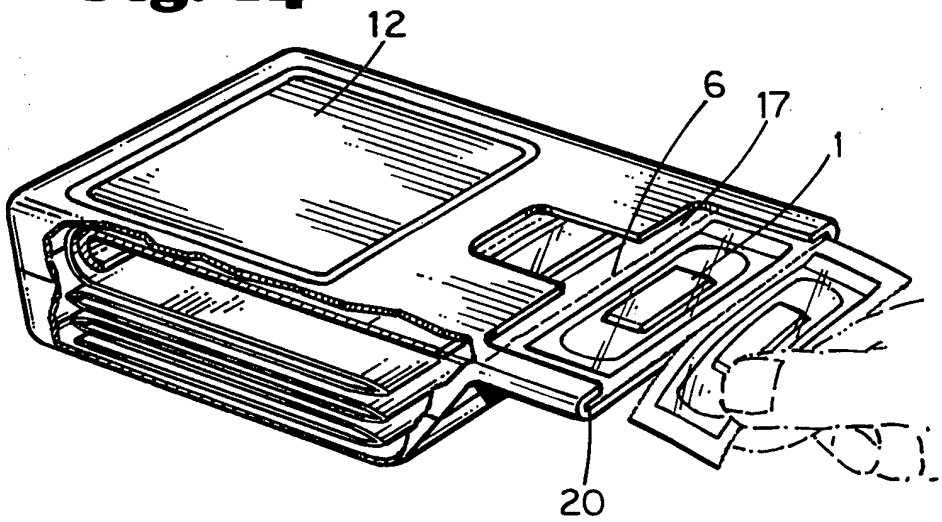


Fig. 15

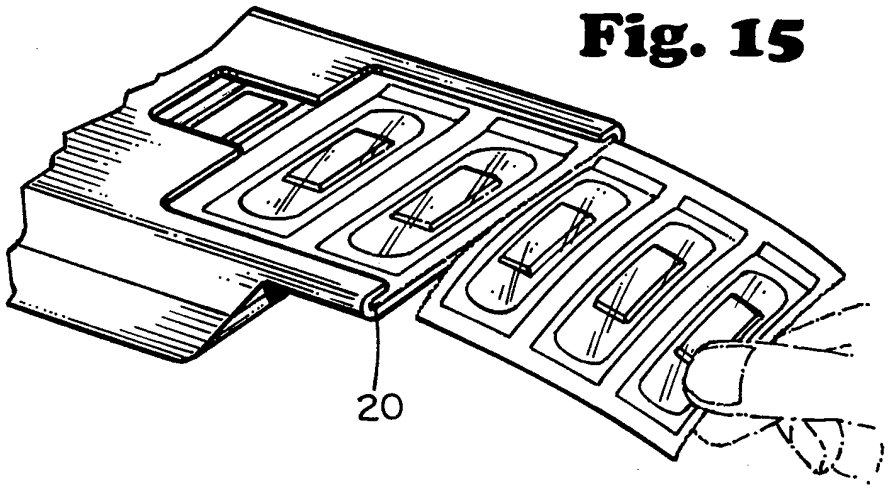
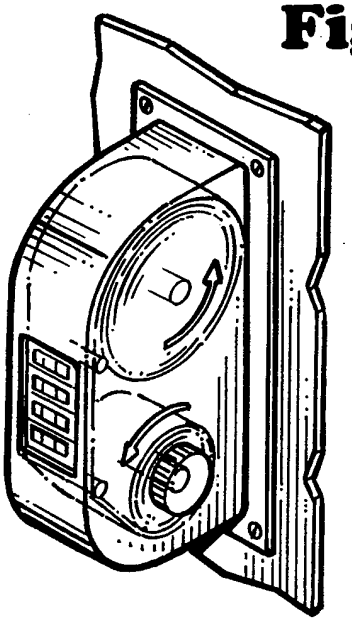


Fig. 16



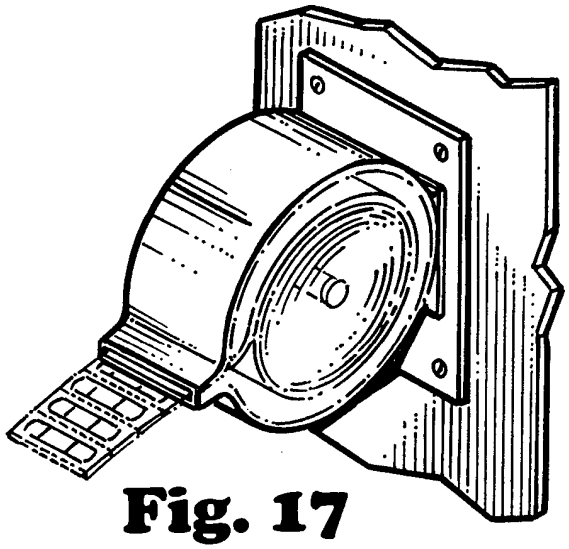


Fig. 17

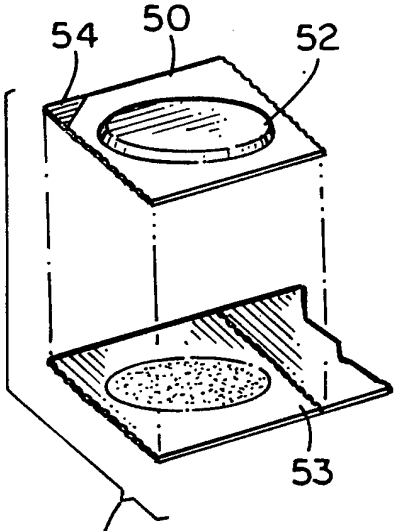


Fig. 18

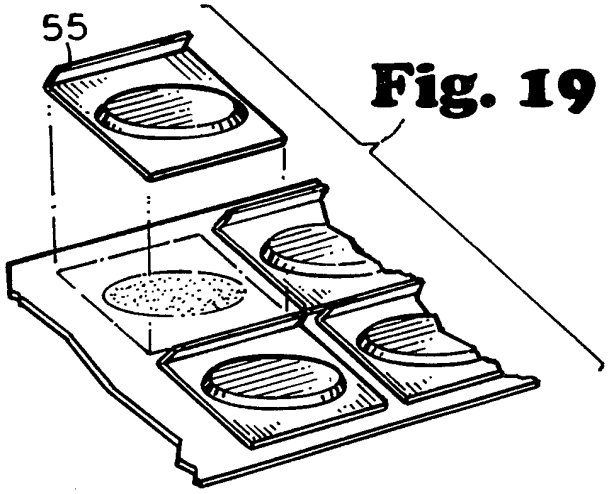


Fig. 19

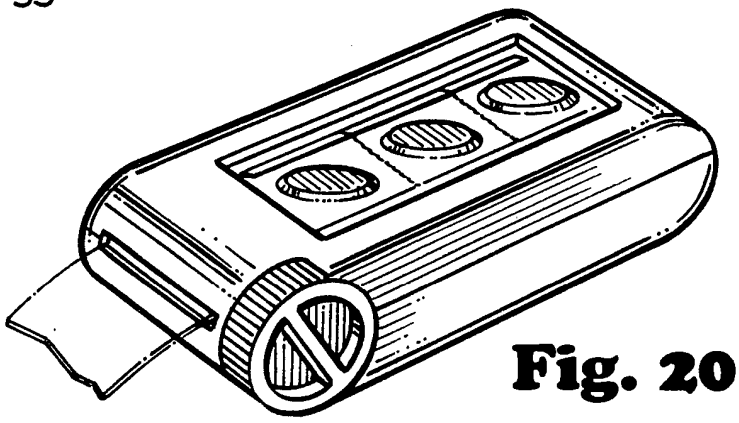
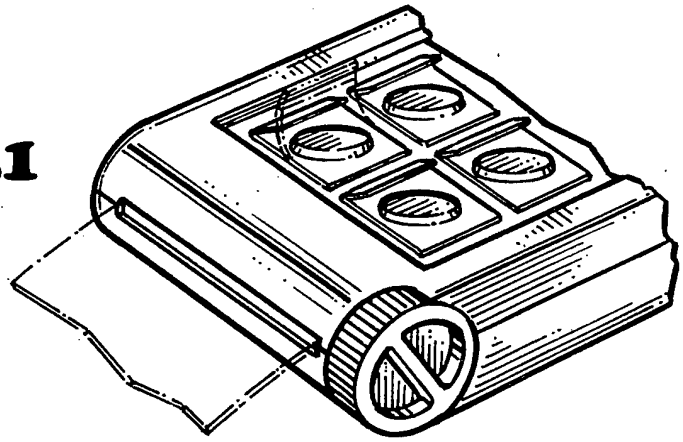
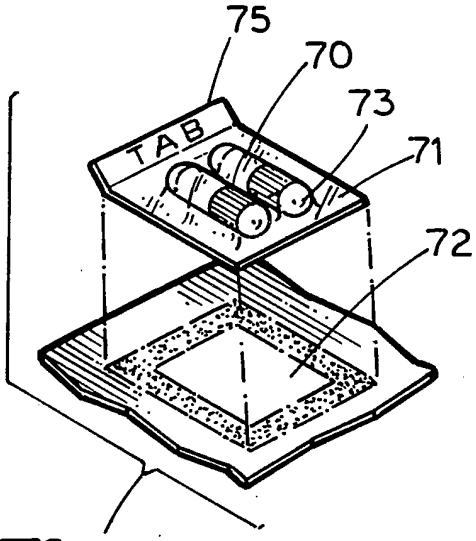


Fig. 20

Fig. 21





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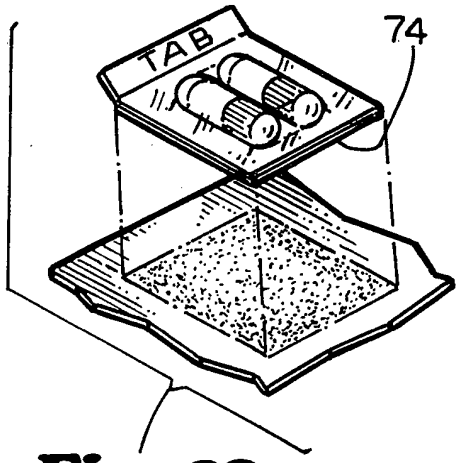


Fig. 23

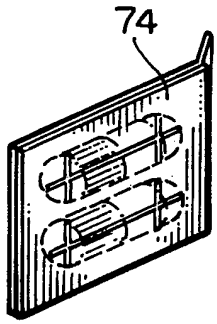


Fig. 24

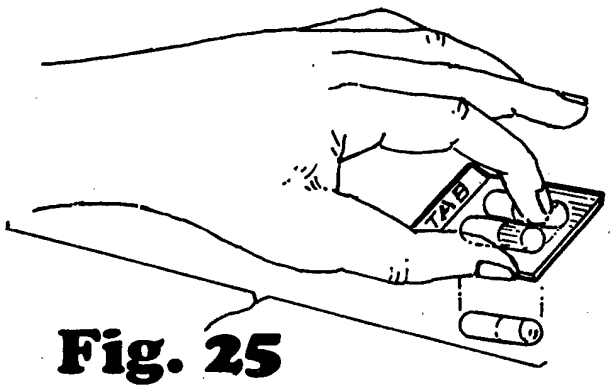


Fig. 25

Fig. 26

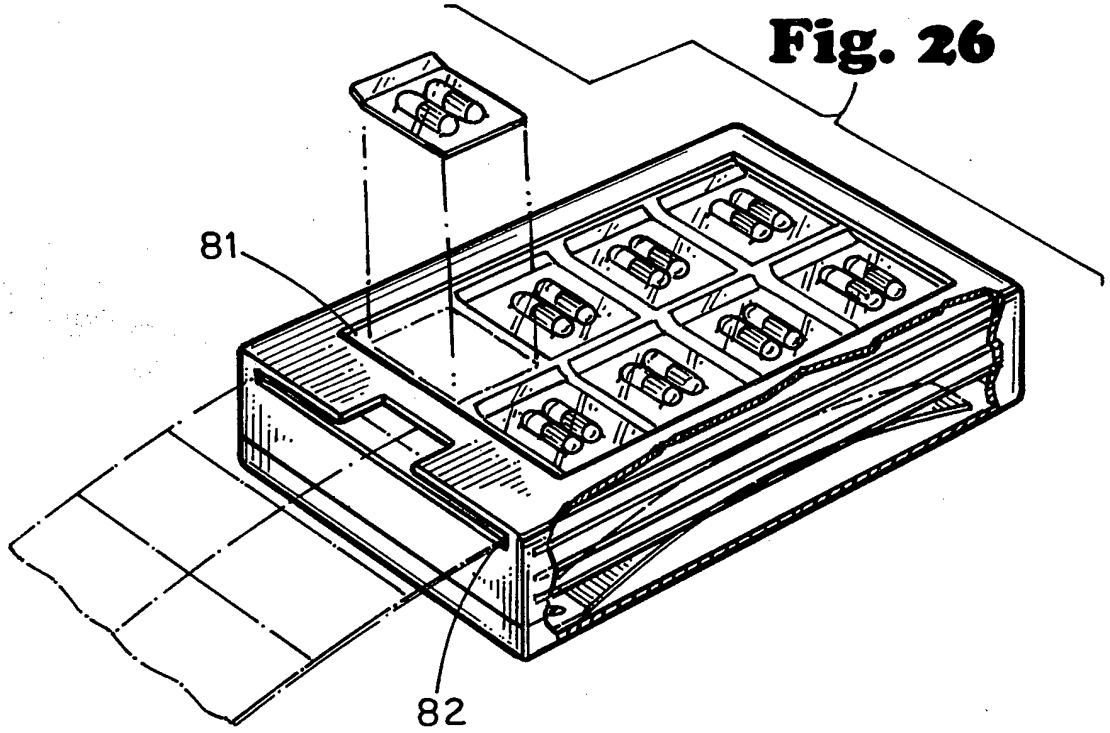
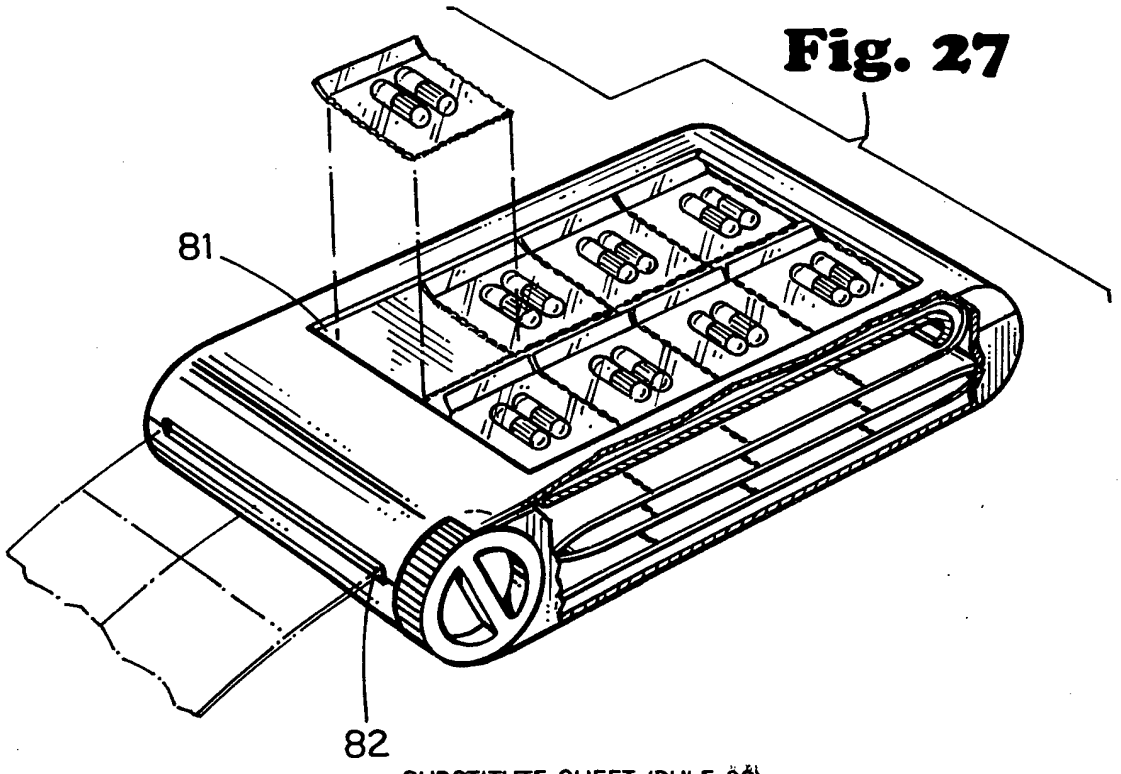


Fig. 27



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/14885

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :Please See Extra Sheet.
US CL :206/528, 440, 441
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 206/528, 440, 441, 820, 534.1, 538

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ---- Y	US, A, 4,265,234 (SCHAAR) 05 May 1991, See the entire document.	1-5, 20-26 ---------- 6-19, 27-41
X ---- Y	US, A, 4,807,753 (GOLDSTEIN) 28 February 1989, See the entire document.	50 ---------- 6-12, 14, 17-19, 27-33, 35, 38, 40

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

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Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer FOR STEVE MEYERS Sheila H. Veney Paralegal Specialist Group 2400 Telephone No. (703) 308-0771

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INTERNATIONAL SEARCH REPORT

International application No.
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X ---- Y	US, A, 4,993,586 (TANLBEE, DECEASED ET AL.) 19 February 1991, See the entire document.	49 ---- 6-13, 17-19, 27-34, 38, 40
X ---- Y	US, A, 4,666,040 (MURATA) 19 May 1987, See the entire document.	51 ---- 6-12, 15, 16-19, 27-33, 36-40
X	US, A, 3,809,221 (COMPERE) 07 May 1974, See the entire document.	41-48
X	US, A, 3,630,346, (BURNSIDE) 28 December 1971, See the entire document.	41-48

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/14885

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6):

B65D 1/09; A61B 19/08

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	95002170
Filing Date	2012-09-10
First Named Inventor	Robert K. Yang
Art Unit	3991
Examiner Name	Diamond, Alan D.
Attorney Docket Number	1199-26 RCE/CON/REX

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	1	5656297		1997-08-12	Bernstein et al.	
	2	5045445		1991-09-03	Schultz	
	3	5380529		1995-01-10	Heusser et al.	
	4	5506046		1996-04-09	Andersen et al.	
	5	5605698		1997-02-25	Ueno	
	6	5653993		1997-08-05	Ghanta et al.	
	7	5679145		1997-10-21	Andersen et al.	
	8	5681873		1997-10-28	Norton et al.	

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	First Named Inventor	Robert K. Yang
	Art Unit	3991
	Examiner Name	Diamond, Alan D.
	Attorney Docket Number	1199-26 RCE/CON/REX

	9	5750145		1998-05-12	Patell	
	10	5750157		1998-05-12	Grosswald et al.	
	11	5766839		1998-06-16	Johnson et al.	
	12	5792494		1998-08-11	Kanca et al.	
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	18	5891461		1999-04-06	Jona et al.	
	19	6103266		2000-08-15	Tapolsky et al.	

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	First Named Inventor	Robert K. Yang
	Art Unit	3991
	Examiner Name	Diamond, Alan D.
	Attorney Docket Number	1199-26 RCE/CON/REX

	20	6667060		2003-12-23	Vandecruys et al.	
	21	5881476		1999-03-16	Strobush et al.	
	22	4136145		1979-01-23	Fuchs et al.	
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	2	20030124176	A1	2003-07-03	Hsu et al.	

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	1	0440462	EP	A1	1991-08-07	Merck & Co., Inc.		☐

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	Filing Date	2012-09-10
	First Named Inventor	Robert K. Yang
	Art Unit	3991
	Examiner Name	Diamond, Alan D.
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	2	1061557	GB		1967-03-15	Ashe Chemical Limited		☐
	3	741362	AU		2001-11-29	LTS Lohmann Therapie Systeme GmbH		☐
	4	196465392	DE		1998-04-14	LTS Lohmann Therapie Systeme GmbH		☐
	5	1997031621	WO		1997-09-04	Warner-Lambert Company		☐
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	1	Stella, V., et al., "Gliadin Films. I: Preparation and in vitro evaluation as a carrier for controlled drug release", Int., J. Pharmaceutics, 121: pp 117-121 (1995).	☐
	2	Bodmeier, Roland, "Evaluation of Drug-Containing Polymer Films Prepared from Aqueous Latexes", Pharmaceutical Research, Vol. 6, No. 8 (1989).	☐
	3	Senel, S., et al., "Chitosan films and hydrogels of chlorhexidine gluconate for oral mucosal delivery", Int. J. Pharmaceutics, 193: pp 197-203 (2000).	☐
	4	Peh et al., "Polymeric Films as Vehicle for Buccal Delivery: Swelling, Mechanical, and Bioadhesive Properties", J. Pharm Pharmaceut Sci 2(2): pp. 53-61 (1999)	☐

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	Filing Date	2012-09-10
	First Named Inventor	Robert K. Yang
	Art Unit	3991
	Examiner Name	Diamond, Alan D.
	Attorney Docket Number	1199-26 RCE/CON/REX

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Application Number	95002170
Filing Date	2012-09-10
First Named Inventor	Robert K. Yang
Art Unit	3991
Examiner Name	Diamond, Alan D.
Attorney Docket Number	1199-26 RCE/CON/REX

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☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

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☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Daniel A. Scola, Jr., Reg. No. 29,855/	Date (YYYY-MM-DD)	2013-01-29
Name/Print	Daniel A. Scola, Jr.	Registration Number	29,855

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4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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Flat medicament preparation for the application and release of buprenorphine or a pharmacologically comparable substance in the buccal cavity, and method of producing the same

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(54) Title: FLAT MEDICAMENT PREPARATION FOR THE APPLICATION AND RELEASE OF BUPRENORPHINE OR A PHARMACOLOGICALLY COMPARABLE SUBSTANCE IN THE BUCCAL CAVITY, AND METHOD OF PRODUCING THE SAME

(54) Bezeichnung: FLACHE ARZNEIZUBEREITUNG ZUR APPLIKATION UND FREISETZUNG VON BUPRENORPHIN ODER EINER PHARMAKOLOGISCH VERGLEICHBAREN SUBSTANZ IN DER MUNDHÖHLE UND VERFAHREN ZU IHRER HERSTELLUNG

(57) Abstract

The invention concerns a solid medicament preparation which can decompose in aqueous media and has a flat-, foil-, paper- or wafer-type presentation for the application and release of active substances in the buccal cavity. The invention is characterized in that it contains buprenorphine, an active substance which is pharmacologically comparable thereto, or a therapeutically suitable salt of buprenorphine or of the pharmacologically comparable active substance.

(57) Zusammenfassung

Eine feste, in wässrigen Medien zerfallsfähige Arzneizubereitung mit flacher, folien-, papier- oder oblatenförmiger Darreichungsform zur Applikation und Freisetzung von Wirkstoffen in der Mundhöhle ist gekennzeichnet durch einen Gehalt an Buprenorphin, einem dem Buprenorphin pharmakologisch vergleichbaren Wirkstoff, oder einem therapeutisch geeigneten Salz des Buprenorphins oder des pharmakologisch vergleichbaren Wirkstoffes.

ABSTRACT

A solid pharmaceutical preparation, disintegratable in aqueous media, with a flat, foil-shaped, paper-shaped or wafer-shaped administration form, for application and release of active substances in the oral cavity is characterized by a content of buprenorphine, of an active substance pharmacologically comparable to buprenorphine, or of a therapeutically suitable salt of bruprenorphine or the pharmacologically comparable active substance.

Flat pharmaceutical preparation for application and release of buprenorphine or of a pharmacologically comparable substance in the oral cavity, and process for the production thereof

The present invention relates to a pharmaceutical preparation for application of buprenorphine or pharmacologically comparable active substances in the region of the oral cavity, respectively the oral mucosa. More particularly, it relates to a preparation that is adapted to be flat and in the form of a foil-, paper- or wafer-shaped administration form.

Flat active substance carriers have already been developed and produced for various purposes. DE-OS 27 46 414 can be regarded as fundamental to this administration form, said document describing a foil-type tape of active substance, binder and further active substances, with a direct relation existing, by reason of the homogeneous thickness, density and width, between a unit of length of the tape and the dose of active substance contained therein. The advantages of the continuous dosage property have been recognized also by other applicants and have been described in specific individual variants. Thus, DE-PS 36 30 603 claims a flat-shaped carrier material, for example in the form of a separating layer, with an active substance-containing coating, the latter being peelable, in doses, off the carrier material after having been previously separated into dosage units.

The practicability of the flat format in general and the advantages afforded in the manufacture of the administration form and in the dosing when employing such administration form have been recognized in the prior art.

Moreover, further advantages of such administration forms can be derived such as the fact that, relative to the weight of the administration form, a relatively large surface may be printed on the said administration form, thereby making it possible to increase intake safety, as well as affording the possibility of discrete intake without any liquid being available.

Despite these obvious advantages, such flat administration forms have hitherto hardly been successful. Obviously, the advantage as compared to conventional administration forms does not suffice for many manufacturers of pharmaceutics to develop products of this type comprising the usual active ingredients and to pursue the legal drug approval thereof. Moreover, existing production machinery and existing know-how cannot be made use of for these novel products; this means that the necessity of large investments would arise. Despite the above-described advantages of flat, film- or paper-like administration forms, the therapeutic and/or economic advantage in administration of common active substances which are also perorally applicable is apparently not great enough as compared to conventional tablets to justify the costs of switching over to these administration forms.

One of the substances that are little suitable for peroral administration is buprenorphine, an opiate which has been successfully used in the therapy of pain for years. After peroral application it is hardly bioavalable, i.e. it appears in the blood circulation only to the very small extent of a few percent of the dose taken (McQuay & Moore, in: Bupenorphine, ed. Cowan & Lewis, New York 1995). Presumably, the reason for the lack in bioavailability lies in the extensive decomposition of the substance during the first liver passage following gastrointestinal absorption ("first-pass effect"). A possibility of avoiding the first-

pass effect in oral administration is to bring the active substance to absorption already on the oral mucosa. In order to enter the central systemic circulation, an active substance which enters into the blood via the oral mucosa does not have to first pass the portal system and thus, in concentrated form, the liver, which metabolizes the active substance. A prerequisite for buccal or sublingual application, however, is a sufficient permeability of the oral mucosa to the active substance, taking into consideration the required dose. Permeability in turn depends to a large extent on the physicochemical properties of the active substance. Since buprenorphine is effective in very small doses, and since it has the required physicochemical characteristics, buccal or sublingual application is very attractive.

In fact, apart from injectable administration forms there are - at least in Germany - no commercially available peroral administration forms, but only so-called sublingual tablets, which comprise buprenorphine (Temgesic® sublingual). It is true that such tablets take into account the fact that sublingual application of the active substance is preferable to peroral administration - even though they do so above all by way of their intake directions as only these suggest the sublingual administration, not the tablet itself. However, they offer a vehicle which has considerable drawbacks for this purpose of application. Among these disadvantages is, firstly, the not inconsiderable disintegration time, which in the case of pressed tablets is at least several minutes even under favorable conditions, and in the case of the commercially available tablets is typically about 5 to 10 minutes. For patients suffering from severe, acute pain this disintegration time results in an unwanted delay of the onset of action; in a substitution or withdrawal therapy, however, this puts a strain on the medicinal personnel with

respect to the time required for administration, since the personnel must supervise that the tablets are used as directed and must prevent improper removal of the non-disintegrated tablet from the mouth. Further disadvantages of the tablet are the foreign body sensation occurring during the disintegration time, but also the great variability in the extent of sublingual absorption, which is caused by the active substance during or after disintegration of the tablet having for the most part no direct contact with the oral mucosa, but being released into the saliva; the saliva, however, can be retained in the oral cavity for a very variable time, which is more or less haphazard, before being swallowed.

The present invention provides, in one aspect thereof, pharmaceutical preparations based on, and having the general advantages of, flat, film-like or paper-like active substance carriers which by reason of the combination with **a special active substance have additional economical and/or therapeutical advantages, apart from those mentioned above, over pharmaceutical preparations of the same active substance based on conventional administration forms such** as tablets. In addition, the present invention preferably provides an administration form for buprenorphine that releases the active substance in the oral cavity while not having the disadvantages described in the prior art.

More specifically, the present invention provides, in one aspect, buccal pharmaceutical preparation for treating acute conditions of pain or for addiction therapy, comprising as active substance buprenorphine or a therapeutically acceptable salt thereof, or an opiate active substance or a therapeutically suitable salt thereof, characterised by a flat, film-like administration form, disintegratable in the aqueous medium of the oral cavity, which has a mucoadhesive, active substance-containing layer based on water-soluble,

film forming polymers of small thickness, for rapid active substance transfer through short diffusion paths, while having a large surface appropriate to the effective dose.

Additionally, the invention provides method of producing a pharmaceutical preparation as herein before described, characterized in that in a first step the active substance(s), together with a water-soluble polymer capable of film-formation, is (are) dissolved in a suitable, hydrophile solvent, optionally in presence of further dissolved or suspended auxiliary agents, that in a second step the solution or suspension is applied, in a continuous process and with even thickness, to a tape or a process sheet or foil, where, in a third step, it is largely freed from the solvent, thereby forming a sheet-shaped or tape-shaped starting material, wherefrom, in a fourth step, the dosage or multidosage units are separated by cutting or punching.

Further, the invention provides method of producing a pharmaceutical preparation as herein before described, characterized in that in a first step the active substance(s), together with a water-soluble, thermoplastic polymer capable of film-formation, is (are) formed, under action of heat and/or pressure, and optionally in presence of further auxiliary substances, into a sheet-shaped or tape-shaped starting material, from which starting material the dosage or multidosage units are separated by cutting or punching.

The invention may be achieved in accordance with the features of the claims providing an administration form on the basis of flat, foil-, paper- or wafer-like active substance carrier, which administration form contains an active substance buprenorphine, respectively one of its therapeutically acceptable salts, or a therapeutically comparable active substance. As will be explained in the following, an

administration form according to Claim 1 may be considered by far superior to a conventional administration form for administering buprenorphine - both from the economical as well as the therapeutical point of view - and it is especially suitable, on the one hand, for analgesia in cases of acute conditions of pain, and, on the other hand, for the therapy of opiate or cocaine addiction in the sense of a substitution therapy or a withdrawal program.

The pharmaceutical preparation according to claim 1 can, upon application, be brought into direct contact with the oral mucosa. Due to the flat design, immediately after application about half of the surface of the administration form, which is large anyway, is located directly on the mucosa. The buprenorphine released thus encounters two factors particularly favorable for entry into the body, namely a short diffusion path and a large diffusion area. This reduces the portion of buprenorphine that is swallowed, which in the case of many other active agents would not be a particular problem. However, with buprenorphine, swallowing of the active substance should be avoided if possible, or should be reduced since, for the above mentioned reasons, swallowed buprenorphine is ineffective. Even in the case of the most simple embodiment according to the invention, and given a disintegration time of a few minutes following application or following introduction into aqueous media, the superiority of a buprenorphine-containing film over a buprenorphine-containing tablet will thus become evident.

An improved contact of the pharmaceutical preparation with the oral mucosa can be achieved through selecting auxiliary substances. It is known of certain orally applicable auxiliary agents which are commonly used in pharmaceutics that they have mucoadhesive properties. Examples for such mucoadhesive substances are polyacrylic acid, carboxy-methylcellulose, tragacanth, alginic acid, gelatin,

hydroxymethylcellulose, methylcellulose and gum arabic. In addition, it is known of various non-mucoadhesive substances that in certain mixing ratios they develop mucoadhesive properties too. An example for such a mixture is glycerol monooleate/water in a ratio of 84:16 (Engström et al., Pharm. Tech. Eur. 7 [1995], No. 2, pages 14-17).

In the case that mucoadhesive auxiliary substances are used, it is preferable for the administration form of the pharmaceutical preparation according to the invention to have a two-layer or multi-layer structure. It can thereby be prevented that the preparation conglutinates various parts of the mucosa with each other, which would lead to sensations of considerable discomfort during application. In addition, it is in such a case preferable for the administration form to have a structure the non-mucoadhesive layer of which has a permeability to the active substance which is relatively smaller than that of the mucoadhesive layer, it thereby being possible to prevent that active substance losses occur due to active substance being released into the saliva instead of to the mucosa.

Pharmaceutical preparations according to the present invention are also those containing, apart from the active substance buprenorphine or an active substance pharmacologically comparable thereto, one or more further active substances. Such a preparation can be advantageous in several respects. On the one hand it is a recognized method for treating several symptoms or conditions occurring simultaneously to administer a fixed active substance combination in a medicament. To this end, it is possible to incorporate any therapeutically appropriate active substances into the preparation according to the present invention. On the other hand, the combination, as according to the invention, of an opiate active substance

with another substance that is capable of reducing the specific risks of opiate administration is especially useful and advantageous.
Thus - possibly partial - opiate antagonists, such as, for example, nalbuphine, naloxone or naltrexone, can be combined with the opiate active substance, which results in the risk of addiction or habituation involved in the repeated administration of the preparation being diminished by reason of the fact that the dose cannot be increased without at the same time accepting an increase of the antagonistic effect. The success of this strategy will depend on the selection of a suitable antagonist as well as the selection of the dose ratio.

Though buprenorphine - optionally in the form of one of its therapeutically acceptable salts - is the most preferred active substance, the invention also relates to such active substances as are pharmacologically similar or comparable to buprenorphine since the advantages of the invention described herein also apply in these cases, though to different extent. Further suitable active substances, which are also described herein as being "pharmacologically similar or comparable", are, in particular, those substances belonging to the opiates or opioids since many of these not only exhibit pharmacodynamic but also pharmacokinetic similarities to buprenorphine, that is a relatively low dose, good capacity for permeating membranes, and a high first-pass effect. Particularly preferred are morphine derivatives or dihydromorphine derivatives as well as substances from the methadone and fentanyl group.

In order not to promote any improper application or one that does not conform to the intended use, pharmaceutical preparations according to the invention will typically be present predivided into doses and separated from each other

in a suitable package, so that when removing a dosage unit it will be possible to remove only one unit at a time, such as in the case of a blister pack, where each dosage unit is sealed individually in a deep-drawn cup. Within programs for treatment of opiate or cocaine addiction it may, however, also be useful to supply physicians who are providing the medical care, for example, with preparations in the form of packaging units wherein said preparations are present as undivided sheet-like or tape-like material, from which the dosage units can be separated for the purpose of application. This facilitates mass application and affords the physicians who are administering the preparations the possibility of separating from one and the same material various dosage units in accordance with the given dosage requirements.

Since the pharmaceutical preparation according to the present invention is expected to exhibit increased bio-availability as compared to known preparations, it will possibly be necessary to adjust the dosage. In the case of buprenorphine the individual analgesic dose will be about 0.1 to 1 mg; in addiction or substitution therapy, however, this value might be considerably higher.
In accordance with the invention the manufacture of the pharmaceutical preparation is performed in several steps. For preparing the web-shaped starting material - from which ultimately either individual doses or entire packaging units will be separated by cutting or punching - two basic process variants are suitable. The first group of processes includes those where a tape, or a process sheet or foil, is evenly coated with aqueous or solvent-containing liquids being in part of higher viscosity, and where this is subsequently subjected to a drying process. To this end, first, a coating mass is prepared, for which purpose at least one water-soluble polymer capable of forming a film, the active substance(s) and a suitable, vaporizable liquid

must be intimately mixed. If required it is possible to incorporate further auxiliary substances such as disintegration-modifying polymers, softeners, fillers, texture-providing substances, pigments, dyes, taste corrigents, solubilizers, substances for adjusting the pH, *smoothing agents, dulling agents, disintegration promoters, etc. As an alternative, the web-like starting material may be made by thermoplastic forming, i.e. without the aid of liquids. Suitable processes are, inter alia, any hot-melt coating methods as well as any extrusion methods. As a prerequisite, the polymer or polymer mixture capable of film-formation must in this case be thermoplastically formable. The required ingredients are mixed and, under action of pressure and/or heat, formed by extruding, blowing or by coating of tapes, sheets or foils, and, after solidification, transferred for further processing. Suitable for the manufacture of preparations according to the present invention that have a multi-layer structure are correspondingly modified methods, it being irrelevant whether several web-shaped materials are simultaneously or subsequently produced and combined.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or group of integers or steps but not the exclusion of any other integer or group of integers or steps.

The reference to any prior art in this specification is not, and should not be taken as, an acknowledgement or any form of suggestion that the prior art forms part of the common general knowledge in Australia.

The claims defining the invention are as follows:

1. Buccal pharmaceutical preparation for treating acute conditions of pain or for addiction therapy, comprising as active substance buprenorphine or a therapeutically acceptable salt thereof, or an opiate active substance or a therapeutically suitable salt thereof, characterised by a flat, film-like administration form, disintegratable in the aqueous medium of the oral cavity, which has a mucoadhesive, active substance-containing layer based on water-soluble, film-forming polymers of small thickness, for rapid active substance transfer through short diffusion paths, while having a large surface appropriate to the effective dose.

2. Pharmaceutical preparation according to claim 1, characterized by a mono- or multi-layered structure having a mucoadhesive active substance-containing layer based on water-soluble, film-forming polymers of small thickness for rapid active substance uptake through short diffusion paths.

3. Pharmaceutical preparation according to claim 1 or 2, characterized by a non-mucoadhesive outer layer, opposed to the mucoadhesive surface, which outer layer has a lower permeability to the active substance.

4. Pharmaceutical preparation according to any one of the preceding claims, characterized by a single-dose buprenorphine content of 0.1 - 1 mg.

5. Pharmaceutical preparation according to any one of the preceding claims, characterized in that it is equipped with bioadhesive or mucoadhesive properties by the addition of an adhesion-promoting auxiliary substance or auxiliary substance mixture.

6. Pharmaceutical preparation according to claim 5, characterized in that further active substance is present which is suitable for treating addiction to opiates.

7. Pharmaceutical preparation according to claim 6, characterized in that further active substance is, at least partially, capable of opiate antagonist action.

8. Pharmaceutical preparation according to claim 7, characterized in that it contains nalbuphine, naloxone or naltrexone.

9. Pharmaceutical preparation according to one or more of the preceding claims, characterized in that it is present as an undivided, sheet-shaped or tape-shaped material, from which it is possible to separate dosage units for the purpose of application.

10. Pharmaceutical preparation according to one or more of the preceding claims, characterized in that it is present predivided into doses.

11. Pharmaceutical preparation according to one or more of the preceding claims, characterized in that, per dosage unit, it has a content of active substance which is suitable for analgesia.

12. Pharmaceutical preparation according to one or more of the preceding claims, characterized in that, per dosage unit, it has a content of active substance which is suitable for opiate or cocaine substitution therapy.

13. Method of producing a pharmaceutical preparation according to one or more of the preceding claims,

characterized in that in a first step the active substance(s), together with a water-soluble polymer capable of film-formation, is (are) dissolved in a suitable, hydrophile solvent, optionally in presence of further dissolved or suspended auxiliary agents, that in a second step the solution or suspension is applied, in a continuous process and with even thickness, to a tape or a process sheet or foil, where, in a third step, it is largely freed from the solvent, thereby forming a sheet-shaped or tape-shaped starting material, wherefrom, in a fourth step, the dosage or multidosage units are separated by cutting or punching.

14. Method of producing a pharmaceutical preparation according to one or more of the preceding claims, characterized in that in a first step the active substance(s), together with a water-soluble, thermoplastic polymer capable of film-formation, is (are) formed, under action of heat and/or pressure, and optionally in presence of further auxiliary substances, into a sheet-shaped or tape-shaped starting material, from which starting material the dosage or multidosage units are separated by cutting or punching.

15. Method of producing a pharmaceutical preparation according to claim 13 or 14, characterized in that a plurality of simultaneously or subsequently prepared, sheet-shaped or tape-shaped starting materials are combined to form a multilayered material, from which the dosage or multidosage units are separated.

16. Buccal pharmaceutical preparations or methods for producing same substantially as herein described with reference to the Examples.

DATED this 20th day of September, 2001

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Die folgenden Angaben sind den vom Anmelder eingereichten Unterlagen entnommen

Prüfungsantrag gem. § 44 PatG ist gestellt

(54) Zubereitung zur Anwendung in der Mundhöhle mit einer an der Schleimhaut haftklebenden, Pharmazeutika oder Kosmetika zur dosierten Abgabe enthaltenden Schicht

(57) Eine Zubereitung zur Anwendung in der Mundhöhle mit einer an der Schleimhaut haftklebenden Schicht ist dadurch gekennzeichnet, daß die haftklebende Schicht eine homogene Mischung enthält, bestehend aus einem wasserlöslichen Polymer, einer Mischung nichtionischer oberflächenaktiver Stoffe, einem Polyalkohol, einem kosmetischen oder pharmazeutischen Wirkstoff, und einem Geschmacks- oder Aromastoff.

DE 196 46 392 A 1

Beschreibung

Zubereitung zur Anwendung in der Mundhöhle mit einer an der Schleimhaut haftklebenden, Pharmazeutika oder Kosmetika zur dosierten Abgabe enthaltenden Schicht.

Derartige an der Mundschleimhaut haftklebende Dosiersysteme zur Anwendung in der Mundhöhle sind bekannt. Die US 5,047,244 beschreibt einen an der Mundschleimhaut haftklebenden Träger zur kontrollierten Abgabe eines therapeutischen Wirkstoffs durch das Schleimhautgewebe, der eine wasserfreie, aber hydratisierbare Polymermatrix und amorphes Siliciumdioxid enthält.

Fakultativ kann ein wasserunlöslicher Film beigefügt werden, um die Oberfläche nichtadhäsiv zu gestalten. Die WO 91/06270 des gleichen Erfinders offenbart einen dreischichtigen Film zur verlängerten Abgabe eines aktiven Wirkstoffs in der Mundhöhle.

In gleicher Weise offenbart US 4,876,092 eine flächenförmige, adhäsive Zubereitung, umfassend eine adhäsive Schicht, welche bestimmte wasserlösliche und wasserunlösliche Polymere und einen wasserunlöslichen Träger enthält, welcher an der Mundschleimhaut haftet und dabei einen aktiven Wirkstoff an die Mundhöhle abgibt.

Alle diese vorgenannten Vorrichtungen sind nicht vollständig wasserlöslich und verbleiben in der Mundhöhle, selbst nach Erreichen des therapeutischen Ziels, und bereiten dem Patienten ein gewisses Unbehagen im Mund, das hauptsächlich durch die Trägerschicht verursacht wird, welche einen unlöslichen Rückstand im Mund zurückläßt.

Eine Reihe von Versuchen wurde unternommen, um das ungute Gefühl in der Mundhöhle zu verringern, welches durch die Starrheit und mangelnde Flexibilität der Trägerschicht verursacht wurde, indem man weiche Filmträger einführte. Die Dokumente EP 0 200 508 und EP 0 381 194 schlagen die Verwendung von Polyethylenfilmen, Polyvinylacetat, Ethylen-Vinylacetat-Copolymeren, Metallfolien, Stofflaminaten, Papier- oder Plastikfilm und ähnlichen Materialien als weiche Träger vor, wobei synthetische Harze wie Polyethylen, Vinylacetat-Homopolymere und Ethylen-Vinyl-Acetat bevorzugte Materialien sind. In gleicher Weise offenbart CA-PS 1 263 312 die Verwendung von Polyolefinen wie Polyethylen, Polypropylen, Polyester, PVC, sowie Vliesstoffen als weiche Trägermaterialien. Dennoch hinterlassen diese beim Patienten eine beträchtliche Menge von Rückständen des wasserunlöslichen Trägerfilms und verursachen dabei immer noch ein unbehagliches Gefühl. Eine naheliegende Lösung zur Überwindung dieses Problems war die Entwicklung schleimhauthaftender Filme, welche vollständig zerfallen oder sich im Speichel auflösen.

Fuchs und Hilmann (DE 24 49 865.5) stellten homogene, wasserlösliche Filme für buccale Zuführung von Hormonen her. Sie schlugen die Verwendung von wasserlöslichen Cellulosederivaten wie Hydroxyethylcellulose, Hydroxypropylcellulose oder Methylhydroxypropylcellulose als Filmbildner vor.

Die beiden Patentschriften DE 36 30 603 und EP 0 219 762 offenbaren die Verwendung von quellbaren Polymeren wie Gelatine oder Maisstärke als Filmbildner, welche nach Applikation in der Mundhöhle langsam zerfallen, wobei sie einen aktiven Wirkstoff freisetzen, der im Film enthalten ist. Die gleichen Polymere können ebenfalls verwendet werden, um Filme herzustellen, die zur Zahnpflege dienen sollen, entsprechend der Beschreibung in EP 0 452 446. Aber auch diese Zubereitungen rufen ebenfalls ein ungutes Gefühl im Mund hervor, insbesondere verursacht durch ihre anfängliche Starrheit und verzögerte Erweichung. Hieraus resultiert ein Bedarf für eine Komposition zur Verwendung in der Mundhöhle, die dem Erfordernis

eines Wohlgefühls im Mund Rechnung trägt.

Der vorliegenden Erfindung liegt daher die Aufgabe zugrunde, eine Zubereitung anzugeben, die geeignet ist, ein angenehmes Gefühl im Mund zu erzeugen, indem sie einen Film zur Applikation an der Mundschleimhaut vorsieht, der eine sofortige Benetzbarkeit aufweist und eine haftklebende Befestigung in der Mundhöhle unter Abgabe pharmazeutischer oder kosmetischer Wirkstoffe, ermöglicht, die sich rasch auflöst bzw. zerfällt.

Die Lösung der Aufgabe gelingt bei einer Zubereitung der im Oberbegriff von Anspruch 1 genannten Art mit der Erfindung dadurch, daß die haftklebende Schicht eine homogene Mischung enthält, bestehend aus einem wasserlöslichen Polymer, einer Mischung nichtionischer oberflächenaktiver Stoffe, einem Polyalkohol, einem kosmetischen oder pharmazeutischen Wirkstoff, und einem Geschmacksstoff.

Mit großem Vorteil ist der daraus resultierende Film charakterisiert durch eine sofortige Benetzbarkeit, welche den Film unverzüglich nach Applikation am Schleimhautgewebe erweichen läßt und beim Patienten ein unangenehmes Gefühl im Mund verhindert.

Der Film ist unter Verwendung konventioneller Beschichtungs- und Trocknungstechniken herstellbar, in Form und Größe nach Anforderungen spezieller Applikation vereinzelbar und in geeignete Packungen verpackbar.

Eine Ausgestaltung der Erfindung sieht vor, daß das wasserlösliche Polymer der Zubereitung Hydroxypropylmethylcellulose, Hydroxy-ethylcellulose, Hydroxypropylcellulose, Polyvinylpyrrolidon, Carboxymethylcellulose, Polyvinylalkohol, Natriumalginat, Polyethylenglycol, Xanthanharz, Traganth, Guarharz, Akazienharz, Gummiarabicum, Polyacrylsäure, Methylmethacrylatcopolymer, Carboxyvinylcopolymere oder deren Mischungen umfaßt.

Dabei ist vorgesehen, daß die Konzentration des wasserlöslichen Polymers in der Trockenmasse der Filmschicht zwischen 20 und 60 Gew.-% beträgt. Eine bevorzugte Konzentration beträgt zwischen 30 und 50 Gew.-%.

Weiterhin ist mit der Erfindung vorgesehen, daß die Mischung der oberflächenaktiven Stoffe vorzugsweise aus zwei Komponenten besteht. Dabei ist die erste Komponente ein Polyethoxysorbitan-fettsäureester oder ein α-hydroω-hydroxypoly(ethoxy)-poly-(propoxy)-poly(ethoxy)-Blockcopolymer.

Die zweite Komponente ist ein Polyethoxy-alkylether oder ein Polyethoxy-rizinusölderivat.

Bevorzugt soll der HLB-Wert der Polyethoxysorbitanfettsäurester zwischen 10 und 20 betragen, wobei ein Bereich zwischen 13 und 17 besonders bevorzugt ist. Das αhydro-ω-hydroxypoly(ethoxy)-poly(propoxy)-poly(ethoxy)-Blockcopolymer soll mindestens 35 Propoxy-Einheiten, bevorzugt mindestens 50 Propoxy-Einheiten enthalten.

Der Polyethoxyalkylether sollte einen HLB-Wert zwischen 10 und 20 besitzen, bevorzugt nicht weniger als 15. Das Polyethoxy-rizinusölderivat soll einen HLB-Wert zwischen 14 und 16 besitzen.

Um die erwünschte, sofortige Benetzbarkeit zu erreichen, soll das Verhältnis zwischen der ersten und der zweiten Komponente einer binären oberflächenaktiven Mischung zwischen 1 : 10 und 1 : 1 gehalten werden, bevorzugt zwischen 1 : 5 und 1 : 3.

Die Gesamtkonzentration der oberflächenaktiven Stoffe im Film hängt ab von den Eigenschaften der anderen Ingredienzien, soll jedoch üblicherweise zwischen 1 und 5 Gew.-% betragen.

Der Polyalkohol wird benötigt, um den erwünschten Weichheitsgrad des Filmes zu erreichen. Beispiele von Polyalkoholen umfassen Glycerin, Polyethylenglycol, Propylenglycol, Glycerinmonoester mit Fettsäuren, oder sonstige

pharmazeutisch verwendete Polyalkohole. Die Konzentration von Polyalkohol in der Trockenmasse des Filmes beträgt üblicherweise 4 bis 25 Gew.-%.

Der Film ist besonders gut geeignet zur Abgabe eines weiten Bereiches pharmazeutisch aktiver Wirkstoffe durch die Schleimhautmembranen eines Patienten, insbesondere durch die buccalen Schleimhäute.

Therapeutische Wirkstoffe, die Absorptionsprobleme infolge begrenzter Löslichkeit, Abbau im Gastrointestinaltrakt oder extensiven Metabolismus haben, sind besonders gut geeignet. Als Beispiele der einsetzbaren therapeutischen Wirkstoffe sind zu nennen: Hypnotica, Sedativa, Antiepileptica, Weckamine, Psychoneurotropica, Neuro-Muskelblokker, Antispasmodica, Antihistaminica, Antiallergica, Cardiotonica, Antiarrhythmica, Diuretica, Hypotensiva, Vasopressoren, Antitussiva, Expectorantia, Thyroidhormone, Sexualhormone, Antidiabetica, Antitumor-Wirkstoffe, Antibiotica sowie Chemotherapeutica und Narcotica. Die im Film einzulagernde Menge von Wirkstoff hängt von dessen Art ab und beträgt üblicherweise zwischen 0,01 und 20 Gew.-%.

Kosmetische Wirkstoffe umfassen Atemerfrischer wie Menthol, andere Geschmacks-, Aroma- oder Duftstoffe, wie sie üblicherweise für Mundhygiene oder Zahnpflege verwendet werden, beispielsweise quartäre Ammoniumbasen. Die Wirkung von Geschmacks- und Aromastoffen kann durch Geschmacksverstärker wie Weinsäure, Zitronensäure, Vanillin oder dergleichen verstärkt werden.

Farbstoffe, welche wahlweise dem Film beigemischt werden, müssen hinsichtlich Toxizität sicher sein und sollten zur Verwendung in Kosmetika durch die zuständigen Behörden zugelassen sein.

Der erfindungsgemäße mucoadhäsive Film kann folgendermaßen hergestellt werden:
Wirkstoff, oberflächenaktive Stoffe, Polyalkohol und andere mögliche Bestandteile außer dem wasserdispersiblen Polymer werden mit einer genügenden Menge eines kompatiblen Lösungsmittels gelöst. Beispiele eines kompatiblen Lösungsmittels umfassen Wasser, Alkohole oder deren Mischungen. Nach Bildung einer klaren Lösung wird das wasserdispersible Polymer oder die Mischung wasserdispersibler Polymere langsam unter Rühren zugegeben, bis eine klare und homogene Lösung gebildet ist. Diese wird auf einen Träger aufgetragen und zu einem Film getrocknet. Das Trägermaterial muß eine Oberflächenspannung haben, die es ermöglicht, die Polymerlösung gleichmäßig über die vorgesehene Beschichtungsbreite zu verteilen. Beispiele für geeignete Materialien umfassen nichtsilikonisierte Polyethylen-Terephthalat-Filme, nichtsiliconisiertes Kraftpapier, oder nichtsiliconisierten Polyethylenfilm. Der Auftrag der Lösung auf das Trägermaterial kann mit jeder geeigneten Vorrichtung ausgeführt werden. Eine speziell bevorzugte Auftragstechnik betrifft eine Walzenrakel-Streichmaschine.

Die Dicke der resultierenden Filmschicht hängt von der Konzentration der Feststoffe in der Beschichtungslösung sowie von der Spaltbreite der Beschichtungsmaschine ab und kann zwischen 5 und 200 µm variieren. Die Trocknung des Films wird in einem Heißluftbad unter Verwendung eines Trockenofens, Trockentunnels, Vakuumtrockners oder anderer geeigneter Trockenvorrichtungen vorgenommen. Um ein unangenehmes Gefühl im Mund zuverlässig zu vermeiden, soll die Filmdicke 70 µm nicht überschreiten. Zur besseren Gebrauchserleichterung kann der Film in Stücke von geeigneter Größe und Form geschnitten und verpackt werden.

Die Erfindung wird anhand nachfolgender Beispiele veranschaulicht.

Beispiel 1

15 g Sorbit, 6 g Glycerin, 0,5 g Polysorbat 80 (Tween 80), 2 g Brij 35, 25 g Zitronenminzearoma, 3 g Aspartam, 15 g l-Menthol und 3 g Zitronensäure werden bei 60°C in einer Mixtur von 250 g Wasser und 250 g Ethanol solange gerührt, bis sich eine klare Lösung gebildet hat. Zu der Lösung werden 30 g Hydroxypropylmethylcellulose langsam unter Rühren zugegeben, bis eine klare und homogene Lösung gebildet ist. Die resultierende Lösung wird dann bis auf Raumtemperatur abkühlen gelassen und unter Verwendung einer üblichen Beschichtungsvorrichtung auf ein geeignetes Trägermaterial aufgestrichen, beispielsweise nichtsiliconisiertes polyethylenbeschichtetes Kraftpapier.

Beschichtungsspalt und Bahngeschwindigkeit müssen so geregelt werden, daß eine Trockenfilmdicke zwischen 20 und 50 µm erreicht wird. Die Trockentemperatur hängt von der Länge des Trockenofens und der Materialgeschwindigkeit ab und soll so eingestellt werden, daß die Lösungsmittel vollständig, oder zumindest weitgehend vollständig vom Film entfernt werden. Der resultierende Film wird vom Träger abgelöst und zum Gebrauch in Stücke von geeigneter Größe und Form zerteilt.

Beispiel 2

3 g Sorbit, 1,5 g Kollidon 30 (Lieferant: BASF), 5 g Glycerin, 5 g Propylenglycol, 5 g Polyethylenglycol, 4 g Polysorbat 80 (Tween 80), 8 g Brij 35, 12 g Pfefferminzaroma, 0,8 g Aspartam werden in einer Mischung von 400 g Wasser und 400 g Ethanol bei 60°C unter Rühren aufgelöst. Zu der klaren Lösung werden 28 g Hydroxypropylmethylcellulose unter Rühren langsam zugegeben. Nach völliger Auflösung des Polymers wird die Lösung auf Raumtemperatur abgekühlt und auf einen Träger unter den gleichen Bedingungen wie in Beispiel 1 aufgestrichen. Der trockene Film wird wieder in Stücke von geeigneter Größe und Form zerteilt.

Beispiel 3

15 g Sorbit, 22,5 g Glycerin, 2,5 Propylenglycol, 2,5 g Brij 35, 2,5 g Poloxamer 407, 3,5 g Cremophor RH 40, 9 g Kräuterminzearoma, 0,5 g Aspartam werden unter ständigem Rühren bei 60°C in einer Mischung von 250 g Wasser und 250 g Ethanol gelöst. Zu der klaren Lösung werden 75 g Hydroxypropylcellulose unter ständigem Rühren langsam zugegeben. Mit der klaren Lösung wird wiederum beschichtet und unter den beschriebenen Bedingungen getrocknet, wie in Beispiel 1; der trockene Film wird in Stücke von geeigneter Größe und Form zerteilt.

Patentansprüche

1. Zubereitung zur Anwendung in der Mundhöhle mit einer an der Schleimhaut haftklebenden Schicht, **dadurch gekennzeichnet**, daß die haftklebende Schicht eine homogene Mischung enthält, bestehend aus einem wasserlöslichen Polymer, einer Mischung nichtionischer oberflächenaktiver Stoffe, einem Polyalkohol, einem kosmetischen oder pharmazeutischen Wirkstoff, und einem Geschmacks- oder Aromastoff.
2. Zubereitung nach Anspruch 1, dadurch gekennzeichnet, daß das wasserlösliche Polymer Hydroxypropylmethylcellulose, Hydroxyethylcellulose, Hydroxypropylcellulose, Polyvinylpyrrolidon, Carboxylmethylcellulose, Polyvinylalkohol, Natriumalginat, Polyethylenglycol, Xanthanharz, Traganth, Guarharz, Akazienharz, Gummiarabicum, Polyacrylsäure, Methylme-

thacrylatcopolymer, Carboxyvinylcopolymere oder deren Mischungen umfaßt.

3. Zubereitung nach Anspruch 1, dadurch gekennzeichnet, daß die Konzentration des wasserlöslichen Polymers in der Trockenmasse der Filmschicht zwischen 20 und 60 Gew.-% beträgt.

4. Zubereitung nach Anspruch 1, dadurch gekennzeichnet, daß die Mischung der oberflächenaktiven Stoffe aus zwei Komponenten besteht.

5. Zubereitung nach Anspruch 4, dadurch gekennzeichnet daß die erste Komponente des oberflächenaktiven Stoffs ein Polyethoxysorbitan-fettsäureester oder ein α-hydroωhydroxypoly(ethoxy)-poly(propoxy)-poly(ethoxy)-Blockcopolymer ist.

6. Zubereitung nach Anspruch 4, dadurch gekennzeichnet, daß die zweite Komponente des oberflächenaktiven Stoffs ein Polyethoxy-alkylether oder ein Polyethoxyrizinusölderivat ist.

7. Zubereitung nach Anspruch 1, dadurch gekennzeichnet, daß der Polyalkohol ausgewählt ist aus Glycerin, Polyethylenglycol, Propylenglycol oder Glycerinmonoestern mit Fettsäuren.

8. Zubereitung nach Anspruch 1, dadurch gekennzeichnet, daß der therapeutische Wirkstoff ausgewählt ist aus der Gruppe von Hypnotica, Sedativa, Antiepileptica, Weckaminen, Psychoneurotropica, Neuro-Muskelblockern, Antispasmodica, Antihistaminica, Antiallergica, Cardiotonica, Antiarrhythmica, Diuretica, Hypotensiva, Vasopressoren, Antitussiva, Expectorantia, Thyroidhormonen, Sexualhormonen, Antidiabetica, Antitumor-Wirkstoffen, Antibiotica sowie Chemotherapeutica oder Narcotica.

9. Zubereitung nach Anspruch 1, dadurch gekennzeichnet, daß der kosmetische Wirkstoff Atemerfrischer wie Menthol, Geschmacks-, Aroma- oder Duftstoffe, wie sie üblicherweise für Mundhygiene verwendet werden, und/oder Wirkstoffe zur Zahn- oder Mundpflege umfaßt, wie quartäre Ammoniumbasen.

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(54) **Sustained release with high and low viscosity HPMC.**

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CHEMICAL ABSTRACTS, vol. 111, no. 16, 16th october 1989, page 393, abstract no.140370f, Columbus, Ohio, US; G. GEISSLINGER et al.: "Therapeutically relevant differences in the pharmacokinetic and pharmaceutical behavior of ibuprofen lysinate as compared to ibuprofen acid", & INT. J.CLIN. PHARMACOL., THER. TOXICOL 1989, 27(7), 324-8

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Description

BACKGROUND OF THE INVENTION

Sustained release formulations containing a pharmacologically active agent and exhibiting a zero order release rate are particularly useful.

Ibuprofen is a well-known analgesic which has been used to treat chronic pain such as that associated with arthritic and rheumatic conditions. In such cases the analgesic is best administered so as to sustain its action over a period of time and to have a uniform level of analgesic action over this extended time period. This objective can partly be achieved by the repeated administration of a rapid release dosage. However, this procedure clearly has patient acceptability problems as well as a repeated raising and lowering of the blood levels of analgesic.

Generally, the release profiles in controlled release formulations follow a classical square root of time relationship, i.e., the release rate decreases with time. In a zero order composition a plot of the rate of release of drug vs. time shows a straight horizontal line, i.e., the release rate is independent of time. Zero order sustained release compositions provide a more uniform delivery of the therapeutic agent over long periods of time.

Sustained release formulations for ibuprofen have been disclosed in EP publication 255,404, however the formulations disclosed do not provide for a zero order release rate. In WO 87/00044 a sustained release formulation, exhibiting a bimodal controlled release, is disclosed. The carrier base is composed of a bimodal hydroxypropylmethylcellulose (HPMC) and the medicament selected from an antiflammatory group such as flurbiprofen. The publication is silent on the formulation of zero order release compositions. The Boots Company PLC, EP 234,670 has disclosed a sustained release composition containing xanthan gum wherein the medicament may be ibuprofen. The Boots formulation does not solve the problem of a zero order release rate.

In FR-A-25555901 a controlled long acting dry pharmaceutical formulation comprised of at least three components selected from (a) 5.5 - 98.5% by weight of hydroxypropyl methylcellulose; (b) 0.25 - 4.5% by weight of hydroxy components selected from (1) 5.5 - 98.5% by weight of hydroxypropyl methylcellulose or (2) 0.25 - 4.5% by weight of hydroxypropyl cellulose; and (c) 1-90% by weight of a carboxyvinyl polymer.

This reference discloses that it is the combination of these 3 elements which is critical to the disclosed invention and it does not disclose that varying the ratio of the high density HPMC to the low density HPMC will affect the delivery characteristics of the system but rather suggests that varying the relative amount of the hydroxypropyl methyl cellulose and hydroxypropyl cellulose and carboxyvinyl polymer elements will affect the delivery rate. Nowhere does this reference disclose a mixture comprising a HPMC having a molecular weight of 60,000 or greater together with a HPMC having a molecular weight of 50,000 or less. US-A-4389393 discloses a sustained release rate formulation wherein the ratio between high molecular weight HPMC and low molecular weight HPMC is 45.5:19.5 or 1:0.4. Furthermore, the formulation of this reference shows a significant % drop of released medicant after only 8 hours. US-A-4259314 discloses a method of producing a controlled long acting pharmaceutical composition wherein hydroxypropyl cellulose is considered an essential ingredient. In fact, the reference specifically discloses that the inadequacy of hydroxypropyl methylcellulose for use in long lasting troches is known. WO-A-8700044 discloses non-zero order formulations which can be achieved only by using the disclosed highly unusual biomodal HPMCs (B-HPMCs). US-A-4871548 discloses particular combinations comprising a "low number average molecular weight hydroxypropy methyl cellulose ether" having an average molecular weight of from about 9,000 to 30,000 and viscosities ranging from 3-106 and a "high number average molecular weight hydroxypropyl methyl cellulose" having an average molecular weight of 30,000 to 350,000 and viscosities ranging from 1,500 to 220,000. The ratio of the high and low molecular weight MPCs disclosed in the formulations of this reference is 1:1. Furthermore, these formulations employ an additional ingredient - lactose.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to a carrier base material for therapeutically active medicaments in a solid dosage formulation wherein
the carrier base comprises:

a) a high viscosity HPMC; and

b) a low viscosity HPMC wherein the high and low viscosity HPMC are in a ratio yielding a zero order release profile for the medicament.

In the present invention it has unexpectedly been found that a zero-order release profile can be obtained by controlling the ratio of high to low viscosity HPMC in a carrier base formulation.

A high viscosity HPMC is defined as one having a molecular weight of 60,000 or greater. A low viscosity HPMC is defined as one having a molecular weight of 50,000 or less.

The preferred low viscosity HPMCs available as Dow Methocel cellulose ethers, are: E5, 28-30% methoxy, 7-12% hydroxypropyl, viscosity = 4-6 cP; E15LV, 28-30% methoxy, 7-12% hydroxypropyl viscosity = 12-18 cP; E50LV, 28-30% methoxy, 7-12% hydroxylpropyl, viscosity = 40-60; and K100LV, 19-24% methoxy 7-12% hydroxypropyl, viscosity = 100 cP. The preferred high viscosity HPMCs, available as Dow Methocel cellulose ethers are: E4M-CR, 28-30% methoxy, 7-12% hydroxypropyl, viscosity = 4000 cP; E10M-CR, 28-30% methoxy, 7-12% hydroxypropyl viscosity = 10,000 cP; K4M, 19-24% methoxy, 7-12% hydroxypropyl, viscosity = 4000 cP; K15M, 19-24% methoxy, 7-12% hydroxypropyl, viscosity = 15,000 cP; and K100M, 19-24% methoxy, 7-12% hydroxypropyl, viscosity = 100,000 cP.

The medicament in the present invention may be selected from ibuprofen, or salts of ibuprofen. Most preferably the medicament is ibuprofen lysine which should be taken to mean all stereoisomeric configurations including racemic ibuprofen lysine and (S)-ibuprofen-(S)-lysine;i.e. the salt formed from (S)-ibuprofen and (S)-lysine.

It should be appreciated that a zero order release profile is obtained only with a certain relative range of high to low viscosity HPMC. This may be illustrated by the combination of 1 part high viscosity E10M CR and a varying amount of any of the preferred low viscosity HPMC wherein a zero order release was found, for example:

(i) 1 part E10M CR: 3 parts E5;
(ii) 1 part E10M CR: 2 to 4 parts E15LV;
(iii) 1 part E10M CR: 3 to 9 parts E5OLV;
(iv) 1 part E10M CR: 3 to 9 parts K100LV.

These ranges are not limited to combinations where the high viscosity HPMC is E10M CR but are to be expected with any of the other preferred high viscosity HPMC.

The medicament, preferably ibuprofen lysine is mixed with Povidone USP (PVP) which functions as a binding agent. Typically the ratio of drug to PVP is 20:1.

The percent of drug/PVP granules in the pharmaceutical composition is 33.3 to 83%.

The range of ibuprofen in this invention is preferably 100 to 600 mg per tablet.

Where the medicament is ibuprofen lysine the weight range is 100 to 600 mg measured in mg ibuprofen.

The percent range of HPMC carrier base is 17-66%.

An example of the composition and processing of the controlled release dosage form is provided below:

Composition:

Ibuprofen Lysine	61.8%
PVP	3.0%
Carrier Base	34.1%
Magnesium Stearate	1.0%
	Total 99.9%

Fillers such as Avicel, lactose, manitol, dicalcium phosphate, starch or pregelatin starch 1500 may be added to the composition. Binders such as corn starch, pregelatin starch 1500, Klucel LF, methocel E3, E5, gelatin or acacia may be added as necessary by those skilled in the art. Besides magnesium stearate, other lubricants such as stearic acid, sodium stearate fumerate or calcium stearate may be employed.

Processing

A batch of ibuprofen lysine granules containing PVP was prepared. An appropriate amount of granules, typically 3.21 grams was removed and mixed in a V-blender for 10 minutes with a carrier base, usually 1.71 grams, chosen from the preferred high viscosity and low viscosity HPMC. The resultant mixture was then mixed in a V-blender for three minutes with magnesium stearate, which had previously been sieved through a #60 mesh screen. Tablets of about 980 mg were compressed on an F-press.

Tables I-V provide release profiles for controlled release tablets prepared following the processing described above and containing 600 mg Ibuprofen Lysine and 330 mg carrier base. Dissolution determinations were conducted using an automated dissolution testing unit such as a Beckman Spectrophotometer, model DU65, connected with a Vanderkamp 600 six-spindle dissolution tester. Samples were taken every hour for at least 12 to 24 hours and absorbance was read spectrophotometrically at 260 nm.

All the HPMC polymers described are available from the Dow Chemical Company. Racemic ibuprofen lysine may be prepared following the description in U.S. Patent 4,279,926. (S)-ibuprofen-(S)-lysine is prepared as described in copending application S.N. 422,466 filed October 18, 1989.

TABLE I

Release Profiles of Ibuprofen Lysine Using 25% E4MCR and 75% of a Low Viscosity HPMC			
Time [hr]	75% E15LV MEAN ABSORBANCE	75% E50 MEAN ABSORBANCE	75% K100LV MEAN ABSORBANCE
0	0.0000	0.0000	0.0000
1	0.1125	0.1160	0.0820
2	0.1885	0.1935	0.1400
3	0.2570	0.2615	0.1940
4	0.3180	0.3230	0.2440
5	0.3735	0.4080	0.2920
6	0.4265	0.5290	0.3375
7	0.4945	0.6265	0.3860
8	0.5975	0.6820	0.4445
9	0.6855	0.7190	0.5045
10	0.7280	0.7405	0.5750
11	0.7520	0.7555	0.6350
12	0.7540	0.7620	0.6845
13	0.7500	0.7675	0.7225
14	0.7445	0.7680	0.7515
15	0.7405	0.7670	0.7695
16			0.7785
17			0.7825
18			0.7835
19			
20			
21			
22			
23			
24			

TABLE II

Release Profiles of Ibuprofen Lysine Using Various Ratios of E10MCR and a Low Viscosity HPMC

Time [hr]	25% E10MCR: 75% E5 MEAN ABSORBANCE	33.3% E10MCR: 66.7% E15LV MEAN ABSORBANCE	20% E10MCR: 80% E15LV MEAN ABSORBANCE
0	0.0000	0.0010	0.0010
1	0.0985	0.1140	0.1615
2	0.1670	0.1720	0.2420
3	0.2335	0.2210	0.3130
4	0.3055	0.2630	0.3760
5	0.3960	0.3050	0.4345
6	0.4800	0.3450	0.5265
7	0.5630	0.3840	0.5975
8	0.6505	0.4220	0.6525
9	0.6875	0.4600	0.7095
10	0.7165	0.4970	0.7475
11	0.7235	0.5345	0.7565
12	0.7255	0.5835	0.7590
13	0.7260	0.6410	0.7600
14	0.7245	0.6915	0.7575
15	0.7240	0.7230	0.7530
16	0.7240	0.7395	0.7525
17	0.7240	0.7425	0.7520
18	0.7245	0.7435	0.7520
19	0.7255	0.7455	
20	0.7265	0.7440	
21	0.7275	0.7420	
22	0.7290	0.7420	
23	0.7290	0.7410	
24	0.7310	0.7395	

TABLE II Cont'd

Time [hr]	25% E10MCR 75% E50 MEAN ABSORBANCE	10% E10MCR 90% E50LV MEAN ABSORBANCE	25% E10MCR 75% K100LV MEAN ABSORBANCE	10% E10MCR 90% K100LV MEAN ABSORBANCE
0	0.0000	0.0005	0.0000	0.0005
1	0.1095	0.1250	0.0790	0.1120
2	0.1855	0.1960	0.1360	0.1775
3	0.2570	0.2540	0.1845	0.2325
4	0.3220	0.3065	0.2300	0.2845
5	0.3870	0.3580	0.2715	0.3325
6	0.4505	0.4110	0.3125	0.3825
7	0.5140	0.4810	0.3525	0.4360
8	0.5780	0.5475	0.3905	0.4900
9	0.6220	0.5990	0.4305	0.5595
10	0.6645	0.6525	0.4730	0.6235
11	0.7020	0.6885	0.5210	0.6785
12	0.7255	0.7080	0.5685	0.7170
13	0.7395	0.7200	0.6045	0.7365
14	0.7510	0.7275	0.6415	0.7390
15	0.7560	0.7310	0.6715	0.7370
16	0.7600	0.7290	0.6905	0.7360
17	0.7630	0.7260	0.7080	0.7340
18	0.7650	0.7260	0.7225	0.7360
19	0.7670		0.7345	
20	0.7680		0.7395	
21	0.7700		0.7440	
22	0.7725		0.7450	
23	0.7740			
24	0.7755			

TABLE III

Release Profiles of Ibuprofen Lysine Using Various Ratios of K4M and a Low Viscosity HPMC				
Time [hr]	50% K4M 50% E5 MEAN ABSORBANCE	25% K4M 75% E15LV MEAN ABSORBANCE	25% K4M 75% E5 MEAN ABSORBANCE	25% K4M 75% K100LV MEAN ABSORBANCE
0	0.0000	0.0000	0.0000	0.0000
1	0.1155	0.1010	0.0995	0.0815
2	0.1795	0.1700	0.1565	0.1390
3	0.2315	0.2335	0.2110	0.1895
4	0.2815	0.2905	0.2630	0.2365
5	0.3655	0.3490	0.3130	0.2815
6	0.4095	0.4360	0.4395	0.3260
7	0.4465	0.5510	0.5270	0.3705
8	0.4925	0.6430	0.5815	0.4225
9	0.5695	0.6990	0.6305	0.4850
10	0.6550	0.7405	0.6580	0.5435
11	0.7045	0.7560	0.6775	0.6000
12	0.7235	0.7565	0.6950	0.6500
13	0.7360	0.7515	0.7060	0.6740
14	0.7400	0.7445	0.7175	0.6920
15	0.7460	0.7415	0.7245	0.7040
16	0.7535	0.7450	0.7260	0.7220
17	0.7525	0.7435	0.7275	0.7315
18	0.7555	0.7415	0.7270	0.7380
19	0.7605	0.7405	0.7305	
20	0.7605	0.7400	0.7305	
21	0.7650	0.7425	0.7320	
22	0.7635		0.7310	
23	0.7660			
24				

TABLE IV

Release Profiles of Ibuprofen Lysine Using Various Ratios of K15M and a Low Viscosity HPMC				
Time [hr]	25% K15M 75% E5 MEAN ABSORBANCE	25% K15M 75% E15LV MEAN ABSORBANCE	25% K15M 75% E50 MEAN ABSORBANCE	25% K15M 75% K100LV MEAN ABSORBANCE
0	0.0000	0.0000	0.0000	0.0000
1	0.1280	0.0935	0.0855	0.0950
2	0.2110	0.1540	0.1425	0.1640
3	0.2830	0.2085	0.1915	0.2225
4	0.3640	0.2590	0.2390	0.2740
5	0.4350	0.3070	0.2810	0.3215
6	0.5060	0.3530	0.3265	0.3665
7	0.6475	0.3980	0.3970	0.4120
8	0.7215	0.4470	0.4890	0.4575
9	0.7360	0.5505	0.5535	0.5040
10	0.7415	0.6200	0.5945	0.5485
11	0.7410	0.6655	0.6125	0.5910
12	0.7395	0.6815	0.6400	0.6245
13	0.7435	0.6850	0.6590	0.6490
14	0.7475	0.7040	0.6910	0.6650
15	0.7490	0.7250	0.7085	0.6845
16	0.7520	0.7365	0.7295	0.7035
17	0.7505	0.7395	0.7395	0.7160
18	0.7515	0.7390	0.7400	0.7235
19	0.7485	0.7405	0.7330	0.7305
20	0.7525	0.7405	0.7355	0.7345
21	0.7500	0.7360	0.7255	0.7385
22				0.7415

TABLE V

Release Profiles of Ibuprofen Lysine Using 25% K100M and 75% of a Low Viscosity HPMC		
Time [hr]	75% E15LV MEAN ABSORBANCE	75% E50 MEAN ABSORBANCE
0	0.0000	0.0000
1	0.0820	0.1005
2	0.1330	0.1615
3	0.1800	0.2180
4	0.2225	0.2680
5	0.2630	0.3150
6	0.3025	0.3630
7	0.3405	0.4230
8	0.3805	0.4950
9	0.4240	0.5465
10	0.4880	0.5940
11	0.5510	0.6350
12	0.5945	0.6715
13	0.6335	0.7000
14	0.6650	0.7215
15	0.6950	0.7370
16	0.7195	0.7485
17	0.7395	0.7575
18	0.7530	0.7655
19	0.7680	0.7710
20	0.7740	0.7755
21	0.7795	0.7770
22	0.7825	0.7785
23		0.7800
24		0.7820

Claims

1. A carrier base material combined with ibuprofen or a salt thereof and shaped and compressed to a solid sustained release pharmaceutical dosage form having a zero order release profile upon administration in which the carrier base material consists essentially of (a) HPMC having a molecular weight of 60,000 or greater, and (b) HPMC having a molecular weight of 50,000 or less; and wherein the ratio of (a) to (b) is from 1:2 to 1:9.

2. A zero order release pharmaceutical formulation according to Claim 1 in which the high viscosity HPMC is selected from a methocel cellulose ether wherein:

a) % methoxy = 19-24. % hydroxypropyl = 7-12, viscosity = 4000 cps;
b) % methoxy = 28-30, % hydroxypropyl = 7-12, viscosity = 10,000;
c) % methoxy = 28-30, % hydroxypropyl = 7-12, viscosity = 4,000;
d) % methoxy = 19-24, % hydroxypropyl = 7-12, viscosity = 15,000;
e) % methoxy = 19-24, % hydroxypropyl = 7-12, viscosity = 100,000;

and the low viscosity HPMC is selected from a methocel cellulose ether wherein:

a) % methoxy = 28-30, % hydroxypropyl = 7-12, viscosity = 4-6;
b) % methoxy = 28-30, % hydroxypropyl = 7-12, viscosity = 12-18;
c) % methoxy = 28-30, % hydroxypropyl = 7-12, viscosity = 40-60;
d) % methoxy = 19-24, % hydroxypropyl = 7-12, viscosity = 100.

3. A zero order release pharmaceutical formulation according to Claim 2 wherein the high viscosity HPMC is 1 part methocel cellulose ether wherein % methoxy = 28-30, % hydroxypropyl = 7-12 and viscosity = 10,000 and wherein the low viscosity HPMC is selected from:

a) 3 parts wherein % methoxy = 28-30, % hydroxypropyl = 7-12, and viscosity = 4-6;

b) 2 to 4 parts wherein % methoxy = 28-30, % hydroxypropyl = 7-12, and viscosity = 12-18;
c) 3 to 9 parts wherein % methoxy = 28-30, % hydroxypropyl = 7-12, and viscosity = 40-60; or
d) 3 to 9 parts wherein % methoxy = 19-24, % hydroxypropyl = 7-12, and viscosity = 100.

4. A zero order release pharmaceutical formulation according to Claim 2 wherein the high viscosity HPMC is 1 part wherein % methoxy = 19-24, % hydroxypropyl = 7-12, and viscosity = 4,000 and wherein the low viscosity HPMC is selected from:
a) 2 to 4 parts wherein % methoxy = 28-30, % hydroxypropyl = 7-12, and viscosity = 12-18;
b) 3 to 9 parts wherein % methoxy = 28-30, % hydroxypropyl = 7-12, and viscosity = 40-60;
c) 3 to 9 parts wherein % methoxy = 19-24, % hydroxypropyl = 7-12, and viscosity = 100.

5. A zero order release pharmaceutical formulation according to Claim 2 wherein the high viscosity HPMC is 1 part wherein % methoxy = 28-30, % hydroxypropyl = 7-12, and viscosity = 4,000 and wherein the low viscosity HPMC is selected from:
a) 1 part wherein % methoxy = 28-30, % hydroxypropyl = 7-12, and viscosity = 4-6;
b) 2 to 4 parts wherein % methoxy = 28-30, % hydroxypropyl = 7-12, and viscosity = 12-18;
c) 3 to 9 parts wherein % methoxy = 28-30, % hydroxypropyl = 7-12, and viscosity = 40-60;
d) 3 to 9 parts wherein % methoxy = 19-24, % hydroxypropyl = 7-12, and viscosity = 100.

6. A zero order release pharmaceutical formulation according to Claim 2 wherein the high viscosity HPMC is one part wherein % methoxy = 19-24, % hydroxypropyl = 7-12, and viscosity = 15,000 and wherein the low viscosity HPMC is selected from:
a) 1 to 3 parts wherein % methoxy = 28-30, % hydroxypropyl = 7-12, and viscosity = 4-6;
b) 1 to 3 parts wherein % methoxy = 28-30, % hydroxypropyl = 7-12, and viscosity = 12-18;
c) 1 to 3 parts wherein % methoxy = 28-30, % hydroxypropyl = 7-12, and viscosity = 40-60;
d) 3 to 9 parts wherein % methoxy = 19-24, % hydroxypropyl = 7-12, and viscosity = 100.

7. A zero order release pharmaceutical formulation according to Claim 2 wherein the high viscosity HPMC is 1 part wherein % methoxy = 19-24, % hydroxypropyl = 7-12, and viscosity = 100,000 and wherein the low viscosity HPMC is selected from:
a) 1 to 3 parts wherein % methoxy = 28-30, % hydroxypropyl = 7-12, and viscosity = 12-18;
b) 1 to 3 parts wherein % methoxy = 28-30, % hydroxypropyl = 7-12, and viscosity = 40-60.

8. A zero order release pharmaceutical formulation according to Claim 2 wherein the medicament is selected from:
a) ibuprofen; or
b) salts of ibuprofen.

9. A formulation according to Claim 8 wherein the medicament is ibuprofen lysine.

10. A formulation according to Claim 9 wherein the medicament is (S)-ibuprofen-(S)-lysine.

11. A formulation according to Claim 10 wherein the amount of medicament as ibuprofen is 100 to 600 mg.

Patentansprüche

1. Trägergrundmaterial, kombiniert mit Ibuprofen oder einem Salz davon und geformt und komprimiert zu einer festen pharmazeutischen Dosierungsform mit langanhaltender Freisetzung mit einem Freisetzungsprofil nullter Ordnung bei der Verabreichung, worin das Trägergrundmaterial im wesentlichen besteht aus (a) HPMC eines Molekulargewichts von 60 000 oder mehr und (b) HPMC eines Molekulargewichts von 50 000 oder weniger und worin das Verhältnis von (a) zu (b) 1:2 bis 1:9 beträgt.

2. Pharmazeutische Formulierung mit einer Freisetzung nullter Ordnung nach Anspruch 1, worin die hochviskose HPMC ausgewählt ist aus einem Methocel-Celluloseether, worin:
a) % Methoxy = 19-24, % Hydroxypropyl = 7-12, Viskosität = 4 000 cps,
b) % Methoxy = 28-30, % Hydroxypropyl = 7-12, Viskosität = 10 000,
c) % Methoxy = 28-30, % Hydroxypropyl = 7-12, Viskosität = 4 000,
d) % Methoxy = 19-24, % Hydroxypropyl = 7-12, Viskosität = 15 000,

e) % Methoxy = 19-24, % Hydroxypropyl = 7-12, Viskosität = 100 000,

und worin das niederviskose HPMC ausgewählt ist aus einem Methocel-Celluloseether, worin:

a) % Methoxy = 28-30, % Hydroxypropyl = 7-12, Viskosität = 4-6,

b) % Methoxy = 28-30, % Hydroxypropyl = 7-12, Viskosität = 12-18,

c) % Methoxy = 28-30, % Hydroxypropyl = 7-12, Viskosität = 40-60,

d) % Methoxy = 19-24, % Hydroxypropyl = 7-12, Viskosität = 100.

3. Pharmazeutische Formulierung mit einer Freisetzung nullter Ordnung nach Anspruch 2, worin die hochviskose HPMC zu einem Teil Methocel-Celluloseether ist, worin % Methoxy = 28-30, % Hydroxypropyl = 7-12 und Viskosität = 10 000 und worin das niederviskose HPMC ausgewählt ist aus:

a) 3 Teilen, worin % Methoxy = 28-30, % Hydroxypropyl = 7-12 und Viskosität = 4-6,

b) 2 bis 4 Teilen, worin % Methoxy = 28-30, % Hydroxypropyl = 7-12 und Viskosität = 12-18,

c) 3 bis 9 Teilen, worin % Methoxy = 28-30, % Hydroxypropyl = 7-12 und Viskosität = 40-60 oder

d) 3 bis 9 Teilen, worin % Methoxy = 19-24, % Hydroxypropyl = 7-12 und Viskosität = 100.

4. Pharmazeutische Formulierung mit einer Freisetzung nullter Ordnung nach Anspruch 2, worin die hochviskose HPMC 1 Teil ist, worin % Methoxy = 19-24, % Hydroxypropyl = 7-12 und Viskosität = 4 000 und worin die niederviskose HPMC ausgewählt ist aus:

a) 2 bis 4 Teilen, worin % Methoxy = 28-30, % Hydroxypropyl = 7-12 und Viskosität = 12-18,

b) 3 bis 9 Teilen, worin % Methoxy = 28-30, % Hydroxypropyl = 7-12 und Viskosität = 40-60,

c) 3 bis 9 Teilen, worin % Methoxy = 19-24, % Hydroxypropyl = 7-12 und Viskosität = 100.

5. Pharmazeutische Formulierung mit einer Freisetzung nullter Ordnung nach Anspruch 2, worin die hochviskose HPMC 1 Teil ist, worin % Methoxy = 28-30, % Hydroxypropyl = 7-12 und Viskosität = 4 000 und worin die niederviskose HPMC ausgewählt ist aus:

a) 1 Teil, worin % Methoxy = 28-30, % Hydroxypropyl = 7-12 und Viskosität = 4-6,

b) 2 bis 4 Teilen, worin % Methoxy = 28-30, % Hydroxypropyl = 7-12 und Viskosität = 12-18,

c) 3 bis 9 Teilen, worin % Methoxy = 28-30, % Hydroxypropyl = 7-12 und Viskosität = 40-60,

d) 3 bis 9 Teilen, worin % Methoxy = 19-24, % Hydroxypropyl = 7-12 und Viskosität = 100.

6. Pharmazeutische Formulierung mit einer Freisetzung nullter Ordnung nach Anspruch 2, worin die hochviskose HPMC 1 Teil ist, worin % Methoxy = 19-24, % Hydroxypropyl = 7-12 und Viskosität = 15 000 und worin die niederviskose HPMC ausgewählt ist aus:

a) 1 bis 3 Teilen, worin % Methoxy = 28-30, % Hydroxypropyl = 7-12 und Viskosität = 4-6,

b) 1 bis 3 Teilen, worin % Methoxy = 28-30, % Hydroxypropyl = 7-12 und Viskosität = 12-18,

c) 1 bis 3 Teilen, worin % Methoxy = 28-30, % Hydroxypropyl = 7-12 und Viskosität = 40-60,

d) 3 bis 9 Teilen, worin % Methoxy = 19-24, % Hydroxypropyl = 7-12 und Viskosität = 100.

7. Pharmazeutische Formulierung mit einer Freisetzung nullter Ordnung nach Anspruch 2, worin die hochviskose HPMC 1 Teil ist, worin % Methoxy = 19-24, % Hydroxypropyl = 7-12 und Viskosität = 100 000 und worin die niederviskose HPMC ausgewählt ist aus:

a) 1 bis 3 Teilen, worin % Methoxy = 28-30, % Hydroxypropyl = 7-12 und Viskosität = 12-18,

b) 1 bis 3 Teilen, worin % Methoxy = 28-30, % Hydroxypropyl = 7-12 und Viskosität = 40-60.

8. Pharmazeutische Formulierung mit einer Freisetzung nullter Ordnung nach Anspruch 2, worin das Medikament ausgewählt ist aus:

a) Ibuprofen oder

b) Salzen von Ibuprofen.

9. Formulierung nach Anspruch 8, worin das Medikament Ibuprofen-Lysin ist.

10. Formulierung nach Anspruch 9, worin das Medikament (S)-Ibuprofen-(S)-Lysin ist

11. Formulierung nach Anspruch 9, worin die Menge des Medikaments als Ibuprofen 100 bis 600 mg beträgt.

Revendications

1. Matériau de base de véhicule associé à de l'ibuprofène ou un sel de celui-ci et façonné et comprimé en une forme pharmaceutique solide à libération prolongée, ayant un profil de courbe de libération d'ordre zéro après administration, caractérisé en ce que le matériau de base de véhicule consiste essentiellement en (a) une HPMC ayant une masse moléculaire de 60 000 ou plus et (b) une HPMC ayant une masse moléculaire de 50 000 ou moins; et en ce que le rapport de (a) à (b) va de 1:2 à 1:9.

2. Composition pharmaceutique à vitesse de libération d'ordre zéro selon la revendication 1, dans laquelle la HPMC à haute viscosité est choisie parmi un éther de cellulose de type Methocel dans lequel:
   a) le pourcentage de groupes méthoxy = 19-24, le pourcentage de groupes hydroxypropyle = 7-12, viscosité = 4 000 centipoises (cP);
   b) le pourcentage de groupes méthoxy = 28-30, le pourcentage de groupes hydroxypropyle = 7-12, viscosité = 10 000 cP;
   c) le pourcentage de groupes méthoxy = 28-30, le pourcentage de groupes hydroxypropyle = 7-12, viscosité = 4 000 cP;
   d) le pourcentage de groupes méthoxy = 19-24, le pourcentage de groupes hydroxypropyle = 7-12, viscosité = 15 000 cP;
   e) le pourcentage de groupes méthoxy = 19-24, le pourcentage de groupes hydroxypropyle = 7-12, viscosité = 100 000 cP;

   et la HPMC à faible viscosité est choisie parmi un éther de cellulose de type Methocel dans lequel:
   a) le pourcentage de groupes méthoxy = 28-30, le pourcentage de groupes hydroxypropyle = 7-12, viscosité = 4-6 cP;
   b) le pourcentage de groupes méthoxy = 28-30, le pourcentage de groupes hydroxypropyle = 7-12, viscosité = 12-18 cP;
   c) le pourcentage de groupes méthoxy = 28-30, le pourcentage de groupes hydroxypropyle = 7-12, viscosité = 40-60 cP;
   d) le pourcentage de groupes méthoxy = 19-24, le pourcentage de groupes hydroxypropyle = 7-12, viscosité = 100 cP.

3. Composition pharmaceutique à vitesse de libération d'ordre zéro selon la revendication 2, dans laquelle la HPMC à haute viscosité consiste en 1 partie d'éther de cellulose de type Methocel dans lequel le pourcentage de groupes méthoxy = 28-30, le pourcentage de groupes hydroxypropyle = 7-12 et la viscosité = 10 000 cP, et dans lequel la HPMC à faible viscosité est choisie parmi:
   a) 3 parties d'une HPMC dans laquelle le pourcentage de groupes méthoxy = 28-30, le pourcentage de groupes hydroxypropyle = 7-12 et la viscosité = 4-6 cP;
   b) 2 à 4 parties d'une HPMC dans laquelle le pourcentage de groupes méthoxy = 28-30, le pourcentage de groupes hydroxypropyle = 7-12 et la viscosité = 12-18 cP;
   c) 3 à 9 parties d'une HPMC dans laquelle le pourcentage de groupes méthoxy = 28-30, le pourcentage de groupes hydroxypropyle = 7-12 et la viscosité = 40-60 cP; et
   d) 3 à 9 parties d'une HPMC dans laquelle le pourcentage de groupes méthoxy = 19-24, le pourcentage de groupes hydroxypropyle = 7-12 et la viscosité = 100 cP.

4. Composition pharmaceutique à vitesse de libération d'ordre zéro selon la revendication 2, dans laquelle la HPMC à haute viscosité consiste en 1 partie d'une HPMC dans laquelle le pourcentage de groupes méthoxy = 19-24, le pourcentage de groupes hydroxypropyle = 7-12 et la viscosité = 4 000 cP, et dans laquelle la HPMC à faible viscosité est choisie parmi:
   a) 2 à 4 parties d'une HPMC dans laquelle le pourcentage de groupes méthoxy = 28-30, le pourcentage de groupes hydroxypropyle = 7-12 et la viscosité = 12-18 cP;
   b) 3 à 9 parties d'une HPMC dans laquelle le pourcentage de groupes méthoxy = 28-30, le pourcentage de groupes hydroxypropyle = 7-12 et la viscosité = 40-60 cP;
   c) 3 à 9 parties d'une HPMC dans laquelle le pourcentage de groupes méthoxy = 19-24, le pourcentage de groupes hydroxypropyle = 7-12 et la viscosité = 100 cP.

5. Composition pharmaceutique à vitesse de libération d'ordre zéro selon la revendication 2, dans laquelle la HPMC à haute viscosité consiste en 1 partie d'une HPMC dans laquelle le pourcentage de groupes méthoxy = 28-30, le pourcentage de groupes hydroxypropyle = 7-12 et la viscosité = 4 000 cP, et dans laquelle la HPMC à faible viscosité est choisie parmi:

a) 1 partie d'une HPMC dans laquelle le pourcentage de groupes méthoxy = 28-30, le pourcentage de groupes hydroxypropyle = 7-12 et la viscosité = 4-6 cP;
b) 2 à 4 parties d'une HPMC dans laquelle le pourcentage de groupes méthoxy = 28-30, le pourcentage de groupes hydroxypropyle = 7-12 et la viscosité = 12-18 cP;
c) 3 à 9 parties d'une HPMC dans laquelle le pourcentage de groupes méthoxy = 28-30, le pourcentage de groupes hydroxypropyle = 7-12 et la viscosité = 40-60 cP; et
d) 3 à 9 parties d'une HPMC dans laquelle le pourcentage de groupes méthoxy = 19-24, le pourcentage de groupes hydroxypropyle = 7-12 et la viscosité = 100 cP.

6. Composition pharmaceutique à vitesse de libération d'ordre zéro selon la revendication 2, dans laquelle la HPMC à haute viscosité consiste en 1 partie d'une HPMC dans laquelle le pourcentage de groupes méthoxy = 19-24, le pourcentage de groupes hydroxypropyle = 7-12 et la viscosité = 15 000 cP, et dans laquelle la HPMC à faible viscosité est choisie parmi:
a) 1 à 3 parties d'une HPMC dans laquelle le pourcentage de groupes méthoxy = 28-30, le pourcentage de groupes hydroxypropyle = 7-12 et la viscosité = 4-6 cP;
b) 1 à 3 parties d'une HPMC dans laquelle le pourcentage de groupes méthoxy = 28-30, le pourcentage de groupes hydroxypropyle = 7-12 et la viscosité = 12-18 cP;
c) 1 à 3 parties d'une HPMC dans laquelle le pourcentage de groupes méthoxy = 28-30, le pourcentage de groupes hydroxypropyle = 7-12 et la viscosité = 40-60 cP; et
d) 3 à 9 parties d'une HPMC dans laquelle le pourcentage de groupes méthoxy = 19-24, le pourcentage de groupes hydroxypropyle = 7-12 et la viscosité = 100 cP.

7. Composition pharmaceutique à vitesse de libération d'ordre zéro selon la revendication 2, dans laquelle la HPMC à haute viscosité consiste en 1 partie d'une HPMC dans laquelle le pourcentage de groupes méthoxy = 19-24, le pourcentage de groupes hydroxypropyle = 7-12 et la viscosité = 100 000 cP, et dans laquelle la HPMC à faible viscosité est choisie parmi:
a) 1 à 3 parties d'une HPMC dans laquelle le pourcentage de groupes méthoxy = 28-30, le pourcentage de groupes hydroxypropyle = 7-12 et la viscosité = 12-18 cP;
b) 1 à 3 parties d'une HPMC dans laquelle le pourcentage de groupes méthoxy = 28-30, le pourcentage de groupes hydroxypropyle = 7-12 et la viscosité = 40-60 cP.

8. Composition pharmaceutique à vitesse de libération d'ordre zéro selon la revendication 2, dans laquelle le médicament est choisi parmi:
a) l'ibuprofène et
b) des sels d'ibuprofène.

9. Composition selon la revendication 8, dans laquelle le médicament est l'ibuprofène lysine.

10. Composition selon la revendication 9, dans laquelle le médicament est le (S)-ibuprofène-(S)-lysine.

11. Composition selon la revendication 10, dans laquelle la quantité de médicament, en tant qu'ibuprofène, va de 100 à 600 mg.

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COMPLETE SPECIFICATION.

New Impregnated or Coated Films.

We, ASHE CHEMICAL LIMITED, a British Company of Ashetree Works, Kingston Road, Leatherhead, Surrey, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to impregnated or coated films.

The conventional forms of foods and medicines for ingestion by, or application to, human beings or animals suffer from certain disadvantages. Thus, for example, formulations in the form of tablets or capsules are difficult to swallow and have to be made up so as to include a predetermined amount of material, which is not necessarily the amount required at the time of use. Again, liquid formulations are often messy in use and it is desirable, where possible, to use solid formulations in their place.

The present invention provides impregnated or coated films which can be used in place of relatively inconvenient formulations heretofore used, and which make it possible readily to measure out the amount of drug, medicine or other material to be used.

The invention consists in self-supporting films of gelatin or rice paper (i.e. dried egg albumen), coated or impregnated with a vitamin, a mineral dietary supplement, a drug for oral administration, a personal deodorant, a shampoo, a perfume, or a hair dye or lotion, or other cosmetic. A suitvitamin is, for example, vitamin C, and suitable drugs (including hormones) for oral administration include especially those which are ordinarily self-administered, e.g. aspirin, hyoscine hydrobromide or caffeine. A suitable shampoo is cylicohexylamine lauryl sulphate. The material applied to the film should not render it appreciably damp, or handling difficulties are liable to arise.

The film may be in any desired shape but ordinarily it will be cut into relatively small squares, circles, or other shapes, each containing one dosage unit of predetermined size. Alternatively, the film may be made up as a relatively large sheet or tape (which may be wound on a spool), preferably marked with graduations showing the amount of active material associated with a defined area.

The coating or impregnation of the film may be carried out in any convenient manner. Ordinarily it will be most convenient to spray the film with a solution of the active material, e.g. in water or alcohol, or to dip it in such a solution, and then to dry the coated or impregnated film. Care must, of course, be taken to prevent the film, which is dispersible in water, from disintegrating at this stage. If the active material can be readily melted it may be applied to the film in the molten state. Alternatively, in appropriate cases the film may be formed with the active material *in situ*, e.g. by casting an aqueous solution of the film-forming substance containing the active material and allowing it to dry.

The following Examples illustrate the invention.

EXAMPLE I

A sheet of "rice paper" is sprayed with an alcoholic solution of hyoscine hydrobromide, dried, and cut into squares each containing 0.5 mg. of the drug. These impregnated squares are more convenient to take than the usual tablets.

EXAMPLE II

A gelatin sheet is coated with molten cyclohexylamine lauryl sulphate and, while

[*Price*

this is still molten, a second gelatin sheet of the same dimensions is applied to the first so as to produce a "sandwich" structure which is then cut into rectangles. These rectangles represent a convenient way of using the detergent, e.g. as a shampoo for dogs. The gelatin acts as a "conditioner".

WHAT WE CLAIM IS:—

1. A self-supporting film of gelatin or rice paper, coated or impregnated with a vitamin, a mineral dietary supplement, a drug for oral administration, a personal deodorant, a shampoo, a perfume, or a hair dye or lotion, or other cosmetic.

2. A coated impregnated film of gelatin or rice paper substantially as described in any one of the foregoing specific Examples.

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(54) Title: DELIVERY SYSTEM FOR LOCALIZED ADMINISTRATION OF MEDICAMENTS TO THE UPPER RESPIRATORY TRACT

(57) Abstract

The present invention pertains to delivery systems for the localized administration of a medicament to the upper respiratory tract. The delivery system comprises: (a) a save and effective amount of a medicament useful for treating the upper respiratory tract; (b) an ionic polysaccharide; and (c) a cross-linking agent. The present invention provides for the controlled, *in situ* formation of a thin, bioadhesive film which may bind to the buccal epithelial cells which form the surface of said upper respiratory tract. Said film formation occurs when the delivery system of the present invention comprising a medicament, an ionic polysaccharide and a cross-linking agent, in a pharmaceutically acceptable carrier, is slowly ingested by dissolution through salivation of the pharmaceutically acceptable carrier. By a series of cross-linking reactions, the cross-linking agent polymerizes the ionic polysaccharide to a film in the form of aggregates, which bind to the buccal epithelial cells in the upper respiratory tract. During the *in situ* cross-linking reaction, the medicament becomes entrapped in the bioadhesive polymer aggregate and thereafter is gradually released, i.e., becomes available through dissolution.

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DELIVERY SYSTEM FOR LOCALIZED ADMINISTRATION OF MEDICAMENTS TO THE UPPER RESPIRATORY TRACT

Background Of The Invention

Field Of The Invention

The present invention pertains to delivery systems for the localized administration of a medicament to the upper respiratory tract and medicated compositions containing the delivery systems. The system comprises (a) a safe and effective amount of a medicament useful for treating the upper respiratory tract; (b) an ionic polysaccharide; and, (c) a cross-linking agent. This invention also relates to methods for preparing and using the delivery systems and compositions.

Description of the Background

Pharyngitis, the acute inflammation of the pharynx, is characterized, inter alia, by sore throat and painful swallowing. Painful swallowing is also often associated with laryngitis, the inflammation of the larynx. Patients suffering from sore throat and painful swallowing seek medication which can provide rapid onset of relief as well as sustained local action. Present therapeutic lozenge formulations do not provide sustained local therapeutic effects because of salivary dilution and rapid swallowing. Moreover, anesthetic-type lozenges tend to have a numbing effect on the entire mouth and tongue area and are not targeted to the oral pharyngeal area.

Various materials and techniques have been used to trap active ingredients and control their release. United States patent no. 4,695,463 discloses a particulate delivery system comprising an insolubilized active ingredient selected from the group consisting of flavoring agents, drugs, coloring agents, sweetening agents, perfumes, and bulking agents, entrapped in a cross-linked alginate or carrageenate matrix.

United States patent no. 5,330,761 discloses a controlled release, solid tablet comprising a bioadhesive mixture of a heterodisperse gum matrix and a bioadhesive agent selected from the group consisting of carbomer, polycarbophil and polyethylene oxide combined with an inert diluent and an active ingredient.

United States patent no. 5,147,648 discloses the improved adherence of gels to the mucous membranes by the separate application to the same area two components capable of forming a gel such as a metallic salt and a polysaccharide. One of the two components is used as a carrier for medicaments.

United States patent no. 4,843,098 discloses an ingestible substantially anhydrous aggregate comprising a pre-swelled hydrocolloid which partially entraps and binds a drug substrate. The hydrocolloid is selected from the group consisting of carboxymethyl cellulose, methyl cellulose, karaya gum, acacia gum, sodium alginate, calcium alginate, and hydroxypropyl methyl cellulose. The substrate is selected from the group consisting of potassium chloride, calcium carbonate, magnesium oxide, cholestyramine, and N-acetyl procainamide.

United States patent no. 4,857,331 discloses a sugarless ingestible gel confectionery delivery system comprising by weight of the final delivery system (a) a pectin gel component in an amount from about 1% to about 5%, (b) an algin gel component in an amount from about 0.2% to about 1.5%, (c) a polymer network gel component in an amount of up to about 5%, and (d) an edible insoluble solid in an amount sufficient to strengthen the internal gel network such that the gel retains its structural integrity during mold removal.

United States patent no. 4,981,698 discloses a sweetener delivery system comprising (a) a first solid natural or artificial high intensity sweetener; (b) a first inner coating selected from

hydrophobic and hydrophobic coating materials, wherein the inner coating and first sweetener are mixed and prepared to form a core; and (c) a second outer coating of a hydrophobic polymer containing a second sweetener. The second outer coating is selected from the group consisting of gum arabic, tragacanth, karaya, ghatti, agar, alginates, carrageenans, furcellaran, and psyllium.

United States patent no. 5,004,595 discloses a free-flowing particulate delivery system comprising (a) a core comprising a flavor in particulate form; and (b) an encapsulating matrix for the core, wherein the matrix comprises an outer coating of a hydrophobic polymer containing an intense sweetener. The outer coating is selected from the group consisting of gum arabic, tragacanth, karaya, ghatti, agar, alginates, carrageenans, furcellaran, and psyllium.

While the above compositions provide various means for controlling the release of ingredients, none of the above compositions are entirely satisfactory for the targeted localized administration of a medicament to the upper respiratory tract.

Summary Of The Invention

The present invention pertains to delivery systems for the localized administration of a medicament to the upper respiratory tract. The delivery system comprises:

(a) a safe and effective amount of a medicament useful for treating the upper respiratory tract,

(b) an ionic polysaccharide, and,

(c) a cross-linking agent.

This invention also pertains to the medicated compositions containing the targeted delivery system in a pharmaceutically acceptable carrier. This invention further pertains to methods for preparing and using the delivery systems and medicated compositions.

Detailed Description Of The Invention

As used herein, the term "upper respiratory tract" refers to the larynx, throat and oral pharyngeal area. The present invention provides for the controlled, in situ formation of a thin, bioadhesive film which may bind to the buccal epithelial cells which form the surface of said upper respiratory tract. Said film formation occurs when the delivery system of the present invention comprising a medicament, an ionic polysaccharide and a cross-linking agent, in a pharmaceutically acceptable carrier, is slowly ingested by dissolution through salivation of the pharmaceutically acceptable carrier. By a series of cross-linking reactions, the cross-linking agent polymerizes the ionic polysaccharide to a film in the form of aggregates, which bind to the buccal epithelial cells in the upper respiratory tract. During the in situ cross-linking reaction, the medicament becomes entrapped in the bioadhesive polymer aggregate and thereafter is gradually released, i.e., becomes available through dissolution. The timing of the cross-linking reaction can be controlled through selection of (a) the ionic polysaccharide, (b) the cross-linking agent, and further, through selection of (c) the pharmaceutically acceptable carrier.

Because the film binds to buccal epithelial cells, the novel delivery system provides both targeted and sustained effects to the upper respiratory tract. Because the delivery systems are targeted delivery systems, compositions containing anesthetic-type agents will minimally affect the mouth and the tongue.

The delivery system may be employed to administer a wide variety of medicaments to the upper respiratory tract. The term "medicament" as used herein refers to drugs and pharmaceuticals useful for treating the upper respiratory tract and may be selected from a wide variety of water-soluble and water-insoluble medicaments. Nonlimiting illustrative categories of such medicaments include analgesics, topical anesthetics, antitussives, topical antimicrobials, antihistamines, decongestants, expectorants, cell and tissue healing agents, bronchodilators, steroidal anti-inflammatory agents, and mixtures thereof.

Nonlimiting illustrative specific examples of topical anesthetic agents include dyclonine, promazine, phenol, hexyl resorcinol, lidocaine, benzocaine, benzyl alcohol, butacaine and their pharmaceutically acceptable salts.

Nonlimiting illustrative specific examples of analgesic agents include acetylsalicylic acid, salicylic acid, acetaminophen, ibuprofen, phenacetin, phenylbutazone, salicylamide, meclofenamic acid, naproxen, sulindac, diflunisal, piroxicam, indomethacin, etodolac, fenoproben, ketoprofen, mefenamic acid, nabumetone, ketorolac tromethamine, diclofenac, evening primrose oil (containing about 72% linoleic acid and about 9% *gamma*-linolenic acid), mesalamine, salsalate, diflunisal, salicylsalicylic acid, choline magnesium trisalicylate and their pharmaceutically acceptable salts.

Nonlimiting illustrative specific examples of antitussive agents include menthol, camphor, dextromethorphan, dextromethorphan, noscapine, carbetapentane, chlophedianol, codeine, carmiphen and diphenhydramine, hydrocodone, hydromorphone, fominoben, noscapine and their pharmaceutically acceptable salts.

Nonlimiting illustrative specific examples of topical antimicrobial agents include cetylpyridinium chloride, quaternary ammonium salts, chlorhexidine, essential oils such as thymol, menthol and eucalyptol, methyl salicylate, hexetidine, triclosan, stannous fluoride, sanguinarine, zinc salts, sodium lauryl sulfate and the like.

Nonlimiting illustrative specific examples of antihistamine agents include chlorpheniramine, brompheniramine, phenindamine, pyrilamine, methapyrilene, doxylamine, pheniramine, diphenhydramine, dexbrompheniramine, azatadine, cyproheptadine, hydroxyzine, clemastine, bromdiphenhydramine, chlorcyclizine, thonzylamine, prilamine, dexchlorpheniramine, triprolidine, acrivastine, astemizole, azelastine, cetirizine, ebastine, ketotifen, lodoxamide, loratidine, levocabastine, mequitazine, oxatomide, setastine, tazifylline, temelastine, terfenadine and their pharmaceutically acceptable salts.

Nonlimiting illustrative specific examples of decongestant agents include phenylephrine, phenylpropanolamine, pseudoephedrine, ephedrine, propylhexedrine, xylometazoline, naphazoline, oxymetazoline and their pharmaceutically acceptable salts.

Nonlimiting illustrative specific examples of expectorant agents include guaifenesin, glyceryl guaiacolate, N-acetyl cysteine, terpin hydrate, bromhexine, ambroxol, ammonium chloride and their pharmaceutically acceptable salts.

Nonlimiting illustrative specific examples of cell and tissue healing agents include natural products such as aloe, primrose oil, fatty acids, Vitamin E, herbal extracts, botanicals and the like.

Nonlimiting illustrative specific examples of steroidal anti-inflammatory agents include flunisolide, triamcinoline, triamcinoline acetonide, beclomethasone diproprionate, betamethasone diproprionate, hydrocortisone, cortisone, dexamethasone, prednisone, methyl prednisolone, and prednisolone and their pharmaceutically acceptable salts.

Nonlimiting illustrative specific examples of bronchodilator agents include ephedrine, epinephrine, racepinephrine, terbutalin, atropine, aminophylline, isoprenaline, metaproterenol, bitoterol, theophylline and their pharmaceutically acceptable salts.

The delivery system may be used to deliver other medicaments. Nonlimiting illustrative categories of such medicaments include antiasmatic agents, antibacterial agents, antifungal agents, antinauseant agents, antipyretic agents, antiviral agents, immunostimulating agents, nutritional supplements, and various alkaloid agents such as caffeine and codeine.

Preferably, the medicament is selected from the group consisting of anesthetics, analgesics and antitussives. More preferably the medicament is dyclonine, menthol, phenol, hexyl resorcinol or benzocaine.

The medicament of the present invention may be used in many distinct physical forms well known in the pharmaceutical art to provide an initial dosage of the medicament and/or a further time-release form of the medicament. Without being limited thereto, such physical forms include free forms and encapsulated forms, and mixtures thereof.

As used herein the term "safe and effective amount" means an amount of a medicament high enough when administered orally to significantly positively modify the condition to be treated, but low enough to avoid serious side effects. The amount of medicament used in the present invention may vary depending upon the recommended or permitted therapeutic dosage for the particular active agent. Such dosages are known to the skilled practitioner in the medical arts and are not a part of the present invention. In general, the amount of medicament in the medicated composition of the present invention may vary from 0.001% to 12% by weight of the total medicated composition.

The ionic polysaccharides of the present invention are bioadhesive agents which have the ability to entrap a medicament useful for treating the upper respiratory tract. As used herein the term "ionic polysaccharide" refers to polysaccharides comprised of saccharide monomers having an acidic nature, e.g., saccharide monomers having -COOH or -SO_4H groups. Ionic polysaccharides belong to a group of substances generally known as hydrocolloids. These substances are strongly hydrophilic macromolecular materials that dissolve or disperse in water, producing a thickening or viscosity effect. Hydrocolloids are both natural and synthetic materials. Natural hydrocolloids are derived from both plant and animal sources. Ionic polysaccharides which may be used in the practice of the present invention may be selected from natural hydrocolloids. Preferred for use in the present invention are algin, carrageenan and pectin with the use of algin especially preferred. Algin and pectin have several carboxylic acid groups along their polymer chains while carrageenan contains sulfuric acid groups. It is preferred to use a monocationic salt of the acid, especially the sodium salt, for solubility considerations, i.e., the salt being more soluble in the aqueous environment of the oral cavity. These ionic polysaccharides swell when hydrated and change from a water-soluble solid to a gel in the presence of multivalent cations such as calcium or magnesium. The multivalent cation forms stable bridges between neighboring molecules resulting in the gel formation. If a suitable amount of the multivalent cation is used precipitation of the film can occur. Where the monovalent cationic salt is used this can occur during a chemical exchange of a multivalent ion for a monovalent ion.

Algin is a generic designation of the derivatives of alginic acid. Alginic acid is a mixed polymer of ß-(1-4)-D-mannosyluronic acid and I-(1-4)-L-gulosyluronic acid, the relative

proportions of which vary with the botanical source and state of maturation of the giant kelp plant Macrocystis pyrifera from which algin is derived. The magnitude and kinetics of the cross-linking reaction of the algin can be controlled by varying the L-guluronic acid and D-mannurinic acid content (also known as G and M blocks). G blocks, having a more buckled, ribbon-like structure will gel quicker. Alginic acid higher in D blocks will be more delayed.

Carrageenan is extracted from Irish moss Chondrus crispus. It consists of alternating copolymers of J-(1-3)-D-galactose and (1-4)-3,6-anhydro-D- or L-galactose. Family members differ in the amount of sulfate ester and/or other substituent groups they carry. They are identified as R-, S- and Q-carrageenan. Kappa and iota form gels, kappa forming stronger gels than iota. Kappa-carrageenan contains only one sulfate group in each disaccharide repeating unit. Iota-carrageenan is the most highly sulfated member of the family.

Pectin is a generic name for a range of products derived from the cell walls of plant tissue classified as pectinic acids. Pectin substances are polymers of 1-4 linked I-galacturonic acid that exist in varying degrees of esterification or neutralization. They are coiled molecules rather than straight. The best gel formation is obtained with pectins wherein the methoxyl level has been reduced.

The amount of ionic polysaccharide in the delivery systems of the present invention may vary depending upon the type of polysaccharide and the type of medicament in the delivery system, as well as the particular result desired. The desirable amount of ionic polysaccharide present will also depend on the pharmaceutical carrier. The ionic polysaccharide may be added to the formulation in a proportion of from 10:1 to 1:10 by weight to the medicament although a ratio of 5:1 to 1:5 by weight would be preferred. It is not a requirement of the present invention that all of the medicament be trapped by the bioadhesive film. Wherein an upper amount of 12% medicament is present in the medicated composition and 1% ionic polysaccharide it is possible that not all of the medicament may be trapped by the film. In general, the ionic polysaccharide will be from about 0.001% to about 1.0%, more preferably from about 0.01% to about 0.6%, by weight of the total medicated composition. For pharmaceutical carriers such as a cooked candy mass wherein processing adversely affects ionic polysaccharides, a lower amount of polysaccharide is desirable.

The cross-linking agents of the present invention are cationic salts that react with the ionic polysaccharide to form a cross-linked polymeric film which adheres to the upper respiratory tract. The rate of gel formation as well as the quality and texture of the resultant gel can be controlled by the solubility and availability of the cation source. Nonlimiting illustrative categories of such cross-linking agents are the salts of multivalent cations such as aluminum, calcium, copper, iron, magnesium, manganese, zinc, and the like, and mixtures thereof. Nonlimiting examples of useful cross-linking compounds are the chloride, sulfate, acetate, and carboxylate salts of calcium, magnesium, copper, zinc, manganese, aluminum, iron, and the like. The preferred multivalent cations are bivalent, and the preferred bivalent cation is calcium. Preferably, the cross-linking agent may be selected from the group consisting of calcium carbonate, stearate, lactate, tartrate, sulfate, chloride, monocalcium phosphate, tricalcium phosphate, dicalcium phosphate dihydrate and mixtures thereof. More preferably, the cross-linking agent is calcium lactate.

The amount of cross-linking agent in the delivery systems of the present invention may depend upon the type of ionic polysaccharide employed as well as the particular result desired, more specifically, the degree of film formation to be achieved. The cross-linking agent may be added to the formulation in amounts sufficient to substantially polymerize the ionic polysaccharide present. Preferably for monocationic salts an excess of multivalent cations are added to insure substantial replacement of the monovalent cation with the multivalent cation.

In general, the amount of cross-linking agent in the delivery system will be from about 0.001% to about 1.2%, more preferably from about 0.01% to about 0.8%, by weight of the total medicated composition.

In another embodiment, the cross-linking agent is premixed with a sequestering agent to further control the timing of the cross-linking reaction. Sequestering agents are compounds that prevent ions from exhibiting their usual properties because of close combination with the sequestering agent. In the present invention, a sequestering agent can form a coordination complex with the metallic ions of the cross-linking agent to delay precipitation of the bioadhesive agent. Nonlimiting examples of useful sequestering agents may be selected from

the group consisting of sodium citrate, tetrasodium phosphate, sodium hexametaphosphate, ethylene diamine tetraacetic acid and the like.

It is preferred to use a sequestering agent in a non-solid application such as in a medicated liquid center wherein the sequestering agent delays an otherwise too rapid polymerization of the ionic polysaccharide. The amount of sequestering agent in the delivery system of the present invention may vary depending upon the cross-linking agent employed and the particular result desired. In general, the amount of sequestering agent in the delivery system will be from about 0.001% to about 1.2%, more preferably from about 0.01% to about 0.8% by weight of the total medicated composition.

Although the sequestering agent may be used per se in the delivery system, it is preferred to use a pharmaceutically acceptable acid in conjunction with the sequestering agent. The pharmaceutically acceptable acids of the present invention are slow-dissolving compounds that react with the sequestered cross-linking agents to release the agent so that the later can react with the monovalent cation salts to form a polymeric film. The timing of the cross-linking reaction can be controlled through selection of the appropriate slow-dissolving pharmaceutically acceptable acid. Nonlimiting examples of useful pharmaceutically acceptable acid are citric, fumaric, malic. tartaric, lactic, adipic, phosphoric, benzoic, glutamic, sorbic, propionic, erythorbic, tannic, succinic, aconitic, and ascorbic. Preferably, the pharmaceutically acceptable acid is selected from the group consisting of citric, fumaric, malic, tartaric, lactic, adipic, and phosphoric. More preferably, the pharmaceutically acceptable acid is citric acid.

The amount of the pharmaceutically acceptable acid in the delivery systems of the present invention may vary depending upon the type of cross-linking agent employed as well as the particular result desired. In general, the amount of pharmaceutically acceptable acid in the delivery system will be from about 0.001% to about 1.2%, more preferably from about 0.01% to about 0.8% by weight of the total medicated composition.

In yet another embodiment, the release of a soluble medicament can be delayed by premixing the medicament with a pharmaceutically acceptable oil and an emulsifier, wherein the emulsifier has a hydrophilic-lipophilic balance in the range from about 1 to about 10.

Nonlimiting examples of useful pharmaceutically acceptable oils may be selected from the group consisting of animal, vegetable, and marine oils, fats, and waxes (such as sunflower oil or shark liver oil), and synthetic oils, fats, and waxes. More preferably, the pharmaceutically acceptable oils are selected from the group consisting of vegetable oils and the like. Most preferably, the pharmaceutically acceptable oil is a vegetable oil. In general, the amount of pharmaceutically acceptable oil in the delivery system will be from about 0.001% to about 1%, more preferably from about 0.01% to about 0.2%, by weight of the total medicated composition.

Nonlimiting examples of useful emulsifiers having a hydrophilic-lipophilic balance in the range from about 1 to about 10 may be selected from the group consisting of decaglycerol decaoleate, lecithin and sorbitan fatty acid esters. Preferably, the emulsifier is decaglycerol decaoleate. In general, the amount of emulsifier in the delivery system will be from about 0.001% to about 1%, more preferably from about 0.01% to about 0.6% by weight of the total medicated composition.

The present invention also concerns medicated compositions comprising the targeted delivery systems. These medicated compositions comprise

(a) a safe and effective amount of a medicament useful for treating the upper respiratory tract,

(b) an ionic polysaccharide,

(c) a cross-linking agent, and,

(d) a pharmaceutically acceptable carrier suitable for administering of a medicament to the upper respiratory tract.

By "pharmaceutically acceptable carrier" is meant one or more filler or encapsulating or carrier materials which are suitable for oral administration to a human. Pharmaceutically acceptable carrier materials suitable for the preparation of dosage forms for oral administration are well-known in the art. The delivery systems useful for the localized administration of a medicament to the upper respiratory tract may be utilized in a wide variety of pharmaceutically acceptable carriers. Various oral dosage forms can be used including but not limited to such solid forms as lozenges, tablets, capsules, granules, and bulk powders and liquid centers such as syrups and suspensions.

The pharmaceutically acceptable carrier of the present invention may contain conventional excipients and additives which function to facilitate processing or storage. Thus coloring agents, flavoring agents, perfumes, sweetening agents, surface active agents, lubricants, softeners, glidants, stabilizing agents, and the like, and mixtures thereof, may be present in the medicated composition. The pharmaceutically acceptable carrier material including optional additives is present in a quantity sufficient to bring the total amount of the medicated composition to 100%.

The present invention is also directed to methods for preparing the medicated compositions. In a specific embodiment, the present invention is directed at a method for preparing a medicated composition useful for the localized administration of medicaments to the upper respiratory tract which comprises the steps of:

(1) providing the following ingredients:

(a) a medicament useful for treating the upper respiratory tract;

(b) an ionic polysaccharide;

(c) a cross-linking agent; and,

(d) a pharmaceutically acceptable carrier suitable for administering of a medicament to the upper respiratory tract;

(2) admixing the ingredients from step (1) to form the composition.

The present invention is also directed to a method for treating the upper respiratory tract. In a specific embodiment the present invention is directed at the local administration of a medicament to the upper respiratory tract which method comprises orally administering to a patient a medicated composition which comprises:

(a) a safe and effective amount of a medicament useful for treating the upper respiratory tract,

(b) an ionic polysaccharide,

(c) a cross-linking agent, and,

(d) a pharmaceutically acceptable carrier suitable for administration of a medicament to the upper respiratory tract.

An important aspect of the present invention includes a hard or soft confectionery composition incorporating the inventive delivery systems and a method for preparing the hard or soft confections. In this form of the invention, the medicated compositions includes the delivery system and a pharmaceutically acceptable carrier such as a confectionery bulking agent, and various additives. The confectionery may be in the form of a lozenge, tablet, toffee, nougat, suspension, chewy candy, and the like. The pharmaceutically acceptable carriers may be prepared from a wide range of materials. Without being limited thereto, such materials include diluents, binders and adhesives, lubricants, disintegrants, coloring agents, bulking agents, flavoring agents, sweetening agents and miscellaneous materials such as buffers and adsorbents in order to prepare a particular medicated confection.

The preparation of confectionery formulations is historically well known and has changed little through the years. Confectionery items have been classified as either "hard" confectionery or "soft" confectionery. The medicated compositions of the present invention can be incorporated into confectionery compositions by admixing the inventive compositions into conventional hard and soft confections.

As used herein, the term confectionery material means a product containing a bulking agent selected from a wide variety of materials such as sugar, corn syrup, and the like, and in the case of sugarless bulking agents, sugar alcohols such as sorbitol and mannitol and the like, and mixtures thereof. Confectionery material may include such exemplary substances as lozenges, tablets, toffee, nougat, suspensions, chewy candy, chewing gum and the like. The bulking agent is present in a quantity sufficient to bring the total amount of confectionery composition to 100%.

Lozenges are flavored medicated dosage forms intended to be sucked and held in the mouth. Lozenges may be in the form of various shapes such as flat, circular, octagonal and biconvex forms. The lozenge bases are generally in two forms: hard, boiled candy lozenges and compressed tablet lozenges.

Hard boiled candy lozenges may be processed and formulated by conventional means. In general, a hard boiled candy lozenge has a base composed of a mixture of sugar and other

carbohydrate bulking agents kept in an amorphous or glassy condition. This amorphous or glassy form is considered a solid syrup of sugars generally having from about 0.5% to about 3% moisture. Such materials normally contain up to about 92% sugar, up to about 55% corn syrup and from about 0.1% to about 5% water, by weight of the final composition. The syrup component is generally prepared from corn syrups, but may include other materials. Further ingredients such as flavoring agents, sweetening agents, acidulants, coloring agents and the like may also be added.

Boiled candy lozenges may also be prepared from non-fermentable sugars such as sorbitol, mannitol, isomalt, and hydrogenated starch hydrolysates. Typical hydrogenated starch hydrolysates are LYCASINÔ, a commercially available product manufactured by Roquette Corporation, and HYSTARÔ, a commercially available product manufactured by Lonza, Inc. The candy lozenges may contain up to about 95% sorbitol, a mixture of sorbitol and mannitol in a ratio from about 9.5:0.5 up to about 7.5:2.5, and hydrogenated starch hydrolysates to about 55%, by weight of the solid syrup component.

Boiled candy lozenges may be routinely prepared by conventional methods such as those involving fire cookers, vacuum cookers, and scraped-surface cookers also referred to as high speed atmospheric cookers.

Fire cookers involve the traditional method of making a boiled candy lozenge base. In this method, the desired quantity of carbohydrate bulking agent is dissolved in water by heating the agent in a kettle until the bulking agent dissolves. Additional bulking agent may then be added and the cooking continued until a final temperature of 1450 C to 1560 C is achieved. The batch is then cooled and worked as a plastic-like mass to incorporate additives such as flavoring agents, coloring agents and the like.

A high-speed atmospheric cooker uses a heat-exchanger surface which involves spreading a film of candy on a heat exchange surface, the candy is heated to 1650 C to 1700 C in a few seconds. The candy is then rapidly cooled to 1000 C to 1200 C and worked as a plastic-like mass enabling incorporation of the additives, such as flavor agents, coloring agents and the like.

In vacuum cookers, the carbohydrate bulking agent is boiled at a temperature from about 1250 C to about 1320 C, vacuum is applied and additional water is boiled off without extra heating. When cooking is complete, the mass is a semi-solid and has a plastic-like consistency. At this point, flavoring agents, coloring agents, and other additives are admixed in the mass by routine mechanical mixing operations.

The optimum mixing required to uniformly mix the flavoring agents, coloring agents and other additives during conventional manufacturing of boiled candy lozenges is determined by the time needed to obtain a uniform distribution of the materials. Normally, mixing times of from about 4 to about 10 minutes have been found to be acceptable.

Once the boiled candy lozenge has been properly tempered, it may be cut into workable portions or formed into desired shapes. A variety of forming techniques may be utilized depending upon the shape and size of the final product desired. A general discussion of the composition and preparation of hard confections may be found in H.A. Lieberman, Pharmaceutical Dosage Forms, Volume 1: Tablets (1989), Marcel Dekker, Inc., New York, N.Y. at Medicated Confections, pages 419-582, which disclosure is incorporated herein by reference.

In contrast, compressed tablet confections contain particulate materials and are formed into structures under pressure. These confections generally contain sugars in amounts up to about 95%, by weight of the composition, and typical tablet excipients such as binders and lubricants as well as flavoring agents, coloring agents and the like.

In addition to hard confectionery materials, the lozenges of the present invention may be made of soft confectionery materials such as those contained in nougat. The preparation of soft confections, such as nougat, involves conventional methods, such as the combination of two primary components, namely (1) a high boiling syrup such as a corn syrup, hydrogenated starch hydrolysate or the like, and (2) a relatively light textured frappe, generally prepared from egg albumin, gelatin, vegetable proteins, such as soy derived compounds, sugarless milk derived

compounds such as milk proteins, and mixtures thereof. The frappe is generally relatively light, and may, for example, range in density from about 0.5 to about 0.7 grams/cc.

The high boiling syrup, or "bob syrup" of the soft confectionery is relatively viscous and has a higher density than the frappe component, and frequently contains a substantial amount of a bulking agent such as a sugar, corn syrup, or a hydrogenated starch hydrolysate. Conventionally, the final nougat composition is prepared by the addition of the "bob syrup" to the frappe under agitation, to form the basic nougat mixture. Further ingredients such as flavoring agents, additional carbohydrate bulking agents, coloring agents, preservatives, medicaments, mixtures thereof and the like may be added thereafter also under agitation. A general discussion of the composition and preparation of nougat confections may be found in B.W. Minifie, Chocolate, Cocoa and Confectionery: Science and Technology, 2nd edition, AVI Publishing Co., Inc., Westport, Conn. (1980), at pages 424-425, which disclosure is incorporated herein by reference.

The procedure for preparing the soft confectionery involves known procedures. In general, the frappe component is prepared first and thereafter the syrup component is slowly added under agitation at a temperature of at least about 650 C, and preferably at least about 1000 C. The mixture of components is continued to be mixed to form a uniform mixture, after which the mixture is cooled to a temperature below 800 C, at which point, the flavoring agent may be added. The mixture is further mixed for an additional period until it is ready to be removed and formed into suitable confectionery shapes.

The novel medicated compositions may also be in the form of a pharmaceutical suspension. Pharmaceutical suspensions of this invention may be prepared by conventional methods long established in the art of pharmaceutical compounding.

Medicated candy is prepared by procedures similar to those used to make soft confectionery. In a typical procedure, a boiled sugar-corn syrup blend is formed to which is added a frappe mixture. The boiled sugar-corn syrup blend may be prepared from sugar and corn syrup blended in parts by weight ratio of about 90:10 to about 10:90. The sugar-corn syrup blend is heated to temperatures above about 1200 C to remove water and to form a

molten mass. The frappe is generally prepared from gelatin, egg albumin, milk proteins such as casein, and vegetable proteins such as soy protein, and the like, which is added to a gelatin solution and rapidly mixed at ambient temperature to form an aerated sponge like mass. The frappe is then added to the molten candy mass and mixed until homogeneous at temperatures between about 650 C and about 1200 C.

The delivery systems of the present invention can then be added to the homogeneous mixture as the temperature is lowered to about 650 C-950 C whereupon additional ingredients can then be added such as flavoring agents and coloring agents. The formulation is further cooled and formed into pieces of desired dimensions.

A general discussion of the lozenge and tablet forms of confectionery may be found in H.A. Lieberman, Pharmaceutical Dosage Forms, Volume 1: Tablets (1989), Marcel Dekker, Inc., New York, N.Y. at Medicated Confections, pages 419-582, which disclosure is incorporated herein by reference.

Throughout this application, various publications have been referenced. The disclosures in these publications are incorporated herein by reference in order to more fully describe the state of the art.

The invention being thus described, it will be obvious that the same may be varied in many ways. Such variations are not to be regarded as a departure from the spirit and scope of the invention and all such modifications are intended to be included within the scope of the following claims.

The present invention is further illustrated by the following examples which are not intended to limit the effective scope of the claims. All parts and percentages in the examples and throughout the specification and claims are by weight of the final composition unless otherwise specified.

Examples

Examples 1 and 2:

Examples 1 and 2 provide a comparison of a medicated cough drop containing the delivery system with a control confectionery. Menthol was used as the active agent. Table 1 below sets out the components in the drops.

Table 1

Medicated Drops

Examples		
Formula %	1[a]	2[b]
sucrose	54.39	54.45
corn syrup	55.40	44.55
water	1.00	1.00
sodium alginate[c]	0.103	---
Candy Base Portion Total	97.338	97.35
calcium lactate	0.012	---
menthol	0.230	0.230
eucalyptus oil	0.200	0.200
citric acid	0.220	0.220
salvage	2.000	2.000
Portion Total	2.662	2.65
Total	100	100

a: delivery system
b: control
c: added as a 4% solution

For example 1 the sucrose, corn syrup (80% dry solids), water and sodium alginate were heated in a cooking pot to approximately 1450C. The menthol, eucalyptus oil, citric acid, calcium lactate (premixed 1:1 with water) were mixed with the salvage portion and then mixed into the mass. The candy was formed by in a drop roller press sized at 2.2g per piece. Each piece contained approximately 5mg menthol.

A test panel evaluated the two comparative samples for degree (intensity) of cooling effects on the nasal passages, the mouth and the throat. The results of the evaluation are set out in Table 2.

Table 2

Test Panel

Examples		
	1[a]	2[b]
Nasal	4.62	5.0
Mouth	5.75	5.62
Throat	6.12	5.25

a: delivery system
b: control

Scale:
On a scale of 1-9 with 1 being very little and 9 being very much

The control was found to have more diffuse vapor action having greater cooling effects in the nasal passages. The inventive sample provided cooling more directly to the throat area, i.e., the inventive sample had less cooling in the nasal passages and more cooling in the throat area, the targeted area.

Examples 3-6:

Examples 3-6 provide a comparison of a medicated anesthetic-type lozenge containing the delivery system (3) with a control confectionery (5), a system containing a polymer added per se (4), and a commercial product (6). The components in the prepared confectionery compositions, Examples 3-5, are set out in Table 3.

Table 3

Anesthetic-Type Lozenge

Examples			
Formula %	3[a]	4[b]	5[c]
Sucrose	54.39	54.44	49.49
Corn Syrup	44.50	44.55	49.49
Coloring Agent	0.01	0.01	0.01
Sodium Alginate	0.10	---	---
Residual Moisture	1.00	1.00	1.00
Candy Base Portion Total	96.05	97.37	97.41
Menthol	0.01	0.01	0.01
Flavoring Agent	0.29	0.29	0.29
Citric Acid	0.15	0.15	0.15
Salvage-portion 1	2.00	2.00	2.00
Dyclonine Hydrochloride	0.14	0.14	0.14
Decaglycerol Decaoleate	0.14	---	---
Vegetable Oil	0.14	---	---
Salvage-portion 2	1.00	---	---
Calcium Lactate.$5H_2O$	0.08	---	---
Carbomer	---	0.04	---
Portion Total	3.95	2.63	2.59
Total	100.00	100.00	100.00

a: delivery system

b: polymer

c: control

For example 3, the candy base was prepared by adding the sucrose, corn syrup (80% dry solids), coloring agent (as a 1% aqueous solution), and sodium alginate (as a 4% aqueous solution) to a cooking pot with sufficient wetting water and cooking the mixture up to a temperature of about 1450 C to 1500 C. The menthol, flavoring agent and citric acid were then admixed with the salvage-portion 1 (sugar and corn syrup). The dyclonine and decaglycerol decaoleate were then mixed, the vegetable oil then admixed with this mixture, and this admixture then mixed with the salvage-portion 2. The menthol-salvage admixture, dyclonine-salvage admixture, and calcium lactate hydrate (premix 1:1 with water) were then folded into the candy. The flavored candy mass was pressed through a candy drop roller and formed into candy pieces. The candy pieces were cooled and shaken and stored in a closed container with dehydrating packets.

For examples 4 and 5, the candy base was prepared by adding the sucrose, corn syrup (80% dry solids), and coloring agent (as a 1% aqueous solution) to a cooking pot with sufficient wetting water and cooking the mixture up to a temperature of about 1450 C to 1500 C. The menthol, flavoring agent, citric acid, and dyclonine, and carbomer when present, were then admixed with salvage-portion 1 and this admixture was then folded into the candy. The flavored candy mass was pressed through a candy drop roller and formed into candy pieces. The candy pieces were cooled and shaken and stored in a closed container with dehydrating packets.

A consumer taste panel evaluated the throat numbing action of the confectionery compositions set out in Table 3, and also a commercial lozenge containing 0.14% dyclonine hydrochloride, for taste and efficacy in random order and the findings were pooled and averaged. The results from the taste panel are set out below in Table 4.

Table 4

Consumer Study

Examples				
	3[a]	4[b]	5[c]	6[d]
Overall Liking	6.2	6.0	5.4	4.9
Perceived Efficacy	5.8	5.5	5.1	5.5
Intensity of Throat Numbing	4.9	4.2	4.6	4.2
Intensity of Mouth Numbing	5.5	5.7	5.5	4.8

a: delivery system
b: polymer
c: control
d: commercial product containing 0.14% dyclonine hydrochloride

Scale:
Overall Liking; on a scale of 1-9, 1 being extremely disliked and 9 being extremely liked.
Perceived Efficacy: on a scale of 1-9, 1 being ineffective and 9 being effective.
Intensity of Throat Numbing: on a scale of 1-9, 1 being very little, 5 being just right, and 9 being too much.
Intensity of Mouth Numbing: on a scale of 1-9, 1 being very little and 9 being very much.

The greatest significance of these findings is that the delivery system (3) provided strongest throat numbing and overall preference. It was especially preferred over the commercial product which was more non-localized in its effect. The test also showed that consumers believed that (3) was more efficacious.

The test further showed that merely adding a polymer (4) does not provide the same result as provided by the delivery system (3) of the present invention.

We claim:

1. A delivery system for the localized administration of a medicament to the upper respiratory tract which comprises:

(a) a safe and effective amount of a medicament useful for treating the upper respiratory tract,

(b) an ionic polysaccharide, and,

(c) a cross-linking agent.

2. The delivery system according to claim 1, wherein the medicament useful for treating the upper respiratory tract is selected from the group consisting of analgesics, topical anesthetics, antitussives, topical antimicrobials, antihistamines, decongestants, expectorants, cell and tissue healing agents, bronchodilators, steroidal anti-inflammatory agents, and mixtures thereof.

3. The delivery system according to claim 2 wherein the medicament is an analgesic, topical anesthetic or antitussive.

4. The delivery system according to claim 3 wherein the medicament is an antitussive.

5. The delivery system according to claim 4 wherein the medicament is menthol.

6. The delivery system according to claim 3, wherein the medicament is a topical anesthetic agent.

7. The delivery system according to claim 6, wherein the medicament is dyclonine hydrochloride.

8. The delivery system according to claim 1, wherein the ionic polysaccharide selected from the group consisting of algin, carrageenan and pectin.

9. The delivery system according to claim 8 wherein the ionic polysaccharide is a monocationic salt.

10. The delivery system according to claim 9 wherein the salt is sodium.

11. The delivery system according to claim 1, wherein the ratio of the ionic polysaccharide to medicament is from 10:1 to 1: 10 by weight.

12. The delivery system according to claim 1, wherein the cross-linking agent contains a multivalent ion selected from the group consisting of aluminum, calcium, copper, iron, magnesium, manganese, zinc, and mixtures thereof.

13. The delivery system according to claim 12, wherein the cross-linking agent is selected from the group consisting of calcium stearate, calcium lactate, calcium tartrate, calcium sulfate, monocalcium phosphate, tricalcium phosphate, dicalcium phosphate dihydrate and mixtures thereof.

14. The delivery system according to claim 13, wherein the cross-linking agent is calcium lactate.

15. The delivery system according to claim 1, wherein the cross-linking agent is premixed with a sequestering agent.

16. The delivery system according to claim 15, wherein the sequestering agent is selected from the group consisting of sodium citrate, tetrasodium phosphate, sodium hexametaphosphate, ethylene diamine tetraacetic acid.

17. The delivery system according to claim 15, wherein the delivery system further comprises a pharmaceutically acceptable acid selected from the group consisting of citric acid, fumaric acid, malic acid, tartaric acid, lactic acid, adipic acid, phosphoric acid, benzoic acid, glutamic acid, sorbic acid, propionic acid, erythorbic acid, tannic acid, succinic acid, aconitic acid, ascorbic acid, and mixtures thereof

18. The delivery system according to claim 17, wherein the pharmaceutically acceptable acid is selected from the group consisting of citric acid, fumaric acid, malic acid, tartaric acid, lactic acid, adipic acid, phosphoric acid, and mixtures thereof.

19. The delivery system according to claim 18, wherein the pharmaceutically acceptable acid is citric acid.

20. The delivery system according to claim 1, wherein the medicament is premixed with a pharmaceutically acceptable oil and an emulsifier having a hydrophilic-lipophilic balance in the range from about 1 to about 10.

21. The delivery system according to claim 20, wherein the pharmaceutically acceptable oil is selected from the group consisting of animal, vegetable, marine, and synthetic oils, fats, and waxes.

22. The delivery system according to claim 20, wherein the emulsifier having a hydrophilic-lipophilic balance in the range from about 1 to about 10 is selected from the group consisting of decaglycerol decaoleate, lecithin and sorbitan fatty acid esters.

23. The delivery system according to claim 21, wherein the pharmaceutically acceptable oil is vegetable oil and the emulsifier is decaglycerol decaoleate.

24. A medicated composition which comprises:

(a) a safe and effective amount of a medicament useful for treating the upper respiratory tract,

(b) an ionic polysaccharide,

(c) a cross-linking agent, and,

(d) a pharmaceutically acceptable carrier suitable for administration of a medicament to the upper respiratory tract.

25. The medicated composition according to claim 24, wherein the medicament useful for treating the upper respiratory tract is selected from the group consisting of analgesics, topical anesthetics, antitussives, topical antimicrobials, antihistamines, decongestants, expectorants, cell and tissue healing agents, bronchodilators, steroidal anti-inflammatory agents, and mixtures thereof.

26. The medicated composition according to claim 25 wherein the medicament is an analgesic, topical anesthetic or antitussive.

27. The medicated composition according to claim 26 wherein the medicament is an antitussive.

28. The medicated composition according to claim 27 wherein the medicament is menthol.

29. The medicated composition according to claim 26, wherein the medicament is a topical anesthetic agent.

30. The medicated composition according to claim 29, wherein the medicament is dyclonine hydrochloride.

31. The medicated composition according to claim 24, wherein the ionic polysaccharide selected from the group consisting of algin, carrageenan and pectin.

32. The medicated composition according to claim 31 wherein the ionic polysaccharide is a monocationic salt.

33. The medicated composition according to claim 32 wherein the salt is sodium.

34. The medicated composition according to claim 24, wherein the cross-linking agent contains a multivalent ion selected from the group consisting of aluminum, calcium, copper, iron, magnesium, manganese, zinc, and mixtures thereof.

35. The medicated composition according to claim 34, wherein the cross-linking agent is selected from the group consisting of calcium stearate, calcium lactate, calcium tartrate, calcium sulfate, monocalcium phosphate, tricalcium phosphate, dicalcium phosphate dihydrate and mixtures thereof.

36. The medicated composition according to claim 35, wherein the cross-linking agent is calcium lactate.

37. The medicated composition according to claim 24, wherein the medicament useful for treating the upper respiratory tract is present in an amount from about 0.001% to about 12%, by weight of the delivery system.

38. The medicated composition according to claim 24, wherein the ionic polysaccharide is present in an amount from about 0.001% to about 1%, by weight of the composition.

39. The medicated composition according to claim 24, wherein the cross-linking agent is present in an amount from about 0.001% to about 1.2%, by weight of the composition.

40. The medicated composition according to claim 24, wherein the cross-linking agent is premixed with a sequestering agent.

41. The medicated composition according to claim 40, wherein the sequestering agent is selected from the group consisting of sodium citrate, tetrasodium phosphate, sodium hexametaphosphate, ethylene diamine tetraacetic acid.

42. The medicated composition according to claim 24, wherein the delivery system further comprises a pharmaceutically acceptable acid selected from the group consisting of citric acid, fumaric acid, malic acid, tartaric acid, lactic acid, adipic acid, phosphoric acid, benzoic acid, glutamic acid, sorbic acid, propionic acid, erythorbic acid, tannic acid, succinic acid, aconitic acid, ascorbic acid, and mixtures thereof

43. The medicated composition according to claim 42, wherein the pharmaceutically acceptable acid is selected from the group consisting of citric acid, fumaric acid, malic acid, tartaric acid, lactic acid, adipic acid, phosphoric acid, and mixtures thereof.

44. The medicated composition according to claim 43 wherein the pharmaceutically acceptable acid is citric acid.

45. The medicated composition according to claim 24, wherein the pharmaceutically acceptable acid is present in an amount from about 0.001% to about 1.2%, by weight of the delivery system.

46. The medicated composition according to claim 24, wherein the medicament is premixed with a pharmaceutically acceptable oil and an emulsifier having a hydrophilic-lipophilic balance in the range from about 1 to about 10.

47. The medicated composition according to claim 46, wherein the pharmaceutically acceptable oil is selected from the group consisting of animal, vegetable, marine, and synthetic oils, fats, and waxes.

48. The medicated composition according to claim 46, wherein the emulsifier having a hydrophilic-lipophilic balance in the range from about 1 to about 10 is selected from the group consisting of decaglycerol decaoleate, lecithin and sorbitan fatty acid esters.

49. The medicated composition according to claim 46, wherein the pharmaceutically acceptable oil is vegetable oil and the emulsifier is decaglycerol decaoleate.

50. A method for preparing a medicated composition useful for the localized administration of medicaments to the upper respiratory tract which comprises the steps of:

(1) providing the following ingredients:

(a) a safe and effective amount of a medicament useful for treating the upper respiratory tract,

(b) an ionic polysaccharide,

(c) a cross-linking agent, and,

(d) a pharmaceutically acceptable carrier suitable for administration of a medicament to the upper respiratory tract;

(2) admixing the ingredients from step (1) to form the medicated composition.

51. A method for the local administration of a medicament to the upper respiratory tract of a patient which comprises orally administering a medicated composition which comprises:

(a) a safe and effective amount of a medicament useful for treating the upper respiratory tract,

(b) an ionic polysaccharide,

(c) a cross-linking agent, and,

(d) a pharmaceutically acceptable carrier suitable for administration of a medicament to the upper respiratory tract.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 97/00252

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/00 A61K47/36 A61K47/02 A61K31/045 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 92 03124 A (ORAMED INC) 5 March 1992 * see in particular example 5, page 8 line 20 - page 9, line 8, and page 30 lines 6 - 15 * ---	1-3,6, 8-12, 24-26, 29, 31-34, 37-39, 50,51
A	EP 0 221 850 A (WARNER LAMBERT CO) 13 May 1987 * see in particular example 1 * --- -/--	1-51

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 April 1997	06.05.1997
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Authorized officer Isert, B

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 97/00252

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

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(54) **Title:** Pharmaceutical compositions for acute glucocorticoid therapy

(57) **Abstract:** The present invention relates to glucocorticoid-containing pharmaceutical compositions or kits for use in acute emergency situations where acute glucocorticoid therapy is required. Notably, the invention relates to pharmaceutical compositions and kits that are designed to be administered by non-medically trained persons outside a hospital or another medical or clinical setting. The invention also relates to a method for treating a disorder requiring acute glucocorticoid therapy by providing a fast onset of action of a glucocorticoid

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Pharmaceutical compositions for acute glucocorticoid therapy

Field of the invention

The present invention relates to glucocorticoid-containing pharmaceutical compositions or kits for use in acute emergency situations where acute glucocorticoid therapy is required. Notably, the invention relates to pharmaceutical compositions and kits that are designed to be administered by non-medically trained persons outside a hospital or another medical or clinical setting. The invention also relates to a method for treating a disorder requiring acute glucocorticoid therapy by providing a fast onset of action of a glucocorticoid.

Background of the invention

Glucocorticoids are important steroids for intermediary metabolism, immune function, musculoskeletal and connective tissue as well as the brain. The importance of the glucocorticoids is best understood in patients with glucocorticoid deficiency. In such patients, the one-year survival rate was only 20% in the 1950s before the availability of glucocorticoid replacement therapy. The major use of glucocorticoids in clinical practice began, however, with their use in the treatment of rheumatoid arthritis in the 1940s. Both natural and synthetic glucocorticoids have been employed in the management of a wide variety of conditions and they play a crucial part of many emergency treatments involving allergic and inflammatory disorders.

The endogenous glucocorticoids are steroids predominantly produced in the adrenal cortex. The main glucocorticoid in the body is cortisol. The production and secretion of cortisol is governed by a complex and highly efficient system that includes the hypothalamus, pituitary and the adrenal glands i.e. hypothalamic-pituitary-adrenal axis (HPA). Cortisol secretion has a circadian release rhythm with peak values in early morning and trough values at midnight. The HPA axis is also activated by several physical and psychological stressors. Thus, under stress conditions, such as physical activity, fever, surgery or mental stress, the serum cortisol concentration is increased.

Adrenocortical deficiency results in a number of complex symptoms that results from deficiency of adrenocortical hormone activity. It may be of a primary type as a result of a disease in the adrenal cortex, a secondary (central) type due to the specific pathology in the hypothalamus and/or the pituitary gland, or a tertiary type due to a suppressed HPA axis after long-term high dose glucocorticoid treatment.

The onset of adrenocortical insufficiency may vary from insidious to an acute life-threatening situation with severe salt and water deficit, which leads to shock and death if not treated fast and adequately.

Therapy of e.g. acute adrenal crisis requires that the one or more glucocorticoids quickly enter (are absorbed) into the systemic circulation at a therapeutically effective concentration interval (therapeutic window). Although a number of various glucocorticoid-containing pharmaceutical compositions already are on the market, most of these are not suitable for the treatment of a disorder requiring acute glucocorticoid therapy as they either result in a too slow appearance in the systemic circulation (e.g. conventional tablets) or in a too low, if any, glucocorticoid serum level (many glucocorticoid-containing pharmaceutical compositions are intended for local treatment e.g. in the nose or on the skin).

There are today two ways of administering glucocorticoids in medical emergencies. One is the parenteral route where an intravenous (IV) infusion has to be set up or a deep intramuscular (IM) injection has to be given. However, one disadvantage of this administration is that an IV route can be challenging to establish particularly in patients with compromised peripheral circulation. Furthermore, parenteral administration requires qualified personnel and is therefore limited to well-crewed ambulances and in-hospital settings.

The other administration route is traditionally by oral administration using a dissolvable betamethasone tablet in water. This route is mainly used in outpatient clinics and for patient self-medication. However, the disadvantages are the considerable lag-time when preparing the solution and the time from intake until a significant serum level of the drug is obtained. The maximum plasma concentration (C_{max}) is usually reached within 1 to 3 hours after administration (T_{max}) It is also well known that the onset of intestinal absorption cannot be earlier than 0.5 hour for these oral immediate release products of a rapidly dissolved and rapidly absorbed drug (a class I drug according to the FDA's Biopharmaceutics Classification System), the gastric emptying being very variable both in the fasted and fed state. Furthermore, it is mandatory that the patient is conscious and has unaffected ability to swallow the solution since a weak gastrointestinal motility results in a further delay in gastric emptying and reduced intestinal absorption (both rate and extent).

Examples of such cumbersome oral administrations are obtained in patients with acute laryngitis, patients with severe distress due to breathlessness, children with croup or severe angiooedema, and in patients with gastroenteritis where gastrointestinal absorption is uncertain.

Accordingly, it would be of great therapeutic advantage to develop pharmaceutical compositions that enable self-administration by patients and administration to patients by non-medically trained persons outside of a hospital, clinic, ambulance, paramedical or similar medical settings and at the same time result in a sufficient treatment of a disorder requiring acute glucocorticoid therapy (e.g. acute adrenal crises) by providing a fast onset of action after administration. Moreover, there is also a need for pharmaceutical compositions that can be administered to a patient who e.g. is unconscious or otherwise unable to swallow a composition (e.g. a tablet or solution) and that does not require medically trained personnel or need be done in a medical setting.

Detailed disclosure of the invention

The present invention meets the above-described needs by providing a pharmaceutical composition comprising one or more glucocorticoids for substantially immediate release, wherein at least about 60% of the one or more glucocorticoids are released from the composition within the first 30 min after start of an in vitro dissolution test according to USP employing USP Dissolution Apparatus No. 2 (paddle), 50 rpm and a suitable dissolution medium such as, e.g., water, simulated saliva or simulated intestinal fluid without enzymes, and wherein a glucocorticoid serum level of a subject of at least 20% of C_{max} is reached within 20 min after administration of the composition via a mucosa of the subject.

The dissolution medium can be chosen depending on the type of composition in question. Accordingly, water or simulated saliva can be used for compositions intended for administration to the oral cavity. A person skilled in the art will know how to chose the right dissolution medium depending on the formulation in question. Normally a dissolution medium based on water and adjusted to a pH in the range of from pH 4.5 to about 8 is suitable irrespective of whether the compositions are intended for administration via nasal, rectal, vaginal mucosa.

In the present context the term "substantially immediate release" is intended to include all types of release which differ from the release obtained from plain tables and provide a release, which is faster than that obtained from plain tablets. In particular, the term is related to a rapid release of the one or more glucocorticoids in an *in vitro* dissolution test according to USP employing USP Dissolution Apparatus No. 2 (paddle), 50 rpm and simulated intestinal fluid without enzymes as dissolution medium.

The term "C_{max}" denotes the average maximum serum//plasma/blood concentration or serum//plasma/blood level obtained after administration of the composition to at least six normal healthy human subjects.

The term "via a mucosa" indicates that the one or more glucocorticoids must enter into the systemic circulation in order to obtain the desired effect and that the administration route is different from that of topical, intravenous and intramuscular administration.

In another aspect, the invention relates to a kit for treating a subject suffering from a disorder requiring acute glucocorticoid therapy comprising one or more containers for housing a pharmaceutical composition according to the invention and instructions for use thereof. In a specific embodiment, the one or more containers are in the form of blisters or blister packs.

In a further aspect, the invention relates to a method for treating a subject suffering from a disorder requiring acute glucocorticoid therapy, the method comprises administering via a mucosa of the subject an effective amount of one or more glucocorticoids to obtain a fast rise in the glucocorticoid serum level to at least 20% of C_{max} within 20 min after administration.

In a still further aspect, the invention relates to the use of an amount of one or more glucocorticoids for the preparation of a pharmaceutical composition or kit as defined herein for the treatment of a disorder requiring acute glucocorticoid therapy by providing a fast rise in the glucocorticoid serum level to at least 20% of C_{max} within 20 min after administration via a mucosa.

As mentioned above, in order to obtain a fast onset of action it is required that a fast rise of glucocorticoid serum level is obtained after administration of a composition of the invention. Accordingly, in specific embodiments least 40% of C_{max} is reached within

30 min and/or at least 75% of C_{max} is reached within 45 min after administration of the composition via a mucosa of the subject.

Normally, T_{max} (i.e. the time it takes to obtain the maximum serum/plasma/blood concentration in the serum/plasma/blood concentration time profile) is reached within 60 min after administration of the composition via a mucosa of the subject. T_{max} is typically within a range of from about 30 to about 75 min such as in a range of from about 45 to about 60 min.

As mentioned above, the pharmaceutical compositions and kits of the present invention are suitable for use in the treatment of a disorder requiring acute glucocorticoid therapy. Examples of such disorders are acute adrenal crises relating to a primary, secondary or tertiary adrenal insufficiency, an anaphylactic reaction, an Addison crisis, a status asthmaticus, a blood transfusion reaction, a brain edema, acute kidney transplant rejection, systemic lupus erythematosus or a severe allergic reaction. Other examples include inflammatory disorders, autoimmune disorders, or medical disorders in which a glucocorticoid forms a part of the first line emergency medical treatment or intense short-time medical treatment. Specific examples of disorders that can be treated according to the present invention are given in the following.

Active substance, dosage and administration routes

In the present context, the term "glucocorticoid" or "glucocorticosteroid" is intended to denote a therapeutically, prophylactically and/or diagnostically active glucocorticoid or a glucocorticoid that has physiologic effect. The term is intended to include the glucocorticoid in any suitable form such as e.g. a pharmaceutically acceptable salt, complex, solvate, ester, active metabolites or prodrug thereof of in any physical form such as, e.g., in the form of crystals, amorphous or a polymorphous form or, if relevant, in any stereoisomer form including any enantiomeric or racemic form, or a combination of any of the above. The glucocorticoid may be a synthetic glucocorticoid.

The one or more glucocorticoids used according to the invention are selected from the group consisting of hydrocortisone, cortisone, prednisolone, prednisone, methylprednisone, triamcinolone, paramethasone, betamethasone, dexamethasone and fludrocortisone including pharmaceutically acceptable esters, salts, complexes and mixtures thereof. In a preferred embodiment of the invention, the glucocorticoid is betamethasone.

Specific examples of pharmaceutically acceptable salt suitable for use according to the invention are phosphates, succinates, lysinates, acetates, cypionates, valerates, hemisuccinates, butyrates and trometamole salts.

As the glucocorticoid is intended for immediate release, the release and/or absorption into the systemic circulation takes place already in the oral cavity in the case the composition is administered orally. In such cases, the glucocorticoid of choice for the first part may be any other than hydrocortisone (as such) or cortisone as these two active substances have a bitter taste. However, these substances may be employed provided that a sufficient taste masking is obtained. In the paragraph relating to "Pharmaceutically acceptable excipients" taste-masking is discussed in more detail. Accordingly, the one or more glucocorticoids of the first part may have an acceptable taste, may be tasteless or it may be effectively taste-masked.

Furthermore, in specific embodiments of the invention, the glucocorticoid used may be a readily water-soluble glucocorticoid (e.g. a water-soluble salt of the glucocorticoid) in order to ensure a fast dissolution of the glucocorticoid from the composition.

In a preferred embodiment of the invention the glucocorticoid is hydrocortisone trometamole (or succinate) due to its high solubility in water, which in turn leads to a rapid absorption into the systemic circulation.

Dosage

In general, the dosage of the glucocorticoids present in a composition according to the invention depends *inter alia* on the specific drug substance, the age and condition of the patient and of the disease to be treated.

The term "hydrocortisone equivalents" is used herein to define the amount in mg of a specific glucocorticoid that corresponds to 1 mg of hydrocortisone for the purpose of glucocorticoid therapy as generally understood by medical practitioners. The term is based on the fact that the individual glucocorticoids have different potency and in order to achieve a desired therapeutic effect different doses of the individual glucocorticoids are required. Equivalent doses of the glucocorticoids can be calculated based on the following table.

Glucocorticoid	Equivalent amount (mg)	Hydrocortisone equivalent (1 mg of the glucocorticoid corresponds to the listed amount in mg of hydrocortisone)
Cortisone acetate	25	0.8
Hydrocortisone	20	1
Prednisolone	5	4
Prednisone	5	4
Methylprednisolone	4	5
Triamcinolone	4	5
Paramethasone	2	10
Betamethasone	0.75	26.66
Dexamethasone	0.75	26.66
Fludrocortisone	0.05	400

In general, a pharmaceutical composition according to the invention contains a total amount of the one or more glucocorticoids expressed as hydrocortisone of from about 1 to about 200 mg. In specific embodiments, the total amount of the one or more glucocorticoids expressed as hydrocortisone is from about 1 to about 175 mg such as, e.g., from about 1 to about 150 mg, from about 1 to about 100, from about 1 to about 75 mg, from about 1 to about 70 mg, from about 1 to about 60 mg, from about 5 to about 50 mg, from about 5 to about 40 mg or from about 10 to about 30 mg.

More specifically, normal dose ranges are given below for acute glucocorticoid therapy

Hydrocortisone	1-200 mg; in acute adrenal crises about 100 mg
Cortisone	1-200 mg such as about 100 mg
Betamethasone	1-20 mg; in increased intracranial pressure e.g. brain oedema about 4 mg daily In chemotherapy or radiation induced nausea 4-8 mg
Prednisolon	1-100 mg; such as from 1 to 30 mg daily; in severe cases 50-60 mg/day

Dexamethasone	0.1-6 mg such as 0.5-2 mg or 1.5-3 mg; in severe cases up to 6 mg/day
Fludrocortisone	0.05-5 mg; in Addison disease to correct inadequate electrolyte balance 0-05-0.2 mg daily; Cortical adrenal hyperplasia ("salt losing adrenogental syndrome") 0.1-0.2 mg
Prednisone	10-100 mg such as 50 mg
Methylprednisolone	2-40 mg such as 2-20 mg

In the following are given suitable doses of the individual glucocorticoids in various treatment regimens.

Acute asthma – adults

betamethasone	4-8 mg
prednisolone	30-60mg
methylprednisolone	40 mg

Acute anaphylaxia - adults

betamethasone	5 mg up to 20 mg
hydrocortisone	200 mg
dexamethasone	4-20mg –80mg

Acute anaphylaxia - children

hydrocortisone	100-200 mg

Septic shock - adults

hydrocortisone	200-300 mg/day
methylprednisone	30 mg/kg

Acute bacterial meningitis

dexamethasone	0.3 mg/kg/dose (max 10 mg) x 4 times daily for 2-4 days
betamethasone	8 mg x 4 times daily

Acute RSV (respiratory syncytial virus) infection with bronchiolitis in children

betamethasone 4-6 mg

Acute croup-children
betamethasone 4-6 mg

Mononucleosis with complications (airway obstruction, thrombocytopenia or haemolytical anaemia)
betamethasone 5-6 mg

Tonsillitis/peritonsillitis – children with airway obstruction
betamethasone 4-6 mg

A composition according to the invention is designed to provide a fast onset of action and upon administration a fast rise in glucocorticoid serum/plasma/blood level is obtained. In the case hydrocortisone is used as the glucocorticoid a serum level of at least about 200 nmol/l is obtained within 20 min after administration. In the case that another glucocorticoid than hydrocortisone is used, a person skilled in the art will know how to determine suitable equivalent serum/plasma/blood concentrations.

For example, hydrocortisone can be rapidly released from a composition during a time period of from about 0 to abut 30 minutes after administration and 5-10 mg of hydrocortisone can be rapidly administered as an extra dose in conjunction with fever etc in patients with adrenal insufficiency. Likewise, 5-20 mg of betamethasone can be rapidly released for most indications in which a rapid glucocorticoid effect is of value.

Administration routes

As mentioned above, the one or more glucocorticoids used according to the invention are administered to the subject (preferably a human) via a mucosa into the systemic circulation. In particular, in specific embodiments of the invention, the mucosa is the mucosa in the oral cavity, the nose, the rectum or in the vagina or via pulmonary, bronchial or respiratory mucosa and ephithelia. Preferably, the mucosa is the oral mucosa.

Figures 11 and 12 show sites of oral mucosal administration suitable for use. Four well-defined sites may be used, namely

"buccal" administration that includes the term "labial" administration and is used for administration of a pharmaceutical composition to a mucosa between the gums (gingiva) and the inside of the cheeks;
"sublingual" administration that refers to administration of a pharmaceutical composition under the tongue;
"palatal" administration that refers to administration of a pharmaceutical composition to the hard and/or soft palate; and
"gingival" administration that refers to administration of a pharmaceutical composition to the upper and/or lower gingiva.

All the above-mentioned sites are suitable for use to obtain a very fast onset of action due to a rapid absorption (transport of active drug) into the systemic circulation. In specific embodiments of the invention the buccal administration route is preferred, i.e. administration of a composition to the oral mucosa between the gums and the inside of the cheeks and thus enabling the absorption to take place from two sites, namely the gingival mucosa and the buccal mucosa.

Pharmaceutical compositions

In the following is given a description of pharmaceutical compositions according to the invention.

Release of the one or more glucocorticoids

A rapid release of the one or more glucocorticoids is necessary in order to obtain a fast onset of action after administration via a mucosa where the glucocorticoid is rapidly absorbed (transported) into the systemic circulation. Accordingly a general requirement is that at least 60% of the one or more glucocorticoids contained in the composition must be released within 30 min when tested in an *in vitro* dissolution test as defined herein. Specific embodiments of the composition fulfil one or more of the requirements given in the following table. In general, it is preferred that the requirement stated within 30 min after start of the dissolution test is fulfilled. In preferred embodiments, at least 70% or at least 80% of the one or more glucocorticoids contained in the composition are released within the first 20 min of the dissolution test.

time after start of the dissolution test	% hydrocortisone equivalents released (based on the content in the

	composition)
within 30 min	at least about 60% such as, e.g., at least about 70%, preferably at least about 80% or more preferably at least about 90%
within 20 min	at least about 60%, preferably at least about 70%, at least about 80% or even more preferred at least about 90%
within 15 min	at least about 60% such as, e.g., at least about 70%, preferably at least about 80%or at least about 90%
within 10 min	at least about 60% such as, e.g., at least about 70%, preferably at least about 80% or at least about 90%
within 5 min	at least about 60%

In specific embodiments (cf. the examples herein) more than 50 % of the one or more glucocorticoids can be released within 2 min, between 50 and 90 % can be released within 5-8 min, and more than 90 % of the dose can be released within 15 min.

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A pharmaceutical composition according to the invention is designed for systemic administration via a mucosa. In a preferred embodiment the mucosa is the mucosa in the oral cavity.

The pharmaceutical composition may be in any suitable form including liquid, semi-solid or solid form.

In a preferred aspect of the invention the pharmaceutical composition is in the form of a dosage form such as a unit dosage form.

Examples of compositions according to the invention suitable for administration via the oral mucosa into the systemic circulation are typically solid or semi-solid dosage forms. The solid dosage form is typically selected from the group consisting of granules, beads, pellets and powders and - when presented in unit dosage form - it may be in the form of a tablet including a chewable tablet, a suckable tablet, an effervescent tablet, a sublingual tablet, a rapid-burst tablet, an immediate release tablet, a rapidly dissolvable tablet, melt tablets, lozenges, pastilles or it may be presented in a more candy-like form, or the like.

A pharmaceutical composition for administration via the oral mucosa into the systemic circulation may also be in the form of a spray, a wafer, a film, a gel, a hydrogel, a patch, a gingival patch, a bioadhesive patch, a sachet, a solution, an inhaler or the like.

Examples of compositions according to the invention suitable for administration via the mucosa in the nose into the systemic circulation are typically in the form of nasal sprays, nasal aerosols, nasal solutions including nasal drops and the like.

Examples of compositions according to the invention suitable for administration via the pulmonary, bronchial and respiratory mucosa and epithelia into the systemic circulation are inhalers including powder inhalers.

Examples of compositions according to the invention suitable for administration via the mucosa in the rectum or the vagina into the systemic circulation include suppositories, vagitories, clysmas etc.

A pharmaceutical composition according to the invention may also have bio/mucoadhesive properties. The absorption of drugs into the systemic circulation from a mucosal drug delivery system is significantly improved if a mucosal bioadhesive component is added in the formulation. It will prevent both swallowing and create a high local concentration of the glucocorticoid adjacent to the absorption site. The mucoadhesive component will be mixed in an appropriate way together with the glucocorticoid and other ingredients in the dosage form. The term "bio/mucoadhesive is used to denote that the composition is able to reversible adhere to a biological mucosa. In some cases a bio/mucoadhesion promoting agent is included in the composition to promote adherence to the mucosa.

In the term bio/mucoadhesion promoting agent mucoadhesion and bioadhesion are used interchangeable even if bioadhesion may have a wider definition meaning that an adhesion to any biological feature available at the mucosa takes place. If present, the bio/mucoadhesion promoting agent may be a polymeric substance, preferable a substance having an average molecular weight above 5 kD. The hydration property is crucial for the bio/mucoadhesion forces and therefore a rapid swelling of the polymer will initiate the bio/mucoadhesion process. A swelling factor by volume when brought into contact with the saliva fluid should be between 10 and 20.

A pharmaceutical composition according to the invention typically contains one or more pharmaceutically acceptable excipients. A general description of pharmaceutically acceptable excipients suitable for use in a composition according to the present invention is given in the paragraph under the heading "Pharmaceutically acceptable excipients". Depending on the specific kind of dosage form a person skilled in the art will know which kinds of excipients to choose, if necessary guided by the teaching in handbooks like Remington's Pharmaceutical Science and Handbook of Pharmaceutical Excipients. In the following is given a description of specific kinds of excipients suitable for use in the formulation of compositions in the form of film or patches especially for administration to the oral cavity.

When the pharmaceutical composition is in the form of a film, patch, wafer, gel, sachet, gingival patch or the like it may contain a pharmaceutically acceptable excipient selected from the group consisting of an acrylic polymer including a derivative thereof, a cellulose derivative, modified starch, polyethylene oxide, chitosan, gelatin, sodium alginate, pectin, scleroglucan, xanthan gum, guar gum, or poly-co-(methyl vinyl ether-maleic anhydride), alone or in combinations thereof. The cellulose derivative may be selected from the group consisting of hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, sodium carboxymethyl cellulose, methyl cellulose, ethyl hydroxyethyl cellulose, carboxymethyl cellulose, microcrystalline cellulose, modified cellulose gum, or crosscaramellose.

A pharmaceutical composition according to the invention may also contain the one or more bio/mucoadhesion promoting agents. Normally such bio/mucoadhesion promoting agents are present in concentration of from about 0.1 to about 25% w/w. Examples of bio/mucoadhesion promoting agents include polymers including synthetic polymers, natural polymers and derivatives thereof, and mixtures thereof. The polymer

may be selected from a carbomer, a polyethylene oxide, a poly co-(methylvinyl ether/maleic anhydride, and mixtures thereof; or it may be a polysaccharide. The polysaccharide may be selected from the group consisting of gelatin, sodium alginate, pectin, scleroglucan, xanthan gum; guar gum, microcrystalline cellulose, crosscaramellose, hydroxypropyl cellulose, methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, ethyl hydroxyethyl cellulose, carboxymethyl cellulose, sodium carboxymethyl cellulose, moderately cross-linked starch, and chitosan.

A pharmaceutical composition according to the invention may also containg a dissolution promoting agent. If present, a dissolution promoting agent is present in a concentration of from about 0.05 to about 5% w/w of the total weight of the composition. The dissolution promoting agent may be selected from the group consisting of sodium lauryl sulphate, a polysorbate, a bile acid, a bile salt, a salt of cholic acid or cholanic acid, isopropyl myristate, methyl laurate, oleic acid, oleyl alcohol, glycerol monoleate, glycerol dioleate, glycerol trioleate, glycerol monostearate, glycerol monolaurate, propylene glycol monolaurate, sodium dodecyl sulfate, and a sorbitan ester.

In specific embodiment the one or more glucocorticoids in a composition of the invention are present as microparticles or nanoparticles. In general, he mean particle size of such particles is 10 μm or less. Furthermore, the micro- or nanoparticles may be encapsulated such as coated with a coating comprising a lechitin or a lechitin based compound.

When the glucocorticoid is present in the form of micro- or nanoparticles, a pharmaceutical composition according to the invention may also comprise a disintegrating agent. Such agents promote the dispersion of microparticles of the glucucorticoid over the administration site in for example the labial and gingival mucosa. Examples of pharmaceutically acceptable disintegrating agents are cross-linked polyvinylpyrrolidone, carboxymethyl starch, natural starch, microcrystalline cellulose, and cellulose gum. If present, it is normally used in a concentration of from 0.5 to 10 w/w based on the total weigh of the composition Different pharmaceutical excipients, such as mannitol and lactose, have been found to be particularly suitable as excipients.

As mentioned above, the pharmaceutical composition according to the invention may further comprise a taste-masking agent. Examples of a taste-masking agent are e.g. menthol, peppermint, vanillin, a terpene based compound, or an artificial sweetener. In a specific embodiment, the one or more glucocorticoids are taste masked by incorporation into an inclusion complex by means of alpha-, beta-, or gamma-cyclodextrins, preferably by beta-cyclodextrins.

In general, the composition of the invention contains from 0.05 up to 50 weight percent such as, e.g., from 0.05 up to 40 weight percent, 0.05 up to 30 weight percent or from about 0.05 up to 20 weight percent of glucocorticoid. More preferably, the compositions contains from 0.05 to 10 weight per cent of glucocorticoid, and especially from 0.1 to 5 weight per cent. The contents can also be expressed as the amount of glucocorticoid in a dose unit of the composition, such as a tablet. In this connection a dose refers to the therapeutically amount of the at least one glucocorticoid, or its derivative, which is to be administered at one time. When the glucocorticoid is used in the form of a pharmaceutically acceptable salt, these percentages and amounts should be recalculated accordingly.

Pharmaceutically acceptable excipients

In the present context the terms "pharmaceutically acceptable excipients" are intended to denote any material, which is inert in the sense that it substantially does not have any therapeutic and/or prophylactic effect *per se*. Such an excipient may be added with the purpose of making it possible to obtain a pharmaceutical, which have acceptable technical properties.

Examples of suitable excipients for use in a solid dosage form according to the invention include fillers, diluents, disintegrants, binders, lubricants etc. or mixture thereof. As the individual parts of a composition or kit according to the invention are used for different purposes (e.g. immediate and extended release), the choice of excipients is normally made taken such different uses into considerations. A person skilled in the art will know which kinds of pharmaceutically acceptable excipients that are suitable choices depending on the specific dosage form in question. Other pharmaceutically acceptable excipients for suitable use are e.g. acidifying agents, alkalising agents, preservatives, antioxidants, buffering agents, chelating agents, colouring agents, complexing agents, emulsifying and/or solubilizing agents, flavours and perfumes, humectants, sweetening agents, wetting agents etc.

Examples of suitable fillers, diluents and/or binders include lactose (e.g. spray-dried lactose, α-lactose, β-lactose, Tabletose®, various grades of Pharmatose®, Microtose® or Fast-Floc®), microcrystalline cellulose (various grades of Avicel®, Elcema®, Vivacel®, Ming Tai® or Solka-Floc®), hydroxypropylcellulose, L-hydroxypropylcellulose (low substituted), hydroxypropyl methylcellulose (HPMC) (e.g. Methocel E, F and K, Metolose SH of Shin-Etsu, Ltd, such as, e.g. the 4,000 cps grades of Methocel E and Metolose 60 SH, the 4,000 cps grades of Methocel F and Metolose 65 SH, the 4,000, 15,000 and 100,000 cps grades of Methocel K; and the 4,000, 15,000, 39,000 and 100,000 grades of Metolose 90 SH), methylcellulose polymers (such as, e.g., Methocel A, Methocel A4C, Methocel A15C, Methocel A4M), hydroxyethylcellulose, sodium carboxymethylcellulose, carboxymethylene, carboxymethylhydroxyethylcellulose and other cellulose derivatives, sucrose, agarose, sorbitol, mannitol, dextrins, maltodextrins, starches or modified starches (including potato starch, maize starch and rice starch), calcium phosphate (e.g. basic calcium phosphate, calcium hydrogen phosphate, dicalcium phosphate hydrate), calcium sulfate, calcium carbonate, sodium alginate, collagen etc.

Specific examples of diluents are e.g. calcium carbonate, dibasic calcium phosphate, tribasic calcium phosphate, calcium sulfate, microcrystalline cellulose, powdered cellulose, dextrans, dextrin, dextrose, fructose, kaolin, lactose, mannitol, sorbitol, starch, pregelatinized starch, sucrose, sugar etc.

Specific examples of disintegrants are e.g. alginic acid or alginates, microcrystalline cellulose, hydroxypropyl cellulose and other cellulose derivatives, croscarmellose sodium, crospovidone, polacrillin potassium, sodium starch glycolate, starch, pregelatinized starch, carboxymethyl starch (e.g. Primogel® and Explotab®) etc.

Specific examples of binders are e.g. acacia, alginic acid, agar, calcium carrageenan, sodium carboxymethylcellulose, microcrystalline cellulose, dextrin, ethylcellulose, gelatin, liquid glucose, guar gum, hydroxypropyl methylcellulose, methylcellulose, pectin, PEG, povidone, pregelatinized starch etc.

Glidants and lubricants may also be included in the composition. Examples include stearic acid, magnesium stearate, calcium stearate or other metallic stearate, talc, waxes and glycerides, light mineral oil, PEG, glyceryl behenate, colloidal silica,

hydrogenated vegetable oils, corn starch, sodium stearyl fumarate, polyethylene glycols, alkyl sulfates, sodium benzoate, sodium acetate etc.

Other excipients which may be included in a composition of the invention are e.g. flavoring agents, coloring agents, taste-masking agents, pH-adjusting agents, buffering agents, preservatives, stabilizing agents, anti-oxidants, wetting agents, humidity-adjusting agents, surface-active agents, suspending agents, absorption enhancing agents, agents for modified release etc.

The composition or kit components according to the invention may also be coated with a film coating, a protective coating, an anti-adhesive coating etc.

A composition according to the invention may also be coated in order to obtain suitable properties e.g. with respect to taste-masking of the one or more glucocorticoids. The coating may also be applied as a readily soluble film. The coating may be applied on single unit dosage forms (e.g. tablets) or it may be applied on a multiple-unit dosage form or on its individual units.

Suitable coating materials are e.g. methylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, acrylic polymers, ethylcellulose, cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl methylcellulose phthalate, polyvinylalcohol, sodium carboxymethylcellulose, cellulose acetate, cellulose acetate phthalate, gelatin, methacrylic acid copolymer, polyethylene glycol, shellac, sucrose, titanium dioxide, carnauba wax, microcrystalline wax, glyceryl monostearate, zein.

Plasticizers and other ingredients may be added in the coating material. The same or different active substance may also be added in the coating material.

Taste masking

In general, it is difficult in most cases to prepare a formulation for oral mucosa or nasal administration with satisfactory safety and stability from a drug having irritating properties or capable of forming molecular aggregates, although it depends on the kind of the drug used. In the case of hydrocortisone, the base has a distinctively bitter taste and a formulation has to be taste masked in order to be applicable for repeated use.

The taste masking agent can be a menthol, a peppermint, a vanillin, or a terpene based compound. In addition, the taste masking agent can be an artificial sweetener, e.g. sorbitol, xylitol or aspartame. Taste masking can also be achieved by microencapsulation of the glucocorticoid as particles. This is for example accomplished with lecithin based compounds. The taste masking agent is carefully mixed with the active drug in order to be present both at the surface and within the administration formulation. Taste masking can also be achieved by formation of inclusion complexes with cyclodextrins.

Typical examples of the cyclodextrin compound are alpha.-cyclodextrin, .beta.-cyclodextrin, .gamma.-cyclodextrin, hydroxypropyl .beta.-cyclodextrin, dimethyl .beta.-cyclodextrin, maltosyl .beta.-cyclodextrin and .beta.-cyclodextrin sulfate. Particularly preferred are .alpha.-cyclodextrin, .beta.-cyclodextrin and .gamma.-cyclodextrin. These cyclodextrin compounds may be used alone or in combination.

The amount of cyclodextrin compound to be used may vary with its solubility and the concentration of hydrocortisone. It is, however, desirable that the amount of cyclodextrin compound is 0.5 to 4.0 moles, preferably 2.0 to 4.0 moles, as much as the mole of hydrocortisone.

Method aspect

A pharmaceutical composition or a kit according to the invention is suitable for use in the treatment of a subject such as a mammal including a human suffering from a disorder requiring acute glucocorticoid therapy.

Accordingly, in a separate aspect the invention relates to a method for treating a subject suffering from a disorder requiring acute glucocorticoid therapy, the method comprises administering via a mucosa of the subject an effective amount of one or more glucocorticoids to obtain a fast rise in the glucocorticoid serum level to at least 20% of C_{max} within 20 min after administration.

Normally, it is preferred that at least 40% of C_{max} is reached within 30 min after administration in order to obtain a fast onset of action. In specific preferred embodimentd, at least 75% of C_{max} is reached within 45 min after administration and/or T_{max} is reached within 60 min after administration of the composition via a mucosa of the subject.

Details concerning other aspects of the invention are described hereinbefore and apply also to the method aspect of the invention.

The method according to the invention can be carried out by the patient itself or by non-medically trained persons due to the fact that the one or more glucocorticoids are not presented in the form of a composition for injection or infusion. Normally, medically trained personnel can only administer such compositions. Accordingly, the present invention provides a method that compared to the known treatment methods requiring acute glucocorticoids is much more simple to handle without the necessity of specialized equipment. It is therefore contemplated that the present invention provides a method that enables a treatment when the condition of the patient requires it, i.e. there is no need for bringing the patient to a hospital or a medical clinic in order to be able to give the necessary treatment.

Moreover, due to the development of compositions that enable a fast onset of action after administration and that can be administered without the need of the patient to swallow the composition (e.g. compositions of the invention in the form of films, bio/mucoadhesive compositions, patches, gingival patches, sprays etc.), the patient may be unconscious or otherwise unable to swallow normal tablets and still be correctly treated with glucocorticoids in acute situations.

Use of a composition or a kit according to the invention

In another separate aspect, the invention relates to the use one or more glucocorticoids for the preparation of a pharmaceutical composition or kit as defined hereinbefore for the treatment of a disorder requiring acute glucocorticoid therapy and to provide a serum level as defined herein.

In the above is given a detailed description of the invention relating one or more aspects of the invention, in particular relating to pharmaceutical compositions. However, all details and particulars disclosed under this aspect of the invention apply *mutatis mutandis* to the other aspects of the invention.

Legends to figures

Figure 1 shows results from Example 11. The plasma concentration-time profile of cortisol following a single dose administration of composition A to a human subject.

Figure 2 shows results from Example 11. The plasma concentration-time profile of cortisol following a single dose administration of composition B to a human subject.

Figure 3 shows results from Example 11. The plasma concentration-time profile of cortisol following a single dose administration of composition C to a human subject.

Figure 4 shows results from Example 12. The plasma concentration-time profile of cortisol following a single dose administration of film A to a human subject. Non-mucoadhesive thin-layer film, 6 cm^2, 10 mg hydrocortisone, buccal administration. Subject has the endogenous glucocorticoid secretion suppressed by synthetic glucocorticoids.

Figure 5 shows results from Example 12. The plasma concentration-time profile of cortisol following a single dose administration of film B to a human subject. Non-mucoadhesive thin-layer film, 6 cm^2, 11.2 mg hydrocortisone acetate, buccal administration. Subject has the endogenous glucocorticoid secretion suppressed by synthetic glucocorticoids.

Figure 6 shows results from Example 13. The plasma concentration-time profile of cortisol following a single dose administration of composition A to a human subject. In vivo plasma profile. Muocadhesive thin-layer film, 10 mg hydrocortisone, buccal administration. Subject has the endogenous glucocorticoid secretion suppressed by synthetic glucocorticoids

Figure 7 shows results from Example 13. The plasma concentration-time profile of cortisol following a single dose administration of composition A to a human subject. Mucoadhesive thin-layer film, 10 mg hydrocortisone, buccal administration. Subject has the endogenous glucocorticoid secretion suppressed by synthetic glucocorticoids

Figure 8 shows results from Example 14. The plasma concentration-time profile of cortisol following a single dose administration of composition C. In vivo plasma profile. Mucoadhesive rapid-release tablet, 10 mg hydrocortisone, buccal administration.

Subject has the endogenous glucocorticoid secretion suppressed by synthetic glucocorticoids

Figure 9 shows results from Example 15 (Composition C from Example 14).

Figure 10 shows results from Example 15 (Composition A from Example 13).

Figures 11 and 12 illustrates different administration sites within the oral cavity

The invention is further illustrated in the following non-limiting examples.

Materials

The materials used in the following examples were

Trade name	*Chemical substance*	*Manufacturer*
Betamethasone	USP/NF	
Carboxymetylcellulose	USP/NF	
Chitosan glutamate	USP/NF	
Crospovidone	USP/NF	
Hydrocortisone	Ph. Eur., Qual. D	Aventis, Switzerland (by Apoteksbolaget)
Hydrocortisone acetate	USP/NF	
Hydrocortisone 21-hemisuccinate sodium	Ph. Eur	Aventis, Switzerland (by Apoteksbolaget)
2-OH-propyl-β-cyclodextrin		
Hydroxypropylmethylcellulose	USP/NF	
Levomenthol	USP/NF	
Menthol	USP/NF	
Methocel E5	Hydroxypropyl-methyl cellulose	Dow Chemicals, USA (by Colorcon)
Methocel® KV 100 LV	USP/NF	Dow Chemicals, USA (by Colorcon)
Metolose®		
Microcrystalline cellulose, Avicel® PH-102	USP/NF	FMC Corporation

Paraffin powder	USP/NF	
PEG 300	USP/NF	
PEG 6000	Polyethylene glycol	Svenska Hoechst AB
PEG 400	Polyethylene glycol	Fluka, Switzerland
Prednisolone	USP/NF	
Polyox WSR 301	Polyethylene oxide	Dow Chemicals, USA
Na-alginate PH157		
Sodium dihydrogen phosphate	$NaH_2PO_4 \cdot 2\ H_2O$	
Sodium stearyl fumarate	USP/NF	
Sorbitol	USP/NF	
Sugar	USP/NF	
Sugar/starch seeds	USP/NF	
Talc	USP/NF	
Triethyl citrate	USP/NF	
Xylitab 300 Xylisorb 300		Xyrofin Kotka, Finland (Danisco Sweeteners Ltd, UK
Xylitol	USP/NF	Roquette, France

Methods

The in vivo experiments reported herein were carried out on healthy volunteers. At 6 pm and 11 pm the day before administration of the test composition, the endogenous cortisol secretion was suppressed by oral administration of 2 mg of betamethasone. The test composition was administered to healthy volunteers. The volunteers were in fasted state and were not allowed to take any food until noon. In the case a tablet is administered, it is ingested together with 200 ml of water. The test composition is administered between 8 am and 10 am on the day following the suppression of endogenous glucocorticoid secretion.

Examples

Example 1

Capsules containing an immediate release pellets (IR pellets)

IR pellets

Sugar/starch seeds, diameter 0.25-0.35 mm	1 kg

are coated in a fluidised bed equipped with a Wurster column with a water suspension containing

Hydrocortisone 21-hemisuccinate sodium	10 %
Hydroxypropyl methylcellulose, 6 cps	3 %
Talc	10 %

to a weight gain of approximately 75 %.

An amount of IR pellets containing 13.4 mg of hydrocortisone 21-hemisuccinate sodium (approximately 70 mg) are filled into hard gelatine capsules size No 3 in a capsule-filling machine.

70 mg pellets will easily fit into a capsule size No. 3 (or even size No. 4) and can be filled in a normal capsule filling machine.

Example 2

Immediate release (IR) tablet

IR tablets for oral or sublingual use:

	Mg per tablet
Betamethasone	0.4
Xylitab®300[a]	40
Lactose anhydrous USP/NF	5
Microcrystalline cellulose USP/NF	10
Crospovidone USP/NF	4
Sodium stearyl fumarate	1
Water	qs

[a] Direct compression xylitol from Danisco Sweeteners Ltd UK

Dry mix lactose and microcrystalline cellulose. Dissolve betamethasone in a small amount of water and disperse the solution over the powder blend. Mix and dry. Add Xylitab and crospovidone and dry mix until the blend is homogeneous.

Add sodium stearyl fumarate and continue blending for another 2 minutes.
Compress the blend to tablets in a tablet press using 6 mm round concave punches.

Example 3

Immediate release (IR) film

Thin films for administration to the oral cavity:

	% by weight
Prednisolone	0.75
PEG 400 USP/NF	2
Methocel E5, Dow Chemical	4
Xylitol, Roquette France	1
Water	up to 100

Methocel was added to approximately 90% of the total amount of distilled water and stirred with a magnetic stirrer until Methocel was completely dissolved. PEG 400 was added under continued stirring, followed by xylitol and prednisolone. Water was added to final weight and stirring was continued during four hours.

330 µl of the solution was pipetted into 16 mm diameter flat-bottomed PVC blisters. The solutions were allowed to dry at room temperature over night and the blister packs were sealed with heat-seal lacquered aluminium foil.

Example 4

Immediate release (IR) oral solution

Oral solution:

Prednisolone acetate	0.9 mg
Sorbitol	60 mg
Menthol	1.2 mg
Sterile water	5 ml

Make a solution and fill into a moisture tight aluminium foliated sachet.

Example 5

Immediate release (IR) sublingual spray

Sublingual spray of hydrocortisone:

	mg/ml
Hydrocortisone acetate	10
Carboxymetylcellulose	0.8 (0.08%)
2-OH-propyl-β-cyclodextrin	40
PEG 300	5
Menthol	0.3
Sorbitol	12
Levomenthol	2.0
$NaH_2PO_4 \cdot 2\ H_2O$	2
Water	qs

Dissolve hydrocortisone acetate in a small amount of water. Mix with 2-OH-propyl-β-cyclodextrin, let stand for 1 hour. Add carboxymetylcellulose and mix. Add PEG 300, menthol, sorbitol, levomenthol and $NaH_2PO_4 \cdot 2\ H_2O$. Add water up to final volume. Dispense into a spray package that delivers 0.58 ml per dose (5 mg of hydrocortisone).

Example 6

Betamethasone IR tablet for peroral or buccal administration

	Mg per tablet
Betamethasone	0.4
Xylitab®300[a)]	45
Microcrystalline cellulose NF	10
Crospovidone NF	4
Water	qs
Sodium stearyl fumarate NF	1

[a)] Direct compression xylitol from Danisco Sweeteners Ltd, UK

Dissolve betamethasone in a small amount of water.
Disperse the solution over the microcrystalline cellulose. Mix and dry.

Add Xylitab and crospovidone and dry mix in a suitable mixer until a homogeneous blend is achieved.
Then add sodium stearyl fumarate and continue mixing another two minutes.
Compress the powder blend in a suitable tablet press using 6 mm round concave punches.

Example 7
Sublingual spray of betamethasone

	mg/ml
Betamethasone	0.4
Carboxymetylcellulose	0.8 (0.08%)
PEG 300	5
Menthol	0.3
Sorbitol	12
Levomenthol	2.0
NaH_2PO_4*2 H_2O	2
Water	qs

Dissolve betamethasone in a small amount of water. Add carboxymetylcellulose and mix. Add PEG 300, menthol, sorbitol, levomenthol and NaH_2PO_4*2 H_2O. Add water up to final volume.

Example 8
Sublingual spray of betamethasone

	mg/ml
Betamethasone	0.4
Chitosan glutamate	10
Menthol	0.1
Levomenthol	1.5
NaH_2PO_4*2 H_2O	2
Water	qs

Dissolve betamethasone in a small amount of water. Add chitosan glutamate and mix. Filter through 0.2µm membrane filter. Add menthol, levomenthol and NaH_2PO_4*2 H_2O. Add water up to final volume.

Example 9

Sublingual spray of hydrocortisone

	mg/ml
Hydrocortisone acetate	10
Carboxymetylcellulose	0.8 (0,08%)
2-OH-propyl-β- cyclodextrin	40
PEG 300	5
Menthol	0.3
Sorbitol	12
Levomenthol	2.0
NaH_2PO_4*2 H_2O	2
Water	qs

Dissolve hydrocortisone in a small amount of water. Mix with 2-OH-propyl-β-cyclodextrin, let stand for 1 hour. Add carboxymetylcellulose and mix. Add PEG 300, menthol, sorbitol, levomenthol and NaH_2PO_4*2 H_2O. Add water up to final volume.

Example 10

Sublingual spray of hydrocortisone

	mg/ml
Hydrocortisone acetate	10
Chitosan glutamate	10
2-OH-propyl-β- cyclodextrin	40
Menthol	0.1
Levomenthol	1.5
NaH_2PO_4*2 H_2O	2
Water	qs

Dissolve hydrocortisone in a small amount of water. Mix with 2-OH-propyl-β-cyclodextrin, let stand for 1 hour. Add chitosan glutamate and mix. Filter through 0.2

µm membrane filter. Add menthol, levomenthol and NaH_2PO_4*2 H_2O. Add water up to final volume.

Example 11

Thin-layer film of hydrocortisone

Composition A:

	% w/w
Hydrocortisone	3%
Na-alginate PH157	2%
Water	95%

Composition B:

Hydrocortisone acetate	3.4%
Na-alginate PH157	2%
Water	94.6%

Composition C:

Hydrocortisone	3%
Metolose 60SH-50	2%
Water	95%

The films were made as described in the following:

1. Amount polymer, glucocorticoid and H_2O were weighed.
2. The glucocorticoid was added to the water during stirring.
3. The formulation was kept on stirring until a suspension was obtained.
4. The polymer was added to the suspension.
5. The formulation was kept on stirring until a uniform gel was obtained (minimum 2h).
6. 0.5g gel was weighed in empty blisters and placed in a heating cupboard (Drying: 25°C for 22h).

Table. In vitro dissolution (rotating basket 100 rpm, phosphate buffer pH=7.0, one unit per 500 ml medium) after 1, 3 ,5, 10 and 15 min as a percentage of 10 mg

hydrocortisone. Units with 10 mg hydrocortisone in polymers of sodium alginate (Na-alg), hypromellose (HPMC) and approx. 7 mg/unit. Two units were tested with Na-alg and HPMC. The mean value is tabulated. The results in the following table reflect the rank order regarding viscosity, i.e. HPMC has the lowest viscosity and Na-alg the highest.

Composition	Polymer	1 min,%	3 min,%	5 min,%	10 min,%	15 min,%
A	Na-alg	15	25	38	65	84
B	Na-alg	15	25	38	65	84
C	HPMC	18	48	67	88	92

In vivo plasma profiles in humans, N=1 per composition
Dexamethasone suppression test, fasting state, otherwise as described in the paragraph denoted "Method".

The results show that the use of hydrocortisone acetate does not seem to be suitable for an immediate release composition. This was further investigated in the following example.

Example 12
Non-mucoadhesive immediate release films

Two films were prepared essentially similar to Example 13 – composition A. Film A contains 10 mg of hydrocortisone and film B contains 11.2 mg of hydrocortisone acetate. The results from in vivo testing after buccal administration are shown in Figures 4 and 5. The results show that even if the films are not bioadhesive, a fast onset of the absorption into the systemic circulation after single dose administration of Film A is obtained. In contrast, the results obtained with the film containing hydrocortisone acetate indicate that this compound does not seem to be suitable when a fast onset of the absorption into the systemic circulation of the glucocorticoid is required.

Example 13
Thin-layer films for immediate release

Batches of glucocorticoid films were prepared from the following compositions A and B:

Rapid-release composition A:

Component	*% w/w*
PEG 400	2.0
Hydrocortisone	3.0
Methocel E5	4.0
Xylitol	1.0
Water	90

Slower release composition B:

Component	*w/w %*
PEG 400	1.3
Hydrocortisone	3.0
Methocel E5	5.7
Water	90

To distilled water (18 ml) in 50 ml round-bottomed glass flask provided with a magnetic stirred was added Methocel E5. After the Methocel had dissolved completely PEG 400 was added under continued stirring, followed by xylitol (Composition A only) and hydrocortisone. Stirring was continued for 4 h.

Into flat-bottomed PVC-blisters (Inpack AB, Lund, Sweden) 16 mm in diameter was pipetted (Finnpipette; automatic) 330 µl of solution A or B into each blister trough. The solutions were allowed to dry at room temperature over night. The next day 10 films were removed for dose analysis. Each film was dissolved in 100 ml of water/ethanol (95%) 9:1 (w/w). The solutions were analysed by UV spectroscopy at 242 nm. Mean contents of 10.19 mg and 9.83 mg hydrocortisone per blister (SD 0.29 and 0.14, respectively) were found for Compositions A and B, respectively.

The hydrocortisone compositions were tested in two human subjects after labial administration. The subjects had their endogenous glucocorticoid secretion suppressed by synthetic glucocorticoids. The plasma concentration of cortisol was monitored during 360 min after the labial administration, and the serum concentration time profiles from these two subjects are shown in Figures 6 and 7.

It is clearly seen that the rate and extent of mucosal uptake of hydrocortisone is high and the appearance of cortisol in serum is rapid, as the first measured plasma concentration was attained already at 10-15 min.

These serum pharmacokinetic data illustrate that a formulation of the invention for oral mucosa administration results in a high rate and extent of mucosal absorption of the active drug, even though a small volume of fluid is available for dissolution at the site of administration and absorption in this route drug delivery.

Example 14

Glucocorticoid tablets for immediate release

Glucocorticoid tablets were manufactured by direct compression of the dry-mixed powderous components to the following composition C:

Rapid-release composition C:

Component	*Per Batch*
PEG 6000	8.7 g
Hydrocortisone	2.5 g
Xylitab 300	8.7 g
Mg stearate	0.16 g

Batch size 100 tablets

The powderous components were sieved (mesh size 0.7 mm) and dry-mixed by shaking by hand in a small tin can for five min. The homogeneity of the mixture was analyzed by the same method as used for analysis of the tablets. Tabletting was carried out with a DIAF tabletting machine using a flat circular punch 7 mm in diameter (with a dividing score). The hydrocortisone dose in 10 tablets was assessed by the same method as used for the films. Mean contents of 9.53 mg hydrocortisone per tablet (SD 0.15) were found for composition C.

Tablet thickness (10 tablets): 1.72-1.76 mm (C);
Friability (20 tablets): 0.6% (C);
Tablet hardness (10 tablets): 23.7 N (C).

The compositions were tested after oral administration to two human subjects (see Figure 8).

The rate of absorption of the glucocorticoid into the systemic circulation from the solid dosage forms of Example 14 was somewhat slower than that of compositions from Example 13, which means that it is possible to adjust the absorption rate of hydrocortisone into the systemic circulation by introducing changes in the composition and function of the labial pharmaceutical formulation.

Example 15

In vitro dissolution profile

The *in vitro* dissolution profiles of hydrocortisone from drug formulations according to Example 20 and 21 were followed over time in a standardized controlled *in vitro* environment. A United States Pharmacopoeia dissolution apparatus II (paddle) coupled to automatic sampling devices and software was used for acquiring release profiles of the drug formulations in a neutral pH environment. The dissolution profile was acquired at 37 °C, 50 rpm of the paddles, in a total of 300 ml of water. Sampling was performed at 0, 1, 3, 5, 7, 10 and 15 minutes following the insertion of the pharmaceutical composition in the example in the dissolution medium.

The dissolution profile from each formulation was monitored in two experiments up to 360 min after administration, and the corresponding dissolution time profiles are shown in Figs. 9 and 10, respectively. The release rate is given as the per cent of dose over time.

The release rate from the solid dosage forms of Example 21 was somewhat slower (Fig. 10). This means that it is possible to adjust the release rate of hydrocortisone by introducing changes in the composition and function of the oronasopharyngeal pharmaceutical preparation.

Claims

1. A pharmaceutical composition comprising one or more glucocorticoids for substantially immediate release, wherein at least about 60% of the one or more glucocorticoids are released from the composition within the first 30 min after start of an in vitro dissolution test according to USP employing USP Dissolution Apparatus No. 2 (paddle), 50 rpm and a suitable dissolution medium, and wherein a glucocorticoid serum level of a subject of at least 20% of C_{max} is reached within 20 min after administration of the composition via a mucosa of the subject.

2. A pharmaceutical composition according to claim 1, wherein at least 40% of C_{max} is reached within 30 min after administration of the composition via a mucosa of the subject.

3. A pharmaceutical composition according to claim 1 or 2, wherein at least 75% of C_{max} is reached within 45 min after administration of the composition via a mucosa of the subject.

4. A pharmaceutical composition according to any of the preceding claims, wherein T_{max} is reached within 60 min after administration of the composition via a mucosa of the subject.

5. A pharmaceutical composition according to any of the preceding claims, wherein at least about 60% of the one or more glucocorticoids are released from the composition within the first 20 min or 15 min of the dissolution test defined in claim 1.

6. A pharmaceutical composition according to any of the preceding claims, wherein at least about 60% of the one or more glucocorticoids are released from the composition within the first 10 min or 5 min of the dissolution test defined in claim 1.

7. A pharmaceutical composition according to any of the preceding claims, wherein at least about 70% of the one or more glucocorticoids are released from the composition within the first 15 min such as, e.g., within the first 10 min or 5 min of the dissolution test defined in claim 1.

8. A pharmaceutical composition according to any of the preceding claims, wherein at least about 80% of the one or more glucocorticoids are released from the composition within the first 15 min of the dissolution test defined in claim 1.

9. A pharmaceutical composition according to any of the preceding claims, wherein at least about 80% of the one or more glucocorticoids are released from the composition within the first 10 min of the dissolution test defined in claim 1.

10. A pharmaceutical composition according to any of the preceding claims, wherein at least about 90% of the one or more glucocorticoids are released from the composition within the first 15 min or within the first 10 min of the dissolution test defined in claim 1.

11. A pharmaceutical composition according to any of the preceding claims for administration to the systemic circulation via a mucosa.

12. A pharmaceutical composition according to claim 11, wherein the mucosa is selected from the mucosa in the oral cavity, the nasal cavity, the lung, the bronchia, the rectum, and the vagina.

13. A pharmaceutical composition according to claim 12, wherein the mucosa is the mucosa in the oral cavity.

14. A pharmaceutical composition according to any of the preceding claims designed for administration to the oral cavity.

15. A pharmaceutical composition according to any of the preceding claims in liquid, semi-solid or solid form.

16. A pharmaceutical composition according to any of the preceding claims in the form of a solid dosage form.

17. A pharmaceutical composition according to claim 35, wherein the solid dosage form is selected from the group consisting of granules, beads, pellets and powders.

18. A pharmaceutical composition according to any of the preceding claims in unit dosage form.

19. A pharmaceutical composition according to claim 18, wherein the unit dosage form is in the form of a tablet including a chewable tablet, a suckable tablet, an effervescent tablet, a sublingual tablet, a rapid-burst tablet, an immediate release tablet, a rapidly dissolvable tablet or the like.

20. A pharmaceutical composition according to any of claims 142-15 in the form of a spray, a wafer, a film, a gel, a hydrogel, a patch, a gingival patch, a bioadhesive patch, a sachet, a pulmonary, bronchial or respiratory inhaler including a powder inhaler, a suppository, a vagitory, a clysma, a solution or the like.

21. A pharmaceutical composition according to any of the preceding claims, wherein the total amount of the one or more glucocorticoids expressed as hydrocortisone is from about 1 to about 200 mg.

22. A pharmaceutical composition according to claim 21, wherein the total amount of the one or more glucocorticoids expressed as hydrocortisone is from about 1 to about 175 mg such as, e.g., from about 1 to about 150 mg, from about 1 to about 100, from about 1 to about 75 mg, from about 1 to about 70 mg, from about 1 to about 60 mg, from about 5 to about 50 mg, from about 5 to about 40 mg or from about 10 to about 30 mg.

23. A pharmaceutical composition according to any of the preceding claims, wherein the one or more glucocorticoids is selected from the group consisting of hydrocortisone, cortisone, prednisolone, prednisone, methylprednisone, triamcinolone, paramethasone, betamethasone, dexamethasone and fludrocortisone or mixtures thereof, including pharmaceutically acceptable esters, salts and complexes thereof.

24. A pharmaceutical composition according to claim 23, wherein the pharmaceutically acceptable salt is a phosphate, a succinate, a lysinate, an acetate, a cypionate, a valerate, a hemisuccinate, a butyrate or a trometamole salt.

25. A pharmaceutical composition according to claim 23 in unit dosage form, wherein the one or more glucocorticoids are cortisone or hydrocortisone including pharmaceutically acceptable esters, salts and complexes thereof in an amount corresponding to from about 1-200.

26. A pharmaceutical composition according to claim 23 in unit dosage form, wherein the one or more glucocorticoids are betamethasone including pharmaceutically acceptable esters, salts and complexes thereof in an amount corresponding to from about 1 to about 20 mg.

27. A pharmaceutical composition according to claim 23 in unit dosage form, wherein the one or more glucocorticoids are prednisolone including pharmaceutically acceptable esters, salts and complexes thereof in an amount corresponding to from about 1 to about 10 mg.

28. A pharmaceutical composition according to claim 23 in unit dosage form, wherein the one or more glucocorticoids are dexamethsone including pharmaceutically acceptable esters, salts and complexes thereof in an amount corresponding to from about 0.1 to about 2 mg.

29. A pharmaceutical composition according to claim 23 in unit dosage form, wherein the one or more glucocorticoids are fludrocortisone including pharmaceutically acceptable esters, salts and complexes thereof in an amount corresponding to from about 0.05 to about 5 mg.

30. A pharmaceutical composition according to claim 23 in unit dosage form, wherein the one or more glucocorticoids are prednisone including pharmaceutically acceptable esters, salts and complexes thereof in an amount corresponding to from about 10 to about 50 mg.

31. A pharmaceutical composition according to claim 23 in unit dosage form, wherein the one or more glucocorticoids are methylprednisolone including pharmaceutically acceptable esters, salts and complexes thereof in an amount corresponding to from about 2 to about 20 mg.

32. A pharmaceutical composition according to any of the preceding claims in the form of a film, patch, wafer, gel, sachet, gingival patch, lozenge or the like.

33. A pharmaceutical composition according to claim 32, wherein the composition comprises a pharmaceutically acceptable excipient selected from the group consisting

of an acrylic polymer including a derivative thereof, a cellulose derivative, modified starch, polyethylene oxide, chitosan, gelatin, sodium alginate, pectin, scleroglucan, xanthan gum, guar gum, or poly-co-(methyl vinyl ether-maleic anhydride), alone or in combinations thereof.

34. A pharmaceutical composition according to claim 33, wherein the cellulose derivative is selected from the group consisting of hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, sodium carboxymethyl cellulose, methyl cellulose, ethyl hydroxyethyl cellulose, carboxymethyl cellulose, microcrystalline cellulose, modified cellulose gum, or crosscaramellose.

35. A pharmaceutical composition according to any of the preceding claims further comprising one or more bio/mucoadhesion promoting agents.

36. A pharmaceutical composition according to claim 35, wherein the one or more bio/mucoadhesion promoting agents are present in concentration of from about 0.1 to about 25% w/w.

37. A pharmaceutical composition according to claim 35 or 36, wherein the one or more bio/mucoadhesion promoting agents are a polymer including a synthetic polymer, a natural polymer and a derivative thereof, and mixtures thereof.

38. A pharmaceutical composition according to claim 37, wherein the polymer is selected from a carbomer, a polyethylene oxide, a poly co-(methylvinyl ether/maleic anhydride, and mixtures thereof.

39. A pharmaceutical composition according to claim 37, wherein the polymer is a polysaccharide.

40. A pharmaceutical composition according to claim 40, wherein the polysaccharide is selected from the group consisting of gelatin, sodium alginate, pectin, scleroglucan, xanthan gum; guar gum, microcrystalline cellulose, crosscaramellose, hydroxypropyl cellulose, methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, ethyl hydroxyethyl cellulose, carboxymethyl cellulose, sodium carboxymethyl cellulose, moderately cross-linked starch, and chitosan.

41. A pharmaceutical composition according to any of the preceding claims further comprising a dissolution promoting agent.

42. A pharmaceutical composition according to claim 41, wherein the dissolution promoting agent is present in a concentration of from about 0.05 to about 5% w/w.

43. A pharmaceutical composition according to claim 41 or 42, wherein the dissolution promoting agent is selected from the group consisting of sodium lauryl sulphate, a polysorbate, a bile acid, a bile salt, a salt of cholic acid or cholanic acid, isopropyl myristate, methyl laurate, oleic acid, oleyl alcohol, glycerol monoleate, glycerol dioleate, glycerol trioleate, glycerol monostearate, glycerol monolaurate, propylene glycol monolaurate, sodium dodecyl sulfate, and a sorbitan ester.

44. A pharmaceutical composition according to any of the preceding claims, wherein the one or more glucocorticoids are present as microparticles or nanoparticles.

45. A pharmaceutical composition according to claim 44, wherein the mean particle size is 10 μm or less.

46. A pharmaceutical composition according to claim 44 or 45, wherein the micro- or nanoparticles are encapsulated.

47. A pharmaceutical composition according to claim 46, wherein the micro- or nanoparticles are encapsulated with a coating comprising a lechitin or a lechitin based compound.

48. A pharmaceutical composition according to any of the preceding claims further comprising a disintegrating agent.

49. A pharmaceutical composition according to claim 48, wherein the disintegrating agent is selected from the group consisting of cross-linked polyvinylpyrrolidone, carboxymethyl starch, natural starch, microcrystalline cellulose, and cellulose gum.

50. A pharmaceutical composition according to claim 48 or 49, wherein the disintegrating agent is present in a concentration of from about 0.5 to about 10% w/w.

51. A pharmaceutical composition according to any of the preceding claims further comprising a taste-masking agent.

52. A pharmaceutical composition according to claim 51, wherein the taste-masking agent is selected from the group consisting of menthol, peppermint, vanillin, a terpene based compound, or an artificial sweetener.

53. A pharmaceutical composition according to any of the preceding claims, wherein the one or more glucocorticoids are taste masked by incorporation into an inclusion complex by means of alpha-, beta-, or gamma-cyclodextrins, preferably by beta-cyclodextrins.

54. A pharmaceutical composition according to any of the preceding claims for buccal administration.

55. A pharmaceutical composition according to claim 54 in the form of a gel, a gum, a wafer, a thin-layer film, a patch, a gingival patch, a tablet, a sachet, a lozenge, a fast-dissolving tablet, a cream or an ointment.

56. A kit for treating a subject suffering from a disorder requiring acute glucocorticoid therapy comprising one or more containers for housing a pharmaceutical composition according to any of claims 1-55, and instructions for use thereof.

57. A kit according to claim 56, wherein the one or more containers are in the form of blisters or blister packs.

58. A method for treating a subject suffering from a disorder requiring acute glucocorticoid therapy, the method comprises administering via a mucosa of the subject an effective amount of one or more glucocorticoids to obtain a fast rise in the glucocorticoid serum level to at least 20% of C_{max} within 20 min after administration.

59. A method according to claim 58, wherein at least 40% of C_{max} is reached within 30 min after administration.

60. A method according to claim 58 or 59, wherein at least 75% of C_{max} is reached within 45 min after administration.

61. A method according to any of claims 58-60, wherein T_{max} is reached within 60 min after administration of the composition via a mucosa of the subject.

62. A method according to any of claims 58-61, wherein the disorder requiring acute glucocorticoid therapy is an acute adrenal crisis.

63. A method according to claim 62, wherein the acute adrenal crisis relates to a primary, secondary or tertiary adrenal insufficiency, an anaphylactic reaction, an Addison crisis, a status asthmaticus, a blood transfusion reaction, a brain edema, a severe allergic reaction, acute asthma, acute anaphylaxia, septic shock, acute bacterial meningitis, acute RSV (respiratory syncytial virus) infection with bronchiolitis in children, acute croup-children, mononucleosis with complications (airway obstruction, thrombocytopenia or haemolytical anaemia), or tonsillitis/peritonsillitis e.g. in children with airway obstruction.

64. A method according to any of claims 58-62, wherein the disorder requiring acute glucocorticoid therapy relates to an inflammatory disorder, an autoimmune disorder, or a medical disorder in which a glucocorticoid forms a part of the first line emergency medical treatment or intense short-time medical treatment.

65. A method according to any of claims 58-64, wherein the mucosa is selected from the mucosa in the oral cavity, the nasal cavity, the lung, the bronchia, the rectum and the vagina.

66. A method according to any of claims 58-65, wherein the mucosa is the mucosa in the oral cavity.

67. A method according to any of claims 58-66, wherein the effective amount of the one or more glucocorticoids expressed as hydrocortisone is from about 1 to about 200 mg.

68. A method according to claim 67, wherein the effective amount of the one or more glucocorticoids expressed as hydrocortisone is from about 1 to about 175 mg such as, e.g., from about 1 to about 150 mg, from about 1 to about 125 mg, from about 1 to about 100 mg, from about 1 to about 75 mg, from about 1 to about 70 mg, from about 1

to about 60 mg, from about 5 to about 50 mg, from about 5 to about 40 mg or from about 10 to about 30 mg.

69. A method according to any of claims 58-68, wherein the one or more glucocorticoids is selected from the group consisting of hydrocortisone, cortisone, prednisolone, prednisone, methylprednisone, triamcinolone, paramethasone, betamethasone, dexamethasone and fludrocortisone or mixtures thereof, including pharmaceutically acceptable esters, salts and complexes thereof.

70. A method according to claim 69, wherein the pharmaceutically acceptable salt is a phosphate, a succinate, a lysinate, an acetate, a cypionate, a valerate, a hemisuccinate, a butyrate or a trometamole salt.

71. A method according to any of claims 58-70, wherein the effective amount of the one or more glucocorticoid is contained in a pharmaceutical composition suitable for administration by the subject itself or by non-medically trained persons.

72. A method according to claim 71, wherein the composition is in a form that can be administered to the subject even if he is unconscious.

73. A method according to claim 71 or 72, wherein the composition is in a form that can be administered to the subject and have effect even if he is unable to swallow the composition.

74. A method according to any of claims 58-73, wherein the one or more glucocorticoids are cortisone or hydrocortisone including pharmaceutically acceptable esters, salts and complexes thereof and wherein the effective amount is in a range of from about 1 to about 100 mg.

75. A method according to any of claims 58-73 wherein the one or more glucocorticoids are betamethasone including pharmaceutically acceptable esters, salts and complexes thereof and wherein the effective amount is in a range of from about 1 to about 20 mg.

76. A method according to any of claims 58-73, wherein the one or more glucocorticoids are prednisolone including pharmaceutically acceptable esters, salts

and complexes thereof and wherein the effective amount is in a range of from about 1 to about 10 mg.

77. A method according to any of claims 58-73, wherein the one or more glucocorticoids are dexamethsone including pharmaceutically acceptable esters, salts and complexes and wherein the effective amount is in a range of from about 0.1 to about 2 mg.

78. A method according to any of claims 58-73, wherein the one or more glucocorticoids are fludrocortisone including pharmaceutically acceptable esters, salts and complexes thereof and wherein the effective amount is in a range of from about 0.05 to about 5 mg.

79. A method according to any of claims 58-73, wherein the one or more glucocorticoids are prednisone including pharmaceutically acceptable esters, salts and complexes thereof and wherein the effective amount is in a range of from about 10 to about 50 mg.

80. A method according to any of claims 58-73, wherein the one or more glucocorticoids are methylprednisolone including pharmaceutically acceptable esters, salts and complexes thereof and wherein the effective amount is in a range of from about 2 to about 20 mg.

81. A method according to any of claims 58-80, wherein the effective amount is administered in the form of a pharmaceutical composition as defined in any of claims 1-55.

82. A method according to any of claims 58-80, wherein the effective amount is administered in the form of a pharmaceutical kit as defined in claims 56 or 57.

83. Use of an amount of one or more glucocorticoids for the preparation of a pharmaceutical composition or kit as defined in any of claims 1-58 for the treatment of a disorder requiring acute glucocorticoid therapy by providing a fast rise in the glucocorticoid serum level to at least 20% of C_{max} within 20 min after administration via a mucosa.

84. Use according to claim 83, wherein at least 40% of C_{max} is reached within 30 min after administration.

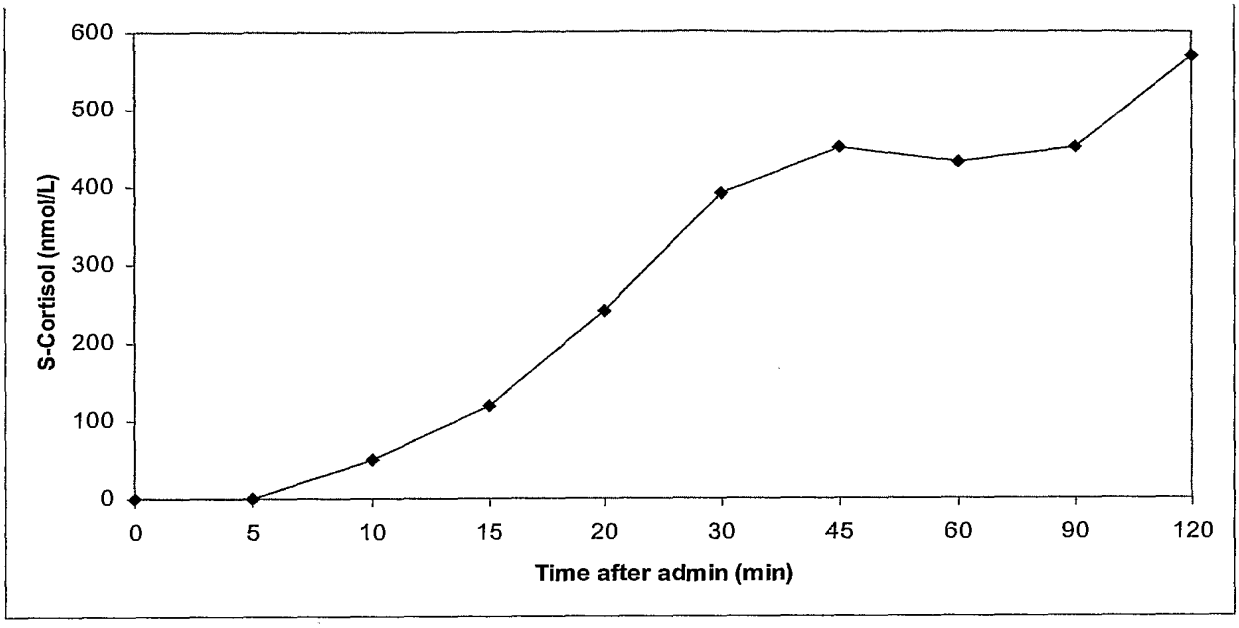
85. Use according to claim 83 or 84, wherein at least 75% of C_{max} is reached within 45 min after administration.

86. Use according to any of claims 83-85, wherein T_{max} is reached within 60 min after administration of the composition via a mucosa of the subject.

87. Use according to any of claims 83-86, wherein an effective amount of the one or more glucocorticoid is contained in a pharmaceutical composition suitable for administration by the subject itself or by non-medically trained persons.

88. Use according to any of claims 83-87, wherein the composition is in a form that can be administered to the subject even if he is unconscious.

89. Use according to claim 87 or 88, wherein the composition is in a form that can be administered to the subject and have effect even if he is unable to swallow the composition.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500
400
300
200
100
0
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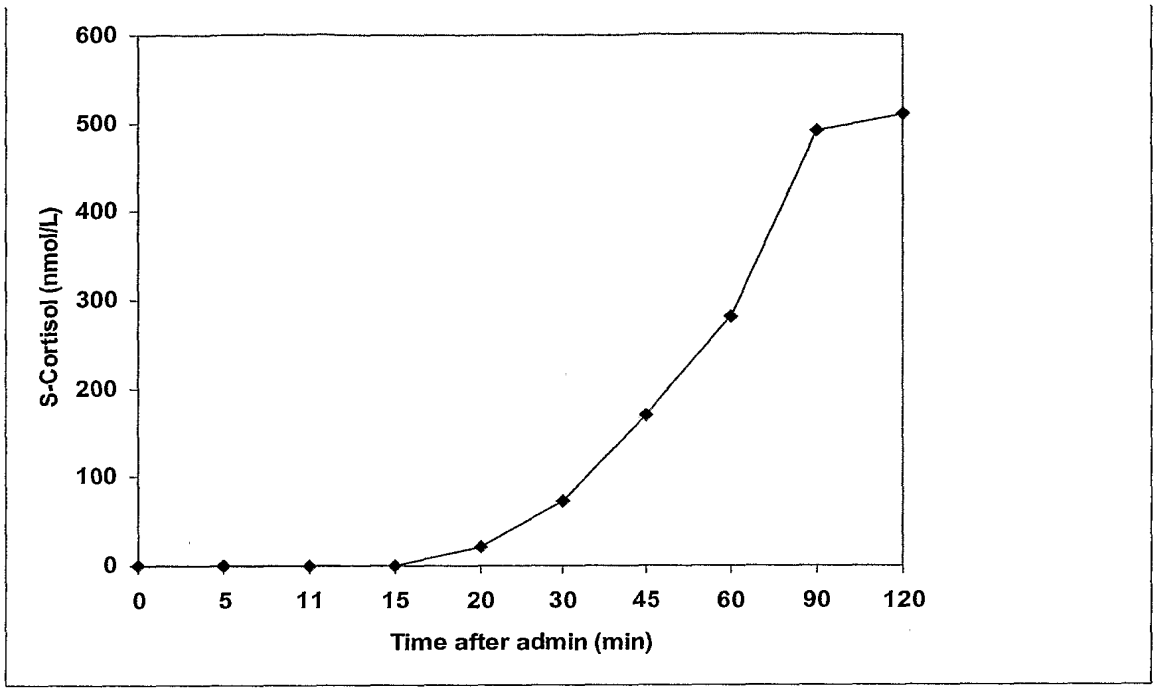
0
5
10
15
20
30
45
60
90
120
Time after admin (min)

Fig. 1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100
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20
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45
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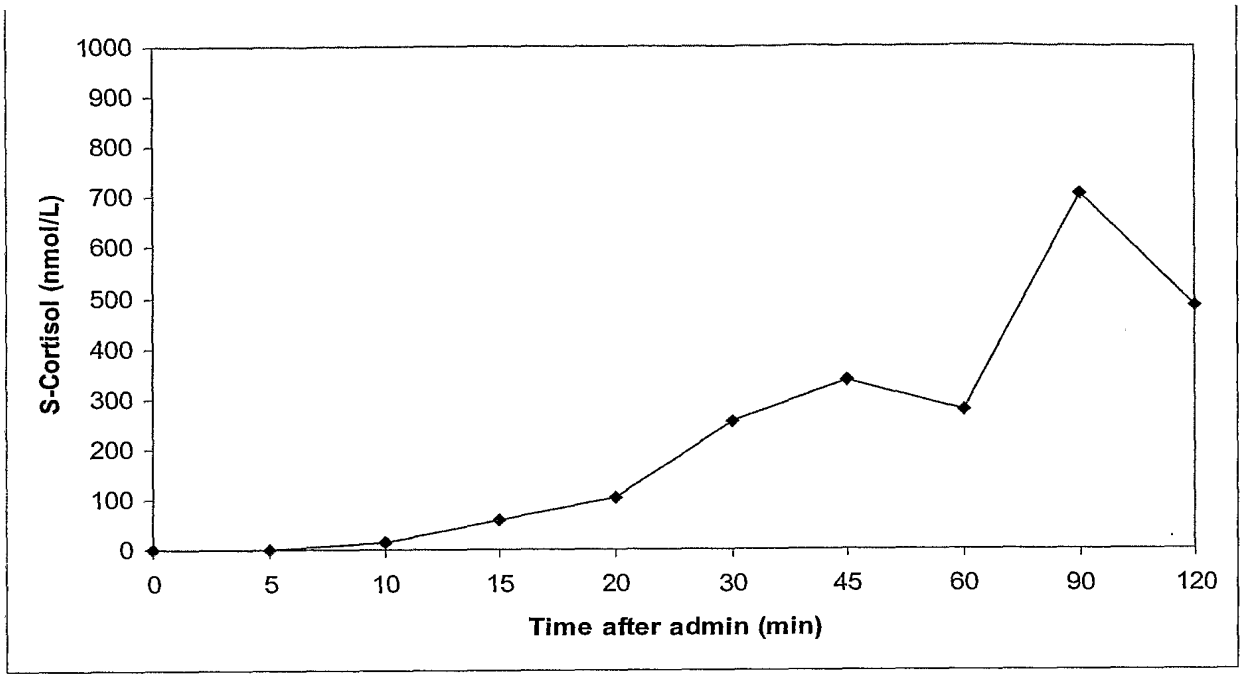
90
120
Time after admin (min)

Fig. 2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800
700
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100
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0
5
10
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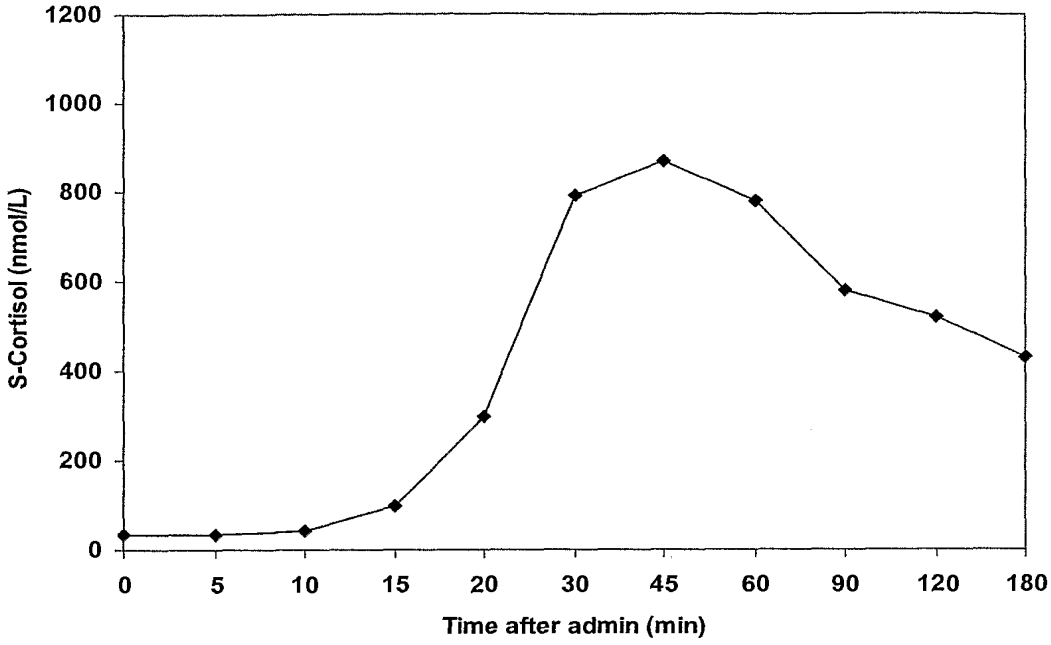
30
45
60
90
120
Time after admin (min)

Fig. 3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1000
800
600
400
200
0
S-Cortisol (nmol/L)
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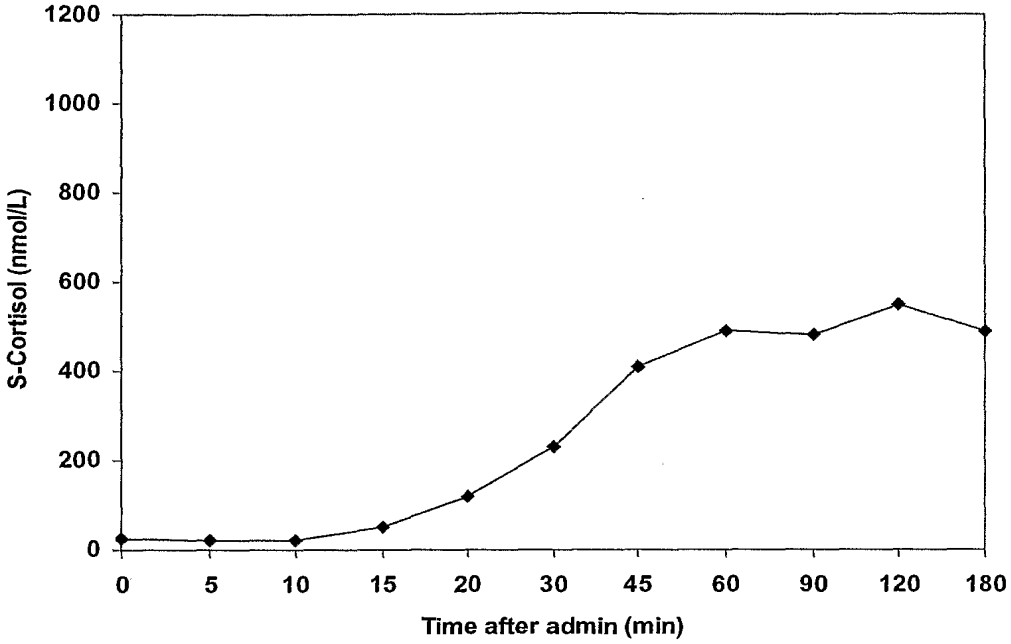
5
10
15
20
30
45
60
90
120
180
Time after admin (min)

Fig. 4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1000
800
600
400
200
0
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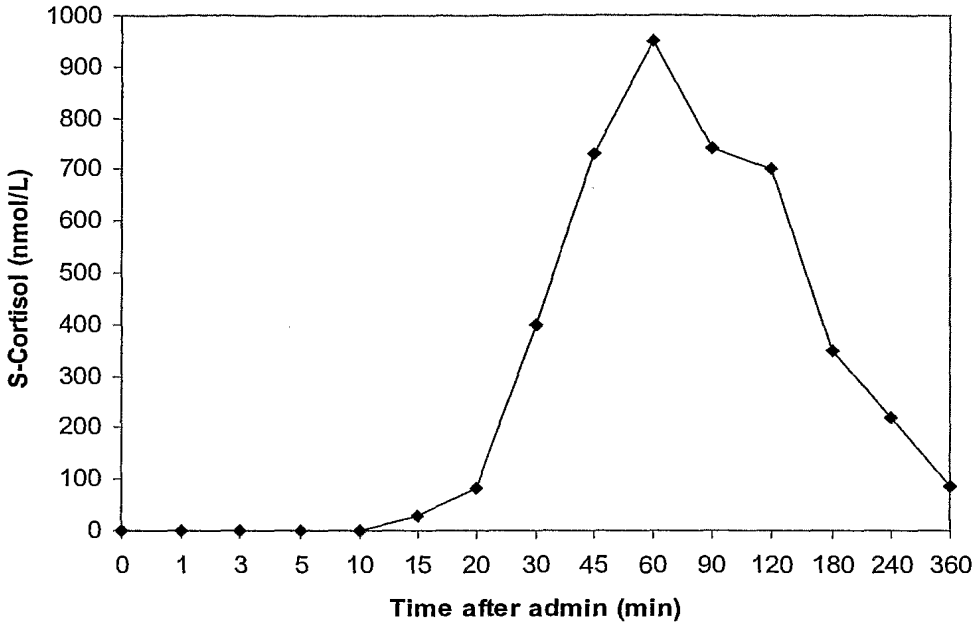
5
10
15
20
30
45
60
90
120
180
Time after admin (min)

Fig. 5


S-Cortisol (nmol/L)
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900
800
700
600
500
400
300
200
100
0
0 1 3 5 10 15 20 30 45 60 90 120 180 240 360
Time after admin (min)

Fig. 6

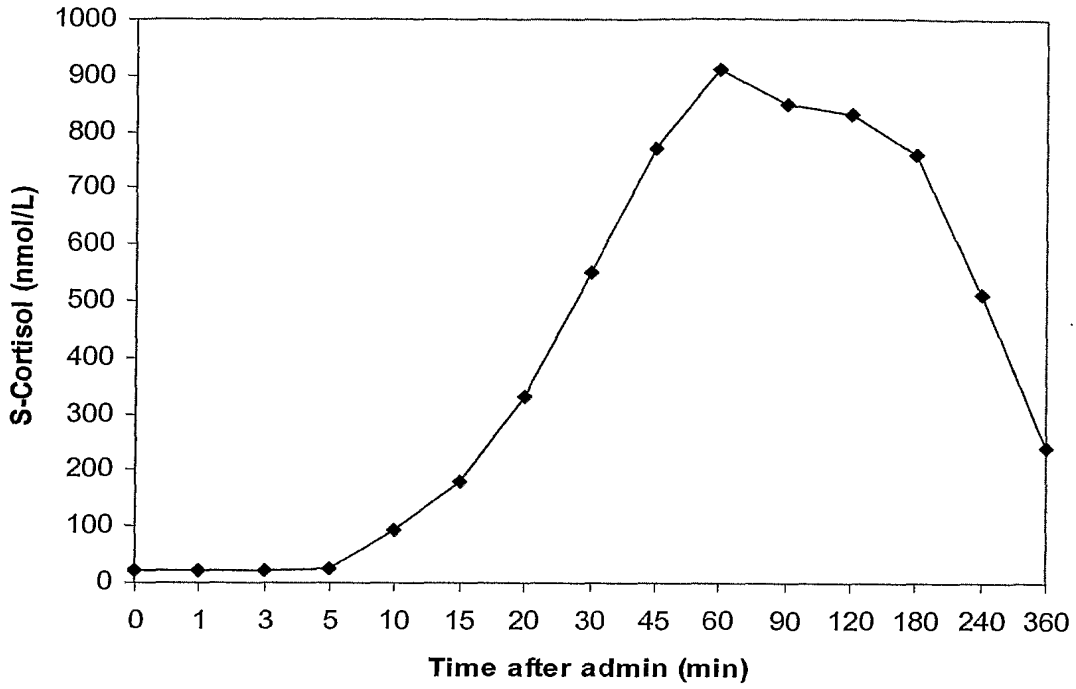
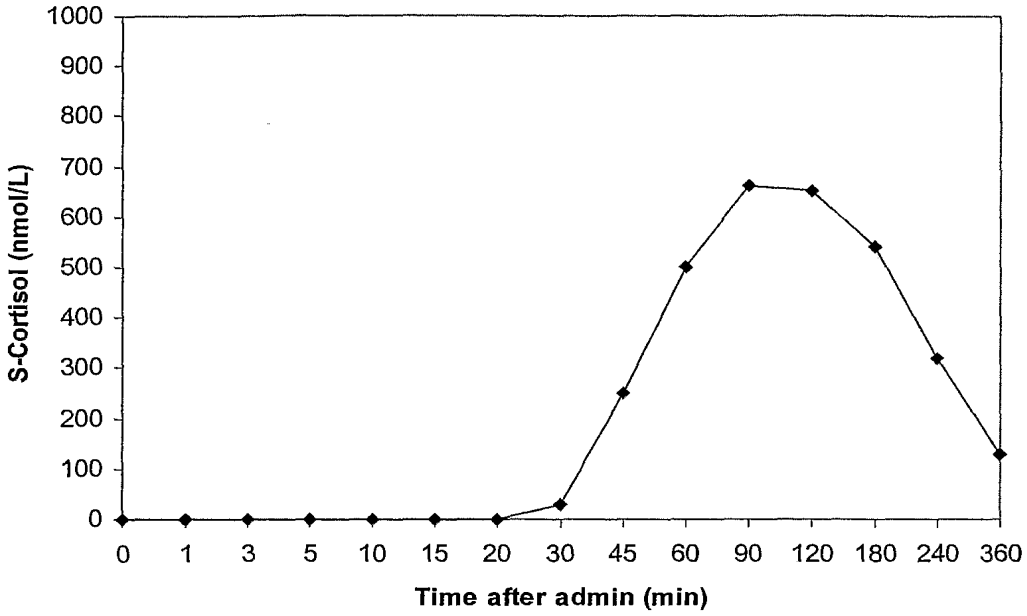

S-Cortisol (nmol/L)
1000
900
800
700
600
500
400
300
200
100
0
0 1 3 5 10 15 20 30 45 60 90 120 180 240 360
Time after admin (min)

Fig. 7


S-Cortisol (nmol/L)
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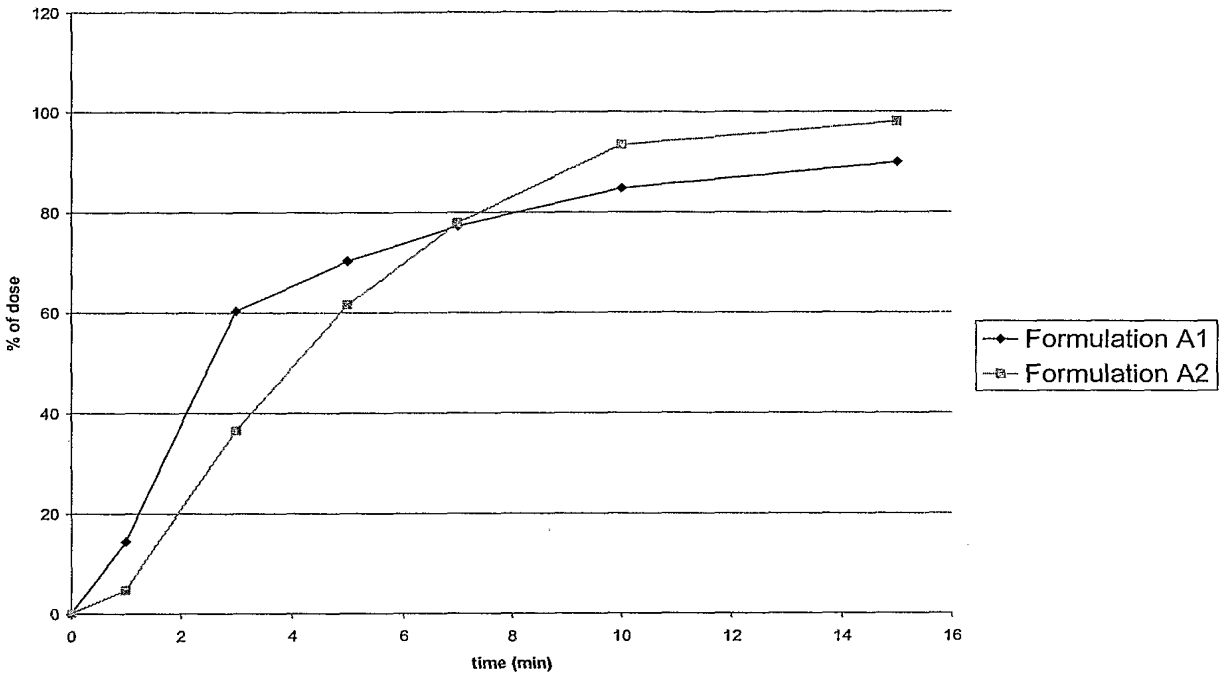
900
800
700
600
500
400
300
200
100
0
0 1 3 5 10 15 20 30 45 60 90 120 180 240 360
Time after admin (min)

Fig. 8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100
80
60
40
20
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% of dose
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2
4
6
8
10
12
14
16
time (min)
Formulation A1
Formulation A2

Fig. 9

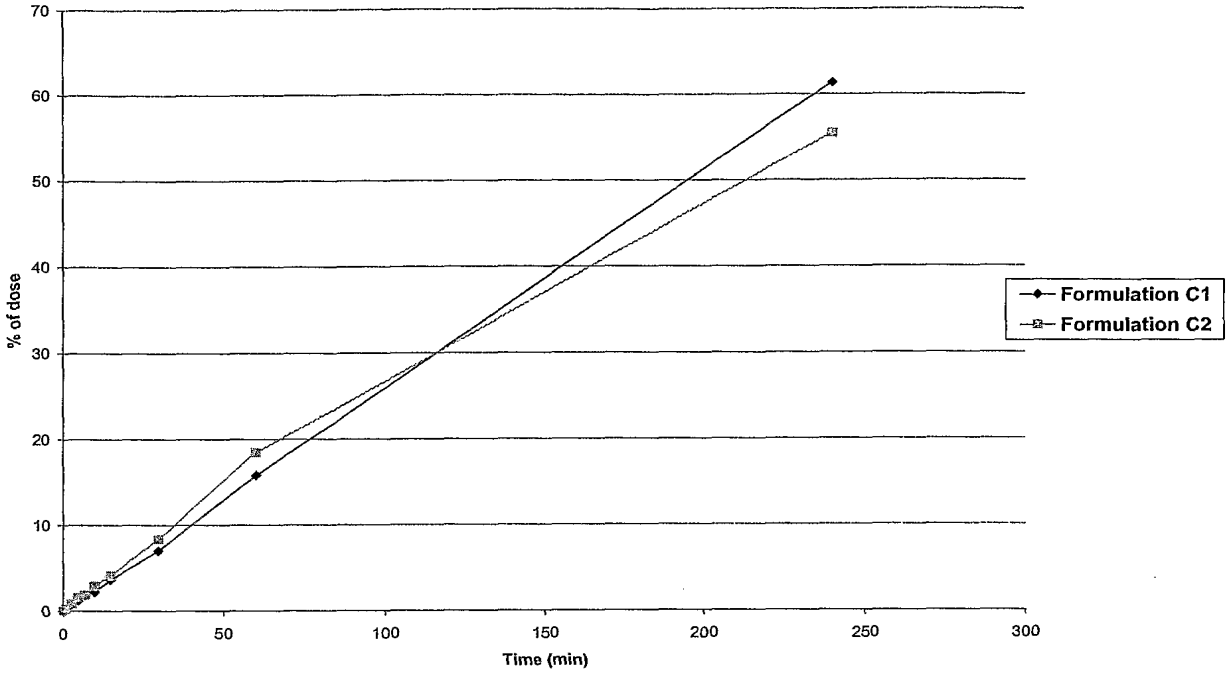
70
60
50
40
30
20
10
0
% of dose
0
50
100
150
200
250
300
Time (min)
Formulation C1
Formulation C2

Fig. 10

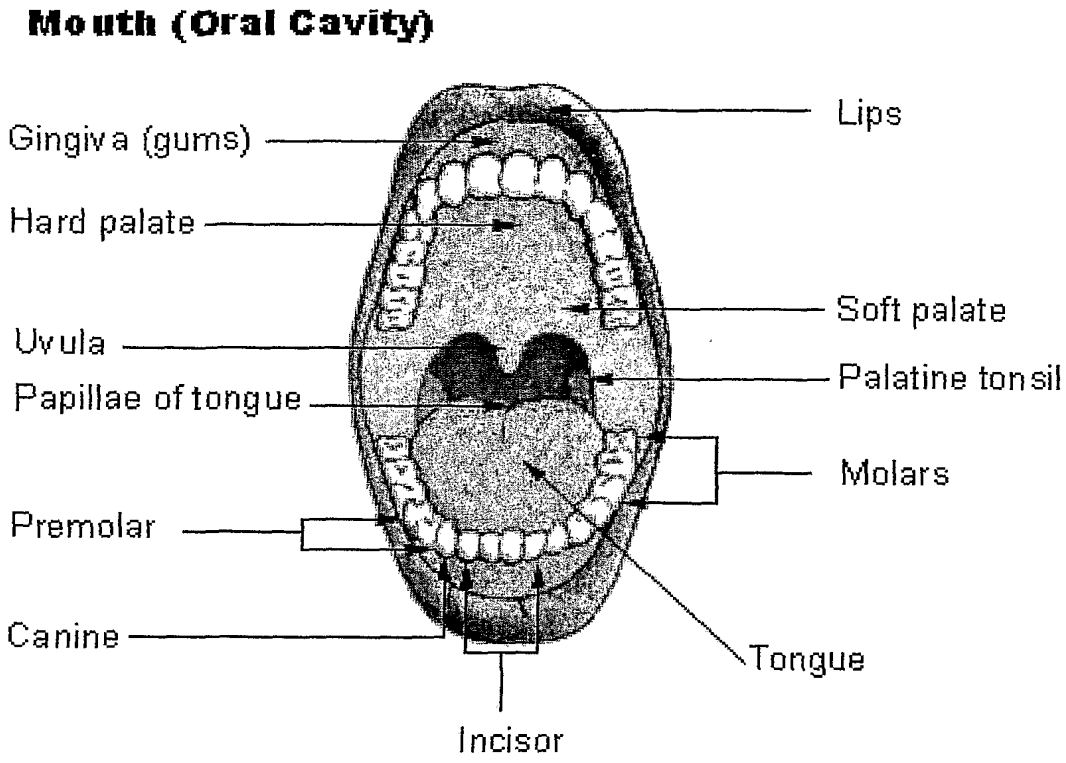
Mouth (Oral Cavity)
Gingiva (gums)
Hard palate
Uvula
Papillae of tongue
Premolar
Canine
Incisor
Lips
Soft palate
Palatine tonsil
Molars
Tongue

Fig. 11

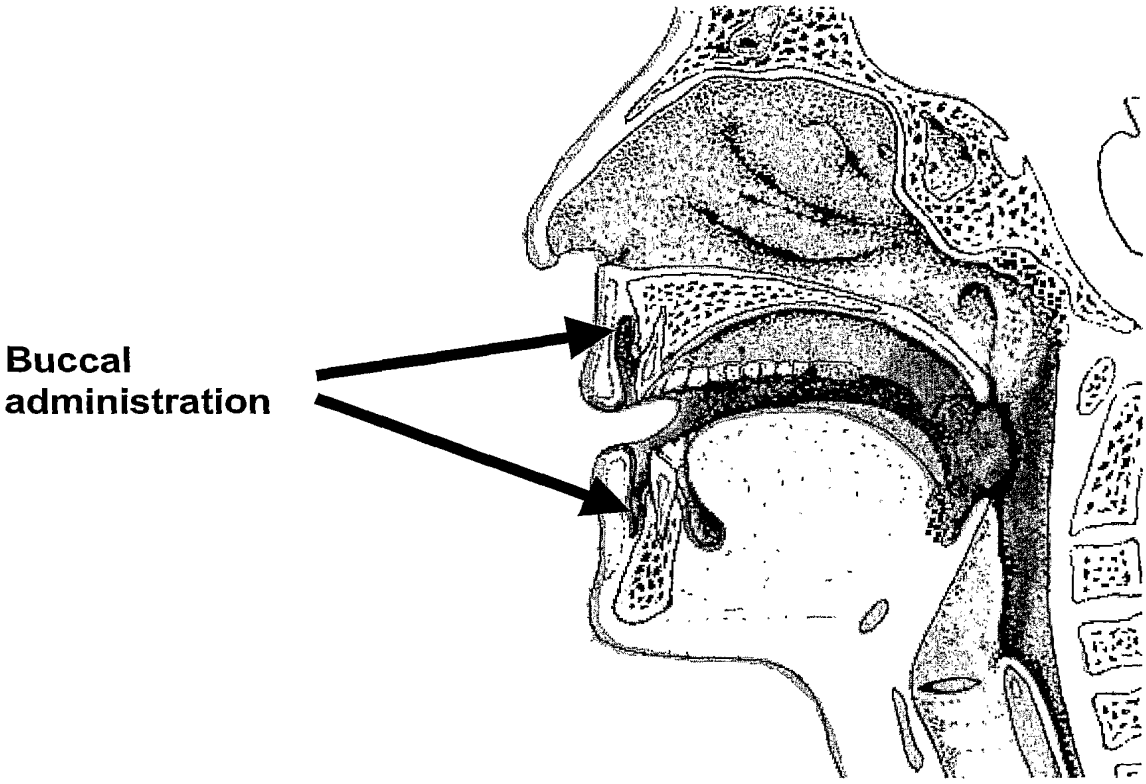

Fig. 12

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(74) Agent: **ALBIHNS A/S**; H.C. Andersens Boulevard 49, DK-1553 Copenhagen V (DK).

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(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(88) Date of publication of the international search report:
22 June 2006

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PHARMACEUTICAL COMPOSITIONS FOR ACUTE GLUCOCORTICOID THERAPY

(57) Abstract: The present invention relates to glucocorticoid-containing pharmaceutical compositions or kits for use in acute emergency situations where acute glucocorticoid therapy is required. Notably, the invention relates to pharmaceutical compositions and kits that are designed to be administered by non-medically trained persons outside a hospital or another medical or clinical setting. The invention also relates to a method for treating a disorder requiring acute glucocorticoid therapy by providing a fast onset of action of a glucocorticoid

WO 2005/102287 A3

INTERNATIONAL SEARCH REPORT

PCT/EP2005/004399

A. CLASSIFICATION OF SUBJECT MATTER
A61K9/20 A61K9/16 A61K9/70 A61K9/08 A61K9/12
A61K31/573 A61K9/00 A61K9/50

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	"Martindale-The complete drug reference" 2000, PHARMACEUTICAL PRESS 242330 , XP002373045 page 1010 - page 1017	1-32, 56-89
X	WO 87/05804 A (THE UPJOHN COMPANY) 8 October 1987 (1987-10-08) examples	1-19, 21-25, 31-37, 39-42, 48-51, 54-73, 80-89

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 March 2006	07/04/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Boulois, D

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 448 774 A (CLEMENTE ET AL) 15 May 1984 (1984-05-15) column 1, line 39 - line 49 column 3, line 50 - column 4, line 6; claims	1-15,18, 21-24, 30,31, 35,36, 41,51, 52,54, 56, 58-74, 79-89
X	US 4 765 983 A (TAKAYANAGI ET AL) 23 August 1988 (1988-08-23) examples 1-3,7,9-18	1-16,18, 20-25, 28, 32-35, 37-41, 48,49, 56-74, 77,81-89
X	EP 0 311 540 A (MEDIBREVEX, SOCIETE CIVILE DITE; MEDIBREVEX SA) 12 April 1989 (1989-04-12) claims 1,2	1-19, 21-24, 32, 54-73, 83-89
X	WO 97/46243 A (THE PROCTER & GAMBLE COMPANY) 11 December 1997 (1997-12-11) page 9 - page 11; examples	1-18, 20-24, 33-37, 39-42, 56-68, 81-89
X	WO 02/03955 A (F.T. HOLDING S.A; ROVERSI, FRANCESCO; CILURZO, FRANCESCO) 17 January 2002 (2002-01-17) page 10; examples 7,8 claims 1,9,10	1-19, 21-24, 32-40, 44, 56-75, 81-89
X	WO 97/38662 A (FLEMINGTON PHARMACEUTICAL CORPORATION; DUGGER, HARRY, A., III) 23 October 1997 (1997-10-23) examples 7,11	1-18,20, 56-66, 83-89

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	AHN J-S ET AL: "Release of triamcinolone acetonide from mucoadhesive polymer composed of chitosan and poly(acrylic acid) in vitro" BIOMATERIALS, ELSEVIER SCIENCE PUBLISHERS BV., BARKING, GB, vol. 23, no. 6, 15 March 2002 (2002-03-15), pages 1411-1416, XP004348149 ISSN: 0142-9612 the whole document	1-18, 20-24, 32-41, 56-68, 81-89
X	NAKAMURA K ET AL: "Uptake and release of budesonide from mucoadhesive, pH-sensitive copolymers and their application to nasal delivery" JOURNAL OF CONTROLLED RELEASE, ELSEVIER, AMSTERDAM, NL, vol. 61, no. 3, 20 September 1999 (1999-09-20), pages 329-335, XP004362987 ISSN: 0168-3659 the whole document	1-18, 20-24, 32-41, 56-68, 81-89

INTERNATIONAL SEARCH REPORT

PCT/EP2005/004399

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 58-89 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

PCT/EP2005/004399

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 8705804	A	08-10-1987	AU	7084587 A	20-10-1987
			DK	624287 A	27-11-1987
			EP	0301006 A1	01-02-1989
			HK	58497 A	09-05-1997
			JP	1501934 T	06-07-1989
			NO	874989 A	30-11-1987
US 4448774	A	15-05-1984	NONE		
US 4765983	A	23-08-1988	DE	3618553 A1	08-01-1987
			FR	2582942 A1	12-12-1986
			GB	2177002 A	14-01-1987
			JP	1717687 C	14-12-1992
			JP	2060644 B	17-12-1990
			JP	61280423 A	11-12-1986
EP 0311540	A	12-04-1989	CA	1328610 C	19-04-1994
			DE	3887066 D1	24-02-1994
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			FR	2621483 A1	14-04-1989
			JP	1128928 A	22-05-1989
			US	5061493 A	29-10-1991
WO 9746243	A	11-12-1997	AU	3153797 A	05-01-1998
			BR	9709650 A	10-08-1999
			CA	2256721 A1	11-12-1997
			EP	0954318 A1	10-11-1999
			JP	11511758 T	12-10-1999
WO 0203955	A	17-01-2002	AU	6778201 A	21-01-2002
			EP	1301174 A1	16-04-2003
			IT	MI20001548 A1	10-01-2002
WO 9738662	A	23-10-1997	AT	288255 T	15-02-2005
			AU	2190697 A	07-11-1997
			CA	2252038 A1	23-10-1997
			DE	69732412 D1	10-03-2005
			DE	69732412 T2	05-01-2006
			EP	0910339 A2	28-04-1999
			ES	2234010 T3	16-06-2005
			PT	910339 T	31-05-2005
			US	6110486 A	29-08-2000

Electronic Acknowledgement Receipt

EFS ID:	14825761
Application Number:	95002170
International Application Number:	
Confirmation Number:	6418
Title of Invention:	POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM
First Named Inventor/Applicant Name:	7897080
Customer Number:	23869
Filer:	Stephen J. Brown
Filer Authorized By:	
Attorney Docket Number:	117744-00023
Receipt Date:	29-JAN-2013
Filing Date:	10-SEP-2012
Time Stamp:	23:40:09
Application Type:	inter partes reexam

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	IDS_Statement.pdf	12791 59b32973e93bf159453436a901e1f2f8c14fb4f8	no	2

Warnings:	
Information:	

2	Information Disclosure Statement (IDS) Form (SB08)	080_IDS4.pdf	616604 d91802d8fb06a82d887b477474ef873ee2e89379	no	7
Warnings:					
Information:					
3	Foreign Reference	AU741362.pdf	421691 a0515f2ca9d83f0bc1627ec0f17c67b824f610f2	no	17
Warnings:					
Information:					
4	Non Patent Literature	Bodmeier.pdf	681346 a42a3a69acef5c0fbf7d209e9c4d8bbb0cf519e5	no	6
Warnings:					
Information:					
5	Foreign Reference	DE19646392.pdf	327762 7e0c5f792c4f0dc0001d343eb6a6fa687a0c1264	no	4
Warnings:					
Information:					
6	Foreign Reference	EP0440462.pdf	699607 a84add673eeb2accd35f2c8aee6ead487f73c2b7	no	13
Warnings:					
Information:					
7	Foreign Reference	GB1061557.pdf	129238 d506fb40484d8183f5fc307afc0049c37dfabac3	no	2
Warnings:					
Information:					
8	Non Patent Literature	Peh.pdf	595983 a8eb5bb8ccea104a55345b3e4b2c6faffeea e51d	no	9
Warnings:					
Information:					
9	Non Patent Literature	Senel.pdf	571441 7d90c218e521987f30f22b2b099e9db7bea91816	no	7
Warnings:					
Information:					
10	Non Patent Literature	Stella.pdf	345058 2afb91f700e4f396252539d9d52600647e2b19f9	no	5
Warnings:					
Information:					

11	Foreign Reference	WO1997031621.pdf	1401860 f5af5e7385f148f564ec21ab81612aac3e8f164e	no	35
Warnings:					
Information:					
12	Foreign Reference	WO2005102287.pdf	2409080 1aa49a5b8ab69a336b9eb05d4735a230751555f0	no	62
Warnings:					
Information:					
			Total Files Size (in bytes):	8212461	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patentee:	Yang et al.	Examiner:	Diamond, Alan D.
Patent No.:	U.S. 7,897,080	Group Art Unit:	3991
Reexamination Control No.:	95/002,170	Confirmation No.	6418
Filed:	September 10, 2012	H&B Docket:	1199-26 RCE/CON/REX
Dated:	January 29, 2013	M&E Docket:	117744-00023

Mail Stop Inter Partes Reexam
Central Reexamination Unit
Commissioner for Patents
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT

Madam:

This Information Disclosure Statement is being submitted pursuant to 37 C.F.R. 1.98, and identifies a number of patents and publication that may be considered relevant. The Patent Holder makes no representation as to the relevance of these documents, but wishes to make these references of record in this reexamination. Consideration of the references recited herein is requested.

If any fee is due with this submission, the Commission is authorized to charge any such fee to Deposit Account No. 08-2461. Should the Examiner have any questions regarding this submission, the undersigned would be pleased to address them.

Respectfully submitted,

/Daniel A. Scola, Jr./
Daniel A. Scola, Jr.
Registration No.: 29,855
Attorney for the Patentee

HOFFMANN & BARON, LLP
6900 Jericho Turnpike
Syosset, New York 11791
(973) 331-1700

CERTIFICATE OF FIRST CLASS SERVICE

It is certified that a copy of this **INFORMATION DISCLOSURE STATEMENT** has been served, by first class mail, on January 29, 2013, in its entirety on the third party requester as provided in 37 CFR § 1.903 and 37 CFR § 1.248 at the addess below.

DANIELLE L. HERRITT
McCARTER & ENGLISH LLP
265 FRANKLIN STREET
BOSTON, MASSACHUSETTS 02110

/Daniel A. Scola, Jr./
Daniel A. Scola, Jr.
Registration No.: 29,855
Attorney for the Patentee

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	95002170
Filing Date	2012-09-10
First Named Inventor	Robert K. Yang
Art Unit	3991
Examiner Name	Diamond, Alan D.
Attorney Docket Number	1199-26 RCE/CON/REX

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	4202966		1980-05-13	Misaki et al.	
	2	7241411		2007-07-10	Berry et al.	
	3	4365423		1982-12-28	Arter et al.	
	4	4851394		1989-07-25	Kubodera	
	5	5759599		1998-06-02	Wampler et al.	
	6	6428825		2002-08-06	Sharma et al.	
	7	6047484		2000-04-11	Bolland et al.	
	8	5137729		1992-08-11	Kuroya et al.	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	95002170
	Filing Date	2012-09-10
	First Named Inventor	Robert K. Yang
	Art Unit	3991
	Examiner Name	Diamond, Alan D.
	Attorney Docket Number	1199-26 RCE/CON/REX

	9	6238700		2001-05-29	Donher et al.	
	10	5028632		1991-07-02	Fuisz	

If you wish to add additional U.S. Patent citation information please click the Add button. Add

U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20050170138	A1	2005-08-04	Berry	

If you wish to add additional U.S. Published Application citation information please click the Add button. Add

FOREIGN PATENT DOCUMENTS Remove

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] ¡	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1							☐

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NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	Endo and Ueda, FABAD J. PHARM. SCI., 29:27-38, 2004	☐
	2	Dr. June V. Engel, "The Benefits of Eating Fibre" from http://www.diabetes.ca/Section_About/fibre.asp	☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	95002170
	Filing Date	2012-09-10
	First Named Inventor	Robert K. Yang
	Art Unit	3991
	Examiner Name	Diamond, Alan D.
	Attorney Docket Number	1199-26 RCE/CON/REX

	3	ATRIDOX(R) (DOXYCYCLINE HYCLATE) product label (Date Unknown).	☐
	4	Cholewinski et al., PHARMACEUTICA ACTA HELVETIAE, 71:405-419, 1996.	☐
	5	Di Donato et al., J. BIOL. CHEM., 268(7): 4745-4751, 1993.	☐
	6	Leathers, APPL. MICROBIOL. BIOTECHNOL., 62:468-473, 2003.	☐
	7	Huus et al., "Thermal Dissociation and Unfolding of Insulin,' Biochemistry, Vol. 44, pp. 11171-11177, 2005.	☐

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	95002170
Filing Date	2012-09-10
First Named Inventor	Robert K. Yang
Art Unit	3991
Examiner Name	Diamond, Alan D.
Attorney Docket Number	1199-26 RCE/CON/REX

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Daniel A. Scola, Jr., Reg. No. 29,855/	Date (YYYY-MM-DD)	2013-01-29
Name/Print	Daniel A. Scola	Registration Number	29,855

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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The information provided by you in this form will be subject to the following routine uses:

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2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Acknowledgement Receipt

EFS ID:	14825766
Application Number:	95002170
International Application Number:	
Confirmation Number:	6418
Title of Invention:	POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM
First Named Inventor/Applicant Name:	7897080
Customer Number:	23869
Filer:	Stephen J. Brown
Filer Authorized By:	
Attorney Docket Number:	117744-00023
Receipt Date:	29-JAN-2013
Filing Date:	10-SEP-2012
Time Stamp:	23:43:12
Application Type:	inter partes reexam

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	IDS_Statement.pdf	12791 59b32973e93bf159453436a901e1f2f8c14fb4f8	no	2

Warnings:

Information:

2	Information Disclosure Statement (IDS) Form (SB08)	080_IDS5.pdf	615946 40c6ecf20e6fb20d01070d43d62ddfd864f6ebde	no	5
Warnings:					
Information:					
3	Non Patent Literature	Atridox.pdf	493259 7ab7c2a91b934cde9ed9254e55149648776efb0a	no	11
Warnings:					
Information:					
4	Non Patent Literature	Cholewinski.pdf	1148833 bfc43b979a3d25050b8b6225e64c10a65f038066	no	15
Warnings:					
Information:					
5	Non Patent Literature	DiDonato.pdf	729068 eea9b9310203ab4db4cd6ffd81be7c9f99040579	no	7
Warnings:					
Information:					
6	Non Patent Literature	Endo.pdf	833581 0a060ef6f80bdcb0d87cc145c08c5f53fd8d19a3	no	12
Warnings:					
Information:					
7	Non Patent Literature	Engel.pdf	218878 f6cfb0d84bbd1a41aceffc89f1299b1e8512c319	no	3
Warnings:					
Information:					
8	Non Patent Literature	Huus.pdf	698010 f3603a2d98fb7225ab0a3ac16e5c5ac45ee8e3ba	no	7
Warnings:					
Information:					
9	Non Patent Literature	Leathers.pdf	503896 998da5c78d7754e2ec0a7032cb723eae5394669e	no	6
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New Applications Under 35 U.S.C. 111

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National Stage of an International Application under 35 U.S.C. 371

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New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patentee:	Yang et al.	Examiner:	Diamond, Alan D.
Patent No.:	U.S. 7,897,080	Group Art Unit:	3991
Reexamination Control No.:	95/002,170	Confirmation No.	6418
Filed:	September 10, 2012	H&B Docket:	1199-26 RCE/CON/REX
Dated:	January 29, 2013	M&E Docket:	117744-00023

Mail Stop Inter Partes Reexam
Central Reexamination Unit
Commissioner for Patents
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT

Madam:

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If any fee is due with this submission, the Commission is authorized to charge any such fee to Deposit Account No. 08-2461. Should the Examiner have any questions regarding this submission, the undersigned would be pleased to address them.

Respectfully submitted,

/Daniel A. Scola, Jr./
Daniel A. Scola, Jr.
Registration No.: 29,855
Attorney for the Patentee

HOFFMANN & BARON, LLP
6900 Jericho Turnpike
Syosset, New York 11791
(973) 331-1700

CERTIFICATE OF FIRST CLASS SERVICE

It is certified that a copy of this **INFORMATION DISCLOSURE STATEMENT** has been served, by first class mail, on January 29, 2013, in its entirety on the third party requester as provided in 37 CFR § 1.903 and 37 CFR § 1.248 at the addess below.

DANIELLE L. HERRITT
McCARTER & ENGLISH LLP
265 FRANKLIN STREET
BOSTON, MASSACHUSETTS 02110

/Daniel A. Scola, Jr./
Daniel A. Scola, Jr.
Registration No.: 29,855
Attorney for the Patentee

PTO/SB/08a (03-08)
Approved for use through 07/31/2008. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	95002170
Filing Date	2012-09-10
First Named Inventor	Robert K. Yang
Art Unit	3991
Examiner Name	Diamond, Alan D.
Attorney Docket Number	1199-26 RCE/CON/REX

U.S.PATENTS

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	95002170
	Filing Date	2012-09-10
	First Named Inventor	Robert K. Yang
	Art Unit	3991
	Examiner Name	Diamond, Alan D.
	Attorney Docket Number	1199-26 RCE/CON/REX

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	10	3536809		1970-10-27	Applezweig	
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If you wish to add additional U.S. Patent citation information please click the Add button.

U.S.PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20010022964	A1	2001-09-20	Leung et al	
	2	20010006677	A1	2001-07-05	McGinity et al	

If you wish to add additional U.S. Published Application citation information please click the Add button.

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99**)		
	Application Number	95002170
	Filing Date	2012-09-10
	First Named Inventor	Robert K. Yang
	Art Unit	3991
	Examiner Name	Diamond, Alan D.
	Attorney Docket Number	1199-26 RCE/CON/REX

	1							☐

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NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	XP-002298105, Poluethylenglykole; Internet www.roempp.com (09/20/2004).	☐

If you wish to add additional non-patent literature document citation information please click the Add button

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(**Not for submission under 37 CFR 1.99**)

Application Number	95002170
Filing Date	2012-09-10
First Named Inventor	Robert K. Yang
Art Unit	3991
Examiner Name	Diamond, Alan D.
Attorney Docket Number	1199-26 RCE/CON/REX

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ None

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Daniel A. Scola, Jr., Reg. No. 29,855/	Date (YYYY-MM-DD)	2013-01-29
Name/Print	Daniel A. Scola, Jr.	Registration Number	29,855

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
95/002,170	09/10/2012	7897080	117744-00023	6418

23869 7590 11/29/2012

Hoffmann & Baron LLP
6900 Jericho Turnpike
Syosset, NY 11791

EXAMINER	
DIAMOND, ALAN D	
ART UNIT	PAPER NUMBER
3991	
MAIL DATE	DELIVERY MODE
11/29/2012	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Transmittal of Communication to Third Party Requester *Inter Partes* Reexamination	Control No.	Patent Under Reexamination	
	95/002,170	7897080	
	Examiner	Art Unit	
	Alan Diamond	3991	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address. --

(THIRD PARTY REQUESTER'S CORRESPONDENCE ADDRESS)

Danielle L. Herrit
McCarter & English LLP
265 Franklin Street
Boston, MA 02110

Enclosed is a copy of the latest communication from the United States Patent and Trademark Office in the above-identified reexamination proceeding. 37 CFR 1.903.

Prior to the filing of a Notice of Appeal, each time the patent owner responds to this communication, the third party requester of the *inter partes* reexamination may once file written comments within a period of 30 days from the date of service of the patent owner's response. This 30-day time period is statutory (35 U.S.C. 314(b)(2)), and, as such, it cannot be extended. See also 37 CFR 1.947.

If an *ex parte* reexamination has been merged with the *inter partes* reexamination, no responsive submission by any *ex parte* third party requester is permitted.

All correspondence relating to this inter partes reexamination proceeding should be directed to the **Central Reexamination Unit** at the mail, FAX, or hand-carry addresses given at the end of the communication enclosed with this transmittal.

OFFICE ACTION IN INTER PARTES *REEXAMINATION*	Control No.	Patent Under Reexamination
	95/002,170	7897080
	Examiner	Art Unit
	Alan Diamond	3991

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address. --

Responsive to the communication(s) filed by:
Patent Owner on _____
Third Party(ies) on _____

RESPONSE TIMES ARE SET TO EXPIRE AS FOLLOWS:

For Patent Owner's Response:
2 MONTH(S) from the mailing date of this action. 37 CFR 1.945. EXTENSIONS OF TIME ARE GOVERNED BY 37 CFR 1.956.
For Third Party Requester's Comments on the Patent Owner Response:
30 DAYS from the date of service of any patent owner's response. 37 CFR 1.947. NO EXTENSIONS OF TIME ARE PERMITTED. 35 U.S.C. 314(b)(2).

All correspondence relating to this inter partes reexamination proceeding should be directed to the **Central Reexamination Unit** at the mail, FAX, or hand-carry addresses given at the end of this Office action.

This action is not an Action Closing Prosecution under 37 CFR 1.949, nor is it a Right of Appeal Notice under 37 CFR 1.953.

PART I. THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892
2. ☐ Information Disclosure Citation, PTO/SB/08
3. ☐ _____

PART II. SUMMARY OF ACTION:

1a. ☒ Claims 1-299 are subject to reexamination.
1b. ☐ Claims _____ are not subject to reexamination.
2. ☐ Claims _____ have been canceled.
3. ☐ Claims _____ are confirmed. [Unamended patent claims]
4. ☐ Claims _____ are patentable. [Amended or new claims]
5. ☒ Claims 1-299 are rejected.
6. ☐ Claims _____ are objected to.
7. ☐ The drawings filed on _____ ☐ are acceptable ☐ are not acceptable.
8. ☐ The drawing correction request filed on _____ is: ☐ approved. ☐ disapproved.
9. ☐ Acknowledgment is made of the claim for priority under 35 U.S.C. 119 (a)-(d). The certified copy has: ☐ been received. ☐ not been received. ☐ been filed in Application/Control No _____.
10. ☐ Other _____

This Office Action is being re-mailed and the period for response is being restarted in response to Patent Owner's November 26, 2012 petition requesting relief available to Patentees affected by hurricane Sandy in view of the memorandum signed by David J. Kappos on November 21, 2012, entitled "Emergency Notice of Relief Available to Patent and Trademark Applicant's, Patentees and Trademark Owners Affected by Hurricane Sandy", which authorized such relief.

Summary of Proceedings

A Request pursuant to 37 CFR 1.913 for inter partes reexamination of claims 1-299 of U.S. Patent 7,897,080 (hereinafter "the '080 patent") was filed September 10, 2012 by Third Party Requester. An Order granting inter partes reexamination of claims 1-299 of the '080 patent accompanies the instant Office action. 37 CFR 1.935.

Art Cited in this Office Action

Chen et al, WO 00/42992, hereafter "Chen".

Staab, U.S. Patent 5,393,528.

Le Person et al, "Near infrared drying of pharmaceutical thin films: experimental analysis of internal mass transport," Chemical Engineering and Processing, Vol. 37, pp. 257-263, (1998), hereafter "Le Person".

Horstmann et al, U.S. Patent 5,629,003, hereafter "Horstmann".

Scope of Claims

In reexamination, patent claims are construed broadly. *In re Yamamoto*, 740 F.2d 1569, 1571, 222 USPQ 934, 936 (Fed. Cir. 1984) (claims given "their broadest reasonable interpretation consistent with the specification"). This reexamination proceeding contains claims 1-299 directed to a process for making a film having a substantially uniform distribution of components and to a process for making a film capable of being administered to a body surface having a substantially uniform distribution of components. Claims 1, 82 and 161 representative:

1. A process for making a film having a substantially uniform distribution of components, comprising the steps of:

(a) forming a masterbatch pre-mix comprising a solvent and a polymer selected from the group consisting of water-soluble polymers, water-swellable polymers and combinations thereof;

(b) adding an active to a pre-determined amount of said masterbatch pre-mix to form a flowable polymer matrix, said matrix having a substantially uniform distribution of said active;

(c) casting said flowable polymer matrix;

(d) evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film within about 10 minutes or fewer to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film; and

(e) forming a resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained.

82. A process for making a film having a substantially uniform distribution of components, comprising the steps of:

(a) forming a flowable polymer matrix comprising a polymer selected from the group consisting of a water-soluble polymer, a water swellable polymer and combinations thereof, a solvent and an active selected from the group consisting of bioactive actives, pharmaceutical actives, drugs, medicaments and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix;

(c) evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film within about 10 minutes or fewer to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film; and

(d) forming a resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained.

161. A process for making a film capable of being administered to a body surface having a substantially uniform distribution of components, comprising the steps of:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and an active, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix;

(c) evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film within about 10 minutes or fewer to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film;

(d) forming a resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained; and

(e) administering said resulting film to a body surface.

Claims 1, 82 and 161 recite a step of forming a flowable polymer matrix comprising a recited polymer, a solvent and an active, said matrix having a substantially uniform distribution of said active. With respect to the "matrix", the '080 patent, for example, states the following:

> When the active is combined with the polymer in the solvent, the type of matrix that is formed depends on the solubilities of the active and the polymer. If the active and/or polymer are soluble in the selected solvent, this may form a solution. However, if the components are not soluble, the matrix may be classified as an emulsion, a colloid, or a suspension (see col. 22, lines 22-28).
>
> After the desired components are combined to form a multi-component matrix, including the polymer, water, and an active or other components as desired ... (see col. 25, lines 55-57).

Accordingly, the "matrix" is taken to be the material that results from mixing the polymer, solvent and active.

With respect to viscoelasticity in steps (d) and (e) of claim 1 and in steps (c) and (d) of claims 82 and 161, it is noted that the matrix prior to evaporating the solvent (water) may be viscoelastic, and the viscoelasticity is present due, for example, to the fact that a hydrocolloid has been added. In particular, the '080 patent teaches the following (bold emphasis added):

> The viscosity of the liquid phase is critical and is desirably modified by customizing the liquid composition to a **viscoelastic** non-Newtonian fluid with low yield stress values .... Formation of a **viscoelastic** or a highly

> structured fluid phase provides additional resistive forces to particle sedimentation. (Col. 8, lines 32-38).
>
> The addition of hydrocolloids to the aqueous phase of the suspension increases viscosity, may produce **viscoelasticity**, and can impart stability depending on the type of **hydrocolloid**, its concentration and the particle composition, geometry, size and volume fraction. (Col. 8, lines 42-46).
>
> For **viscoelastic** fluid systems, a rheology that yields stable suspensions for extended time period, such as 24 hours, must be balanced with the requirements of high-speed film casting operations. (Col. 8, line 66 through Col. 9, line 2).
>
> The rheology requirements for the inventive compositions and films are quite severe. This is due to the need to produce a stable suspension of particles, for example 30-60 wt. %, in a **viscoelastic** fluid matrix with acceptable viscosity values throughout a broad shear rate range...
>
> In film casting or coating, rheology is also a defining factor with respect to the ability to form films with the desired uniformity. Shear viscosity, extensional viscosity, **viscoelasticity**, structural recovery will influence the quality of the film. (Col. 9, lines 9-20).
>
> Desirably, the films or film-forming compositions of the present invention have a very rapid structural recovery, i.e. as the film is formed during processing, it doesn't fall apart or become discontinuous in its structure and compositional uniformity. Such very rapid structural recovery retards particle settling and sedimentation. Moreover, the films or film-forming compositions of the present invention are desirably shear-thinning pseudoplastic fluids. Such fluids with consideration of properties, such as **viscosity and elasticity**, promote thin film formation and uniformity. (Col. 9, lines 31-40).
>
> Compositions P-R show the effects of **visco-elastic** properties on the ability to coat the film composition mixture onto the substrate for film formation .... This product coated the substrate but would not stay level due to the change in the **visco-elastic** properties of the wet foam. (Col. 35, lines 55-57, and 61-63).

While the '080 does not state what is an example of a hydrocolloid, a well-known hydrocolloid in the art is the water-soluble polymer hydroxypropyl methylcellulose (HPMC), which is used in most of the examples of the '080

patent. The Chen reference teaches that HPMC is a hydrocolloid (see p. 14, lines 22-27).

The preamble of claims 1, 82 and 161 recite "for making a film having a substantially uniform distribution of components". These claims later recite "locking-in or substantially preventing migration" of the active, and also recite that the matrix has a "substantially uniform distribution of the active". None of these terms is given a special definition in the '080 patent. However, the '080 patent teaches at col. 31, lines 37-44, that a "uniform distribution of components" can be determined by examination by either the naked eye or under slight magnification, and that "by viewing the films it was apparent that they were substantially free of aggregation, i.e. the carrier and the actives remained substantially in place and did not move substantially from one portion of the film to another ... [t]herefore, there was substantially no disparity among the amount of active in any portion of the film." An alternative means for evaluating uniformity is to cut the film into individual doses and measure the weight of the doses (col. 31, line 46 through col. 32, line 45). The '080 patent notes that "films of substantially similar size cut from different locations of the same film contain substantially the same amount of active." (col. 32, lines 37-39).

Claims 16 and 32 are identical. So are claims 95 and 111; and claims 177 and 193.

Proposed Claim Rejections - 35 USC § 102 and § 103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1. Claims 1, 4, 5, 8-18, 20-32, 34, 36-40, 44-47, 51, 53, 54, 59, 62-71, 82-84, 87-97, 99-111, 113, 115-119, 123-126, 130, 132, 133, 138, 141-150, 161-166, 169-179, 181-193, 195, 197-201, 205-208, 212, 214, 215, 220, 223-232, 243, 244, 246, 247, 249-262, 264, 265, 267-280, 282, 283 and 285-299 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Chen.

The rejection of claims 1, 4, 5, 8-18, 20-32, 34, 36-40, 44-47, 51, 53, 54, 59, 62-71, 82-84, 87-97, 99-111, 113, 115-119, 123-126, 130, 132, 133, 138, 141-150, 161-166, 169-179, 181-193, 195, 197-201, 205-208, 212, 214, 215, 220, 223-232, 243, 244, 246, 247, 249-262, 264, 265, 267-280, 282, 283 and 285-299 under 35 USC 102(b) over Chen and the rejection of claims 65-69, 71, 144-148, 150, 226-230, 232, 253, 271 and 289 under 35 USC 103(a) over Chen

were proposed by Third Party Requester and **are adopted** for the reasons that follow. The rejection of claims 1, 4, 5, 8-18, 20-32, 34, 36-40, 44-47, 51, 53, 54, 59, 62-64, 70, 82-84, 87-97, 99-111, 113, 115-119, 123-126, 130, 132, 133, 138, 141-143, 149, 161-166, 169-179, 181-193, 195, 197-201, 205-208, 212, 214, 215, 220, 223-225, 231, 243, 244, 246, 247, 249-252, 254-262, 264, 265, 267-270, 272-280, 282, 283, 285-288 and 290-299 under 35 USC 103(a) over Chen is Examiner initiated.

Chen teaches a dosage unit including a water-soluble hydrocolloid, mucosal surface-coat-forming film, such film including an effective dose of an active agent (see p. 3, lines 30-32). In Examples 5-8, Chen prepares hydroxypropyl methylcellulose (HPMC, i.e., "Methocel E5") based quick dissolving intraoral films containing active agents (see p. 20, lines 17-20 and Tables 5 and 7). In particular, the films in Examples 5-8 contain an active agent, e.g., nicotine, hydromorphone, oxybutynin or estradiol; HPMC; and a solvent, i.e., water (see Tables 5 and 7). Further, the film in Tables 7 and 8 of Chen uses sildenafil citrate as an active ingredient and is prepared using HPMC, i.e. "Methocel E15", and water as the solvent. The film in Chen's Example 1 contains HPMC; peppermint, citric acid and aspartame as actives; and water as the solvent (see Tables 1 to 4). The film in Chen's Example 2 contains "Pullalan (P-20) [sic, Pullulan (P-20)]" as the polymer; peppermint, citric acid and aspartame as actives; and water and ethanol as solvents (see Tables 1 and 2). Peppermint, citric acid and aspartame are also actives in Chen's Examples 5-8, and peppermint and aspartame are actives in the film in Chen's Tables 7 and 8.

Under the category of "Actives", the '080 patent teaches flavors such as mint oil, flavor enhancers such as citric acid, and sweeteners such as aspartame (see col. 21, lines 35-63 and col. 22, lines 9-13). Peppermint is also a breath freshener; and the '080 patent teaches that breath fresheners are drugs (col. 20, lines 35-38). Additionally, peppermint has a high menthol content, and the '080 patent teaches menthol is a breath freshener (col. 21, lines 35-36). Other taste modifying agents, i.e., taste masking agents, are disclosed at p. 10, lines 7-14 of Chen.

The specific water-soluble polymer, solvent and actives exemplified in Chen are identical to those exemplified in the '080 patent. HPMC is employed in almost every example of the '080 patent. HPMC and pullulan are taught by the '080 patent as being water soluble (col. 15, lines 45-57). The same solvent, i.e., water is employed in almost every example in the '080 patent. Sildenafil is exemplified in Examples CI and FB of the '080 patent (see Tables 16 and 30). Likewise, peppermint oil and/or sweetener are used in numerous examples in the '080 patent, such as Examples A, B, C, D, F, G, H, BA, BB, BC, etc (see Tables 1 and 9).

The following is a list of hydrocolloid polymers, including said HPMC and pullulan, disclosed by Chen for forming the film (see p. 14, line 12 through page 15, line 3):

> In embodiments of the invention, the hydrocolloid may be a water soluble non-gelling (at room temperature) natural polysaccharide or derivatives including pectin and derivatives, guar gum arabic, tragacanth gum, xanthan gum, gellan sodium salt, propyleneglycol alginate, starches (amylose, amylopectin), modified starches, hydroxyethyl starch, pullulan,

> carboxymethyl starch, gum ghatti, okra gum, karaya gum, dextrans, dextrins and maltodextrins, konjac, acemannan from aloe, locust bean gum, tara gum, quince seed gum, fenugreek seed gum, scleroglucan, gum arabic, psyllium seed gum, tamarind gum, oat gum, quince seed gum, carrageenans, scleraglucan, succinoglucan, larch arabinogalactan, flaxseed gum, chondroitin sulfates, hyaluronic acid, curdlan, chitosan, deacetylated konjac, and rhizobium gum.
>
> In embodiments of the invention, the hydrocolloid may be a water soluble non-gelling polypeptide or protein exemplified by gelatins, albumins, milk proteins, soy protein, and whey proteins. The hydrocolloid may further be selected from a group of synthetic hydrocolloids exemplified by any of the following: polyethylene-imine, hydroxyethyl cellulose, sodium carboxymethyl cellulose, carboxymethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, methyl cellulose, ethyl cellulose, polyacrylic acids, low molecular weight polyacrylamides and their sodium salts (carbomers), polyvinylpyrollidone, polyethylene glycols, polyethylene oxides, polyvinyl alcohols, pluronics, tetronics, and other block co-polymers, carboxyvinyl polymers, and colloidal silicon dioxide. A preferred embodiment of the invention utilizes a hydroxypropyl methyl cellulose having a methoxy content of about 19-30% and hydroxypropyl content of 7-12% and a molecular weight of approximately 50,000-250,000 daltons (Table 9).

In addition to the specific active materials noted above, i.e., nicotine, hydromorphone, oxybutynin, estradiol, sildenafil citrate, peppermint, citric acid and aspartame, the following is a list of active agents disclosed by Chen (see p. 10, line 22 through page 11, line 12):

> Active agents (for human and veterinary applications) include therapeutic agents, nutritional supplements and hygiene aids. The therapeutic agents are exemplified by analgesics, a-adrenergic receptor blockers, anti-Alzheimer's disease medication, antianginal, antianxiety, antiarrythmics, antiarthritics, antibiotics, anticoagulants/thrombolytics, anticonvulsants/anti-Parkinson medication, anti-depressants, anti-diabetics, anti-diarrheal, anti-epileptics, anti-fungal, anti-gout, anti-heartworm medication for dogs, anti-histamines, anti-hypertensives, anti-inflammatories, anti-infectives, antimigraines, anti-nasuants/anti-emetics, anti-neoplastics/anti-tumor active agents, anti-pruitics, anti-psychotics, anti-pyretics, anti-spasmodics, anti-virals, bronchial dilators/anti-asthmatics, calcium antagonists, cardiac agents, cardiotonics, central

> nervous system actives, contraceptives, coronary vasodilators, cough/cold remedies, dietary supplements, including vitamins and minerals, diuretics, fertility active agents, flea control agents for animals (Ivermectin), H_2 receptor antagonists, herbal actives, hormones, hypoglycemics, hypolipidemics, muscle relaxants, ovulation stimulators, peptide active agents, polypeptide active agents, proteins such as insulin, calcitonin, LHRH and the like. Sedatives and hypnotics, sexual dysfunction active agents, sleep aids, smoking cessation aids, steroids and steroidals, tranquilizers, laxatives, ophthalmic preparations, nutritional supplements, breath fresheners, breath deodorants, saliva substitutes, antigingivitis agents, anti-cavity agents, anti-plaque agents, diagnostic indicators, and local anesthetics. Also included are active agents for treatment of osteoporosis, hormone replacement, treatment of periodontal disease, antiseptics, corticosteroids, non steroidal anti-inflammatory agents, antiviral agents and vaccines.
> In the method of preparation of the films, the HPMC or pullulan, which

Chen teaches is a hydrocolloid, is dissolved in water under agitated mixing to form a uniform and viscous solution which reads on the instant masterbatch pre-mix, and the additional ingredients are added under agitated mixing until they are uniformly dispersed (i.e., suspended) or dissolved in the hydrocolloid (see p. 14, line 22 through p. 15, line 3; and p. 17, lines 6-19). The resultant mixture, i.e. the instant flowable polymer matrix, is degassed in a vacuum chamber until trapped air bubbles are removed, and then coated, i.e., casted as per step (b) of claims 82 and 161 and as per step (c) of claim 1, on the non-siliconized side of a polyester film (see p. 17, lines 13-15).

With respect to steps (c) and (d) of claims 82 and 161, and with respect to steps (d) and (e) of claim 1, Chen evaporates water from the cast matrix in 9 minutes of drying in a hot air circulating oven at 50°C (see p. 17, lines 13-15 and Fig. 2). As seen schematically in Chen's Fig. 2, the air flow is less direct at the film surface at the beginning of the drying and becomes more direct as the film

proceeds through the drying oven, which has an aeration controller (see also p. 5, line 31 through p. 6, line 3). Chen's Example 1 starts with 74.42% water content and is dried to 1.7% water content (see Tables 1 and 4). Chen's Examples 5 to 8 start with 73.03%, 71.51%, 70.72% and 72.94% water content and are dried to 2.93%, 2.42%, 2.32% and 2.31% water content, respectively. Chen's Example 2 starts with 10.6% ethanol and 67.025% water and, after drying for 9 minutes at 50°C, the water content is 8.5% (see Tables 1 and 2).

The claimed "substantially uniform distribution of components" and "locking-in or substantially preventing migration" of the active in independent claims 1, 82 and 161, and the variation of active content of 10% or less in dependent claims 254-255, 272-273 and 290-291, are inherent in Chen's exemplified films and process. Inherency is based on the following: As discussed above, Chen uses the same materials and method as here claimed. Chen's ingredients are mixed until they are uniformly dispersed or dissolved in the hydrocolloid (p. 17, lines 8-11). Chen uses the same criteria discussed above with respect to the '080 patent in the Scope of Claims section for evaluation of substantial uniform distribution, i.e., weight of dosages and visual inspection. In particular, Chen's dried film product of Example 1 is cut into dosage units ready for packing (p. 17, lines 31-32) and has a weight of 0.028 $\pm$ 0.001 g/dosage film, a density of 1.0485 $\pm$ 0.009 g/cm^2, a water content of 1.7 $\pm$ 0.24%, and as noted above, a thickness of 2.1 $\pm$ 0.12 mil (see Table 4); and the dried films are glossy and substantially transparent (p. 17, line 15), i.e., they are visually free of aggregation. The 0.028 $\pm$ 0.001 g/dosage film has variation of

(0.001/0.028) x 100 = 3.6%. When film weight is rounded to two decimal places as in Table 2 at col. 31 of the '080 patent, then the weight is 0.03 gram/dosage film with a variation of 0%.

Furthermore, as noted in the Rule 1.132 Declaration of Edward D. Cohen (hereafter "Cohen Declaration") submitted with the request, when working with a homogeneous or completely dissolved coating mixture as in Chen, it would be difficult for a person of ordinary skill in the film art not to obtain a film that has a uniform content of active, and the drying method disclosed in Chen would not be expected to create any agglomeration, aggregation or otherwise non-uniform content of active (see ¶¶ 8-10).

Further with respect to steps (c) and (d) of claims 82 and 161 and steps (d) and (e) of claim 1, and with respect to viscoelasticity, either Chen's mixture before drying is viscoelastic and the resulting dried film also is viscoelastic, or alternatively, if Chen's mixture before drying is not viscoelastic, then it becomes viscoelastic as the drying proceeds.

In particular, as noted above, the '080 patent teaches that "[t]he addition of hydrocolloids to the aqueous phase of the suspension increases viscosity, may produce viscoelasticity, and can impart stability depending on the type of hydrocolloid, its concentration and the particle composition, geometry, size and volume fraction (see col. 8, lines 42-46). Chen adds the same hydrocolloid as in the '080 patent, i.e. said HPMC, to water, and Chen's wet matrix before drying has a viscosity of 500-15,000 cps (p. 15, line 26), which is within the '080 patent's disclosed range of about 400-100,000 cps and overlaps the most

preferred range of about 1,000-40,000 cps (see the paragraph bridging cols. 16 and 17 of the '080 patent). Accordingly, Chen's films in Examples 1, 2 and 5-8 and the Example in Tables 7 and 8 are inherently viscoelastic before drying.

Alternatively, to the extent that Chen's wet film in Examples 1, 2, 5-8 and the example in Tables 7 and 8 before drying are not viscoelastic, then at some time during the 9 minutes of drying in the hot air circulating oven at 50°C, a viscoelastic film is inherently formed. In particular, in order to arrive at a dried film product as in Chen, which is made using the same materials as disclosed in the '080 patent and the same basic process steps here claimed, wherein the dried film is glossy and substantially transparent and has the gram per dosage, thickness, density and water content noted above for Example 1, then a viscoelastic film is inherently formed during Chen's 9-minute drying.

While Chen does not discuss viscoelasticity or that the films resulting from its process have a "substantially uniform distribution of components" or disclose "locking-in or substantially preventing migration" of the active, Chen, as cited above, discloses a process which reasonably appears to be either the same as or an obvious variation of the instantly claimed process. Accordingly, claims 1, 4, 5, 8-18, 20-32, 34, 36-40, 44-47, 51, 53, 54, 59, 62-71, 82-84, 87-97, 99-111, 113, 115-119, 123-126, 130, 132, 133, 138, 141-150, 161-166, 169-179, 181-193, 195, 197-201, 205-208, 212, 214, 215, 220, 223-232, 243, 244, 246, 247, 249-262, 264, 265, 267-280, 282, 283 and 285-299, if not anticipated under 35 USC 102(b), would be obvious under 35 USC 103(a).

With respect to claims 16, 32, 95, 111, 177 and 193, which require that the active is a biological response modifier, it is noted that all of the actives listed by Chen at p. 10, line 22 through page 11, line 12 are biological response modifiers. Alternatively, biological response modifiers are well-known actives in the art. It would have been obvious to one of ordinary skill in the art to have used any well-known active, such as a biological response modifier, as the active in Chen's film with the resulting expectation of preparing a film for delivery of the agent and so as to take advantage of the agent's known function.

With respect to claims 25, 104 and 186, which require that the active is an anti-tussive, Chen, as noted above, teaches that its active can be a cough/cold remedy (see p. 10, line 32 through page 11, line 1). A cough/cold remedy encompasses and thus, anticipates or renders obvious an anti-tussive, i.e., cough relieving/depressing, agent.

With respect to claims 65-69, 144-148 and 226-230, which require that the active is coated with a controlled release composition, Chen discloses that its films may release the active agent over a period of time that is determined by a number of different factors (see page 6, line 30 through page 7, line 21). More specifically, Chen discloses: "Depending on the optimal program for a specific application of the invention, the disintegration time and the dissolution time can be controlled within a prescribed range by adjustment of the formulation and the thickness of the film. In some cases, it is desirable for release of the active agent to occur after dissolution of the film. For these applications, the active agent may be encapsulated in a material with dissolution properties that are different from

those of the hydrocolloid. Encapsulation of the active agent may also be utilized to achieve masking of taste for active agents that are bitter. In some cases, two or more different active agents may be included in the film." (See page 9, lines 9-16). Slow release films are also discussed, e.g., at page 7, lines 16-21. Accordingly, immediate, delayed, sustained or sequential release of active as here claimed, if not anticipated by the teachings of Chen, would have been obvious so as to obtain a desired release of the active(s).

With respect to claims 70, 149, 231, 259, 260, 277, 278 and 295-297, Chen teaches that the active material can be in the form of a particle, e.g., a colloid particle or microencapsulated (see p. 7, lines 17-21). As noted above, Chen's polymers such as HPMC are hydrocolloids (p. 14, line 24-31), and Chen's matrix has the ingredients uniformly dispersed, i.e., suspended, in the hydrocolloid (p. 17, lines 6-11).

With respect to claims 71, 150 and 232, which require the addition of a degassing agent, as noted above Chen teaches peppermint (see p. 10, line 9; Examples 1-8 and the example in Tables 7 and 8). During prosecution US patent application Serial No. 11/858,214, Patent Owner admits that peppermint is a foam reducing flavoring agent which "act[s] to both flavor the film and prevent and/or remove air from the film-forming compositions." (See the last paragraph on p. 5 of the response filed 12/20/10 and claim 5 of the 11/858,214 application).

With respect to claims 162, 163, 249-252, 258, 267-270, 276, 285-288 and 294, Chen teaches that the films are suitable for administration of the active material through buccal, gingival, sublingual and mucosal surfaces (see p. 8,

lines 4 and 9-10, and Fig. 1). With respect to claim 164, Chen teaches that the mucosal surface can be a wound (see p. 7, lines 31-32).

With respect to claim 253, 271 and 289, which require that the film provides administration of the active within the body of the individual during surgery, as noted above, Chen teaches that its films can be applied to a mucosal surface, which refers to any moist surface in the body, including a wound (see p. 7, lines 31-32 and p. 8, line 4). Accordingly, Chen's films can be administered at any time, including surgery. Chen discloses several active agents that are highly suitable for use "during surgery", including sedatives, local anesthetics, antiseptics, anti-inflammatory agents, anti-viral agents, muscle relaxants, and steroids (see p. 10, line 29 through p. 11, line 12). Further, Chen teaches that "[e]mbodiments of the invention include .... for a quick dissolving film for local and systemic delivery of pharmaceutical agents to a mucosal surface in a subject .... The dosage unit of the invention may be applied to any mucosal surface as deemed appropriate for the systemic or local delivery of an active agent including vaginal, rectal and ocular surfaces ... [e]mbodiments [may be administered easily by] physicians, parents, patients ..." (*see* p. 8, lines 2-4, 6-10, and 19-20). Chen also teaches the application of films to a wound surface "where lymph fluid bathes the tissue surface" at p. 7, lines 32 through p. 8, line 1. Thus, Chen anticipates or renders obvious that its film "provides administration of said active to an individual by administration within the body of the individual during surgery" as here claimed.

2. Claims 2, 3, 6, 7, 19, 33, 35, 41-43, 48-50, 52, 55-58, 60, 61, 85, 86, 98, 112, 114, 120-122, 127-129, 131, 134-137, 139, 140, 167, 168, 180, 194, 196, 202-204, 209-211, 213, 216-219, 221, 222, 245, 248, 263, 266, 281 and 284 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen.

This rejection was proposed by Third Party Requester and **is adopted** for the reasons that follow.

Chen, as relied upon for the reasons stated above, teaches the limitations of the instant claims other than the differences discussed below.

With respect to claims 2 and 3, Chen does not specifically teach that its premix of polymer and solvent, i.e., instant masterbatch premix, is controllably fed via a first metering pump and a control valve to a first mixer and a second mixer, and that the first and second mixers are arranged in parallel, series or a combination thereof.

However, metering pumps, mixing vessels and control valves are standard equipment in the art, and so is their arrangement in parallel, series or a combination thereof. Accordingly, it would have been obvious to one of ordinary skill in the art at the time was made to have used metering pumps, mixing vessels and control valves when preparing Chen's wet film because such equipment is standard in the art, and so as to mix Chen's masterbatch premix and active.

With respect to claims 6, 7, 85, 86, 167 and 168, Chen does not specifically teach using combinations of its hydrocolloids, such as a mixture of

the exemplified HPMC with any of the other hydrocolloids taught by Chen such as ethylcellulose, polyacrylic acid polymer, etc.

However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have used combinations of Chen's hydrocolloids in place of a single hydrocolloid with the expectation that a film for mucosal delivery of active agent would be obtained. The rationale to use a combination of Chen's hydrocolloids flows logically from their each having been individually taught as useful as the hydrocolloid component of Chen's film.

The remaining claims in this rejection, i.e., claims 19, 33, 35, 41-43, 48-50, 52, 55-58, 60, 61, 98, 112, 114, 120-122, 127-129, 131, 134-137, 139, 140, 180, 194, 196, 202-204, 209-211, 213, 216-219, 221, 222, 245, 248, 263, 266, 281 and 284 are directed to particular active materials. These active agents are either well-known in the art or are species of the generic active agents taught by Chen at p. 10, line 22 through p. 11, line 12. See also the discussion of these claims in the claim chart of the request on pp. 77-82 and 84-89, which are hereby incorporated by reference.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have used the actives here claimed so as to prepare Chen's film because such actives are well-known in the art or are species of the generic active agents taught by Chen; the reasonable expectation of success in preparing a film for mucosal delivery of the active; and so as to take advantage of the active's known function.

3. Claims 2, 3, 16, 32, 55, 72-81, 95, 111, 134, 151-160, 177, 193, 216 and 233-242 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teaching of Chen and Staab.

On pages 89-105 of the request, Third Party Requester proposes that claims 1-3, 16, 32, 55, 65-69, 72-75, 78-82, 95, 111, 134, 144-148, 151-154, 157-161, 177, 193, 216, 226-230, 233-236, 239-242, 254, 255, 257-259, 272, 273, 275-277, 290, 291 and 293-295 be rejected under 35 USC 103(a) as being obvious over the combined teachings of Chen and Staab. Likewise, on pages 143-151 of the request, Third Party Requester proposes that claims 1, 8, 9, 17, 71, 82, 87, 88, 96, 150, 161, 169, 170, 178, 232, 260, 278 and 296-299 be rejected under 35 USC 103(a) as being obvious over the combined teachings of Chen and Staab. For the reasons that follow, the proposed rejection of claims 1, 8, 9, 17, 65-69, 71, 82, 87, 88, 96, 144-148, 150, 161, 169, 170, 178, 226-230, 232, 254, 255, 257-260, 272, 273, 275-278, 290, 291 and 293-299 **is not adopted**. For the reasons that follow, the proposed rejection of claims 2, 3, 16, 32, 55, 72-75, 78-81, 95, 111, 134, 151-154, 157-160, 177, 193, 216, 233-236 and 239-242 **is adopted**. The rejection of claims 76, 77, 155, 156, 237 and 238 is Examiner initiated.

As noted above, Chen anticipates or renders obvious claims 1, 8, 9, 17, 65-69, 71, 82, 87, 88, 96, 144-148, 150, 161, 169, 170, 178, 226-230, 232, 254, 255, 257-260, 272, 273, 275-278, 290, 291 and 293-299. Reliance on the teachings of Staab is not needed to reject these claims, and thus, the proposed rejection of claims 1, 8, 9, 17, 65-69, 71, 82, 87, 88, 96, 144-148, 150, 161, 169,

170, 178, 226-230, 232, 254, 255, 257-260, 272, 273, 275-278, 290, 291 and 293-299 over the combined teachings of Chen and Staab is not adopted.

With respect to claims 2 and 3, to the extent that Chen does not render obvious controllably feeding its master batch pre-mix via a metering pump and a control valve to a first mixer and a second mixer such that the first and second mixer are arranged in parallel, series or a combination thereof, then such is rendered obvious in combination with the teachings of Staab.

Staab teaches films made of dissolvable polymer material and/or complex carbohydrate material which are food grade materials, wherein the films also contain an agent such as a drug or medication (see abstract). Staab teaches that "[t]he agent material is evenly distributed throughout the film, so as the film slowly dissolves, it releases the agent material in the proper dosage ...." (see col. 5, line 68 through col. 6, line 3). Staab also discloses that "[t]he device of the invention thus is composed of a biologically compatible material that has been blended homogeneously" with the drug (see col. 6, lines 6-10). Staab teaches forming a pre-mix including a water soluble polymer and water in proper concentrations at a first temperature in a first vessel and then transferring to another vessel of a cooler temperature (in series with the first vessel), and then stirring in heat sensitive ingredients (see col. 7, lines 37-48). Staab's Fig. 5 depicts three mixing vessels that can readily be employed for practicing the claimed method, the top two vessels being in parallel with each other, the lower vessel being in series with the top two vessels. Any transfer from one vessel to another would inherently or obviously involve a metering pump and control valve.

Arrangement of the vessels in parallel would accommodate a choice of heat sensitive ingredients, such as those disclosed in Staab (see col. 7, lines 37-51).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have prepared Chen's matrix by forming a pre-mix including a water soluble polymer and water in proper concentrations at a first temperature, then to have transferred the contents of the vessel to another vessel of a cooler temperature, and then to have stirred in heat sensitive ingredients, e.g., drug(s) as in Staab, so as to protect the drug(s), which is usually the most expensive component.

With respect to claims 16, 32, 95, 111, 177 and 193, to the extent that Chen does not teach or render obvious that its active can be a biological response modifier, then such is rendered obvious in combination with the teachings of Staab. Likewise, with respect to claims 55, 134 and 216, to the extent that Chen does not teach or render obvious that its active can be a decongestant, then such is rendered obvious in combination with the teachings of Staab.

Staab teaches that its active agent can be monoclonal antibodies, i.e., biological response modifiers, such as those useful against cell surface components or against pathogenic organisms such as HIV (see col. 6, lines 49-53). Likewise, Staab teaches that its active agent can be a decongestant (see col. 7, line 1).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have used a monoclonal antibody or decongestant for

Chen's active because such actives are conventional in the art, as shown by Staab; so as to take advantage of the active material's known function; and the reasonable expectation of success.

With respect to claims 72-81, 151-160 and 233-242, Chen does not specifically teach providing a second film layer. Staab teaches that its film may be a laminate of two or more layers (see col. 5, lines 30-31; col. 9, lines 28-43; and Fig. 2). Staab teaches that the laminates can be formed in the conventional manner, for example the mixture in liquid form is poured or cast onto a plate or into a mold and allowed to begin to set, at which time another liquid mixture with different composition is poured on the first mixture, and both mixtures are allowed to set up completely producing a laminate or layers of different materials (see col. 5, lines 51-58). The extruding and spraying of the second film in claims 76, 77, 155, 156, 237 and 238 are conventional methods that are obvious variants of the pouring and casting exemplified by Staab.

Staab teaches that the first and second layers can comprise an active. In particular, referring to Fig. 2, Staab teaches the following at col. 9, lines 28-43:

> A first film layer 13 is made of, for example, a faster dissolving polymer material for release of a drug material 14a. A second film layer 15 is made of slower dissolving polymer material for release of more drug or another drug material 14b in combination, for example, a spermicide and an anti-infective or anti-inflammatory medication. A third (and additional) layer(s) 16 with additional drug can also be employed for sustained release of the drug.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have laminated a second film to Chen's drug-containing

film as per the teachings of Staab so as to control the release rate of the drug, provide for release of more drug, or provide for release of another drug in addition to the drug in Chen's film.

4. On pages 105-108 and 200-208 of the request, Third Party Requester proposes that claims 1, 8, 9, 17, 45, 53, 71, 82, 87, 88, 96, 124, 132, 150, 161, 169, 170, 178, 206, 214, 232, 254, 272 and 290 be rejected under 35 USC 103(a) as being obvious over the combined teachings of Chen and Le Person.

This proposed rejection **is not adopted** for the reasons that follow.

As noted above, Chen anticipates or renders obvious claims 1, 8, 9, 17, 45, 53, 71, 82, 87, 88, 96, 124, 132, 150, 161, 169, 170, 178, 206, 214, 232, 254, 272 and 290. While it is acknowledged that Le Person further teaches, for example, the use of infrared drying (p. 258, col. 1), none of said claims is limited to this feature. Accordingly, the teachings of Le Person are not needed to reach the limitations of said claims, and thus, the proposed rejection of said claims over the combined teachings of Chen and Le Person is not adopted.

5. On pages 227-236 of the request, Third Party Requester proposes that claims 1, 4, 13, 15, 17, 45, 53, 71, 82, 83, 92, 94, 96, 124, 132, 150, 161, 165, 174, 176, 178, 206, 214 and 232 be rejected under 35 USC 103(a) as being obvious over the combined teachings of Chen and Horstmann.

This proposed rejection **is not adopted** for the reasons that follow.

As noted above, Chen anticipates or renders obvious claims 1, 4, 13, 15, 17, 45, 53, 71, 82, 83, 92, 94, 96, 124, 132, 150, 161, 165, 174, 176, 178, 206, 214 and 232. While it is acknowledged that Horstmann teaches, for example, forming a homogeneous mixture (col. 5, lines 1 and 44; and col. 6, line 9), so does Chen (p. 17, lines 6-11). Accordingly, reliance on the teachings of Horstmann is not needed, and thus, the proposed rejection of said claims over the combined teachings of Chen and Horstmann is not adopted.

6. Claims 1-5, 10, 12-16, 21, 24, 25, 32, 44-46, 54, 55, 59, 63-70, 72-75, 78-84, 89, 91-95, 100, 103, 104, 111, 123-125, 133, 134, 138, 142-149, 151-154, 157-166, 171, 173-177, 182, 185, 186, 193, 205-207, 215, 216, 220, 224-231, 233-236, 239-242, 249-252, 254, 255, 257-260, 267-270, 272, 273, 275-278, 285-288, 290, 291 and 293-299 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Staab.

The rejection of claims 1-5, 10, 12-15, 21, 24, 25, 44-46, 54, 55, 59, 63-70, 72-75, 78-84, 89, 91-94, 100, 103, 104, 123-125, 133, 134, 138, 142-149, 151-154, 157-166, 171, 173-176, 182, 185, 186, 205-207, 215, 216, 220, 224-231, 233-236, 239-242, 249-252, 254, 255, 257-260, 267-270, 272, 273, 275-278, 285-288, 290, 291 and 293-299 under 35 USC 102(b) as anticipated by Staab and the rejection of claims 16, 32, 95, 111, 177 and 193 under 35 USC 103(a) as being obvious over Staab were proposed by Third Party Requester and **are adopted** for the reasons that follow. The 35 USC 102(b) rejection of

claims 16, 32, 95, 111, 177 and 193 and the 35 USC 103(a) rejection of claims 1-5, 10, 12-15, 21, 24, 25, 44-46, 54, 55, 59, 63-70, 72-75, 78-84, 89, 91-94, 100, 103, 104, 123-125, 133, 134, 138, 142-149, 151-154, 157-166, 171, 173-176, 182, 185, 186, 205-207, 215, 216, 220, 224-231, 233-236, 239-242, 249-252, 254, 255, 257-260, 267-270, 272, 273, 275-278, 285-288, 290, 291 and 293-299 are Examiner initiated.

Staab teaches the preparation of a film for local administration of an active agent in an internal body area (see col. 2, lines 34-62). Staab teaches films made of dissolvable polymer material, e.g., PEO and/or HPMC, both of which are identified as water soluble polymers in the '080 patent at col. 15, lines 50-51, and Staab's film also contains a drug or medication as the active agent (see Abstract; and col. 2, lines 34-46). Staab teaches that "[t]he agent material is evenly distributed throughout the film, so as the film slowly dissolves, it releases the agent material in the proper dosage..." (See col. 5, line 68 through col. 6, line 3). Staab teaches that "the polymer solids, water, or other solvent, contraceptive [i.e., an active]..., are admixed in the proper concentrations and the mixture heated to the appropriate temperature for dissolution and formation of a uniform blend to take place." (See col. 7, lines 37-41). In the Example at cols. 11-12, the ingredients are mixed together in a blender until just blended (see col. 11, lines 222-27). As such, Staab teaches formation of a flowable polymer matrix. A masterbatch pre-mix as in instant claim 1 can be formed containing polymer and solvent, and the pre-mix is then transferred to a cooler vessel for addition of heat-sensitive pharmaceuticals or other agents (see col. 7, lines 37-51). Other

polymers that can be used along with PEO and/or HPMC include polyvinyl alcohol (see col. 2, line 41; and col. 4, lines 22-61).

The active agents that can be used in Staab's film include spermicides for contraceptive use and/or drugs or medications (see col. 5, lines 66-68). The following is a list of active agents taught by Staab at col. 6, line 35 through col. 7, line 3:

> (1) anti-infectives such as antibiotics, sulfonamides, antivirals, antifungals, antiprotozoan and antibacterials;
>
> (2) anti-inflammatories, such as hydrocortisone, dexamethasone, triamcinolone, and various prednisolone compounds;
>
> (3) estrogenic steroids, such as estrone;
>
> (4) progestational agents, such as progesterone;
>
> (5) prostaglandins;
>
> (6) coronary vasodilators;
>
> (7) antitussives;
>
> (8) antihistamines;
>
> (9) anesthetics and
>
> (10) decongestants.
>
> Monoclonal antibodies [which are biological response modifiers] such as those useful against cell surface components or against pathogenic organisms such as the human-immuno-deficiency (HIV) family of viruses may be incorporated into the device of the present invention ... . Other drugs include clotrimazole, miconazole, ticonazole, benzalkonium chloride, nystatin, dermally active steroids, hormones, benzocaine, sulfas, biologically prepared actives, decongestants, cough/cold remedies, psychotropics, nitroglycerine, etc.

Staab also teaches the use of flavors, fragrances and coloring agents (see col. 7, lines 28-29). Thus, Staab's active material can be taste-masked.

Staab also discloses that "[t]he device of the invention thus is composed of a biologically compatible material that has been blended homogeneously" with the drug (see col. 6, lines 5-10). In the Example at cols. 11-12, Staab prepares a four-foot wide film which is then cut into two inch by two inch films each weighing 190 mg and containing 19 mg of benzalkonium chloride as the active agent (see col. 11, line 52 through col. 12, line 3). Accordingly, Staab's films inherently have the instantly claimed substantially uniform distribution of components and active. Also, in view of the fact that each film contains 19 mg of benzalkonium chloride and in view of said homogeneous blending, the variation of active in the dosage units is 0%, as per claims 254, 255, 272, 273, 290 and 291.

With respect to step (c) in claim 1 and with respect to step (b) in claims 82 and 161, Staab further discloses that "the mixture in liquid form will be poured or cast on to a plate or into a mold..." (See col. 5, lines 51-58 and the casting lines depicted in Fig. 5). In the Example at cols. 11-12, the blended mixture is poured onto a glass plate and spread to an even 3 mil thick film covering the surface of the glass (see col. 11, lines 41-44).

With respect to steps (d) and (e) in claim 1 and with respect to steps (c) and (d) in claims 82 and 161, Staab discloses drying the film in a temperature regulated oven for approximately 20 minutes at 160°F, i.e., 71°C, or for 20 to 40 minutes when using a continuously moving belt that enters a drier (see col. 11, lines 45 and 65). The ingredients blended to prepare the film are 52.5% HPMC,

37.5% glycerin and 10.0% of a 50% aqueous solution of the benzalkonium chloride (see col. 11, lines 30-34). Accordingly, within 10 minutes or fewer (i.e. half the 20 minute drying time), at least a portion of the water has been evaporated to form the film. Since the water content before drying is 5% (i.e., half of the 10% of the 50% aqueous solution of benzalkonium chloride), the dried film must have a water content of 10% or less as here claimed.

Further, either Staab's mixture in the Example at cols. 11-12 before drying is viscoelastic and the resulting dried film also is viscoelastic, or alternatively, if the blended mixture before drying is not viscoelastic, then it becomes viscoelastic as the drying proceeds.

In particular, as noted above, the '080 patent teaches that "[t]he addition of hydrocolloids to the aqueous phase of the suspension increases viscosity, may produce viscoelasticity, and can impart stability depending on the type of hydrocolloid, its concentration and the particle composition, geometry, size and volume fraction (see col. 8, lines 42-46). Staab uses the same hydrocolloid as in the '080 patent, i.e. said HPMC. Accordingly, Staab's film in the Example at cols. 11-12 is inherently viscoelastic before drying. Accordingly, after drying for about 10 minutes, a viscoelastic film having less water that before drying is formed.

Alternatively, to the extent that Staab's blended mixture before drying is not viscoelastic, then within about 10 minutes of the drying, a viscoelastic film is inherently formed. In particular, in order to arrive at a dried film product as in Staab, which is made using the same materials as disclosed in the '080 patent and the same basic process steps here claimed and having a substantially

uniform distribution of components as discussed above, then a viscoelastic film is inherently formed within about 10 minutes of the drying.

While Staab does not discuss viscoelasticity or that the films resulting from its process have a "substantially uniform distribution of components" or disclose "locking-in or substantially preventing migration" of the active, Staab, as cited above, discloses a process which reasonably appears to be either the same as or an obvious variation of the instantly claimed process. Accordingly, claims 1-5, 10, 12-16, 21, 24, 25, 32, 44-46, 54, 55, 59, 63-70, 72-75, 78-84, 89, 91-95, 100, 103, 104, 111, 123-125, 133, 134, 138, 142-149, 151-154, 157-166, 171, 173-177, 182, 185, 186, 193, 205-207, 215, 216, 220, 224-231, 233-236, 239-242, 249-252, 254, 255, 257-260, 267-270, 272, 273, 275-278, 285-288, 290, 291 and 293-299, if not anticipated under 35 USC 102(b), would be obvious under 35 USC 103(a).

Further, with respect to claims 2 and 3, as noted above, Staab teaches a masterbatch pre-mix can be formed containing polymer and solvent, and the pre-mix is then transferred to a cooler vessel, i.e., a second vessel in series, for addition of heat-sensitive pharmaceuticals or other agents (see col. 7, lines 37-51). Staab's Fig. 5 depicts three mixing vessels, the top two vessels being in parallel with each other, the lower vessel being in series with the top two vessels. Any transfer from one vessel to another would inherently or obviously involve a metering pump and control valve.

With respect to claims 65-69, 144-148 and 226-230 which require that the active is coated with a controlled release composition, and with respect to claims

72-75, 78-81, 151-154, 157-160, 233-236 and 239-242 which require providing a second film layer, Staab teaches that its film may be a laminate of two or more layers (see col. 5, lines 30-31; col. 9, lines 28-43; and Fig. 2). Staab teaches that the laminates can be formed in the conventional manner, for example the mixture in liquid form is poured or cast onto a plate or into a mold and allowed to begin to set, at which time another liquid mixture with different composition is poured on the first mixture, and both mixtures are allowed to set up completely producing a laminate or layers of different materials (see col. 5, lines 51-58). Staab teaches that the first and second film can comprise an active. In particular, referring to Fig. 2, Staab teaches the following at col. 9, lines 28-43:

> A first film layer 13 is made of, for example, a faster dissolving polymer material for release of a drug material 14a. A second film layer 15 is made of slower dissolving polymer material for release of more drug or another drug material 14b in combination, for example, a spermicide and an anti-infective or anti-inflammatory medication. A third (and additional) layer(s) 16 with additional drug can also be employed for sustained release of the drug.

Thus, the layers provide for controlled release of the drug material, i.e., a fast and slow release, and thus a sequential release, and also a sustained release. Staab also teaches immediate release since Staab teaches that "in case of medications to be administered via the oral cavity, it is advantageous that dissolution take place fairly rapidly." (See col. 4, lines 59-61). Immediate release and sustained release are also exemplified at col. 13, lines 13-41.

With respect to claims 70, 149, 231, 259, 260, 277, 278 and 295-297, Staab teaches many actives that are particulate, such as monoclonal antibodies

(see col. 5, lines 49-53). The particulate monoclonal antibodies would be dispersed, i.e., suspended, in the matrix during the uniform blending (see col. 6, lines 5-10; col. 7, line 41; and col. 11, lines 26-35). Also, it is noted that polymers such as said PEO and HPMC are hydrocolloids.

With respect to claims 162, 163, 249-252, 258, 267-270, 276, 285-288 and 294, Staab teaches that if the drug can be applied on or in a moist area of the body, such as the mouth, vagina, rectum or eye, then the film can be used to deliver the drug effectively (see col. 7, lines 3-8). Application on or in the mouth either anticipates or renders obvious gingival, sublingual and buccal application. With respect to claim 164, Staab teaches the treatment of burn wounds with its films (see col. 7, lines 7-9).

7. Claims 8, 9, 76, 77, 87, 88, 155, 156, 169, 170, 237 and 238 are rejected under 35 U.S.C. 103(a) as being unpatentable over Staab.

On pages 135-143 of the request, Third Party Requester proposes that claims 6-9, 76, 77, 85-88, 155, 156, 167-170, 237 and 238 be rejected under 35 USC 103(a) as being obvious over Staab. The proposed rejection of claims 6, 7, 85, 86, 167 and 168 **is not adopted** for the reasons that follow. The proposed rejection of claims 8, 9, 76, 77, 87, 88, 155, 156, 169, 170, 237 and 238 **is adopted** for the reasons that follow.

With respect to claims 6, 7, 85, 86, 167 and 168, Staab does not teach or render obvious the combination of polymers required in these claims. Claims 6, 85 and 167 require, in addition to a material such as HPMC, the further presence

of a particular water-insoluble polymer. Staab teaches dissolvable polymers such as PEO, polyvinyl alcohol, and/or a complex carbohydrate such as HPMC (col. 4, line 6 through col. 5, line 29), but does not teach or render obvious the further inclusion of a water-insoluble polymer. The further polymers set forth in claims 7, 86 and 168 are also not taught by Staab, and the combination of these further polymers with, for example, HPMC or polyvinyl alcohol is not rendered obvious by Staab.

Staab is relied upon for the reasons stated above in rejection No. 6.

With respect to claims 8, 9, 87, 88, 169, and 170, Staab teaches that its polymer can be a dissolvable complex carbohydrate (col. 4, line 6 through col. 5, line 29), but does not specifically teach the complex carbohydrates here claimed, such as sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum and starch. However, these are conventional dissolvable polymers in the art. Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have used sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum and/or starch for the dissolvable complex carbohydrate to prepare Staab's film because these are conventional, dissolvable complex carbohydrates in the art and the reasonable expectation of success in preparing Staab's film.

With respect to claims 76, 77, 155, 156, 237 and 238, Staab does not specifically teach that its second film layer is extruded or sprayed onto its first film layer. As noted above, Staab teaches that the laminates can be formed in the conventional manner, for example the mixture in liquid form is poured or cast

onto a plate or into a mold and allowed to begin to set, at which time another liquid mixture with different composition is poured on the first mixture, and both mixtures are allowed to set up completely producing a laminate or layers of different materials (see col. 5, lines 51-58). The instantly claimed extrusion and spraying are well known alternative techniques to coating and casting for forming a layer.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have used extrusion or spraying in place of coating and casting to form Staab's second film layer because extrusion and spraying are well known alternative techniques to coating and casting, and the resulting reasonable expectation of success in preparing Staab's second film layer.

8. On pages 163-199 of the request, Third Party Requester proposes that claims 1-5, 10, 12-16, 21, 24, 25, 32, 44-46, 54, 55, 59, 63-70, 72-75, 78-84, 89, 91-95, 100, 103, 104, 111, 123-125, 133, 134, 138, 142-149, 151-154, 157-166, 171, 173-177, 182, 185, 186, 193, 205-207, 215, 216, 220, 224-231, 233-236, 239-242, 249-252, 254, 255, 257-260, 267-270, 272, 273, 275-278, 285-288, 290, 291 and 293-299 be rejected under 35 USC 103(a) as being obvious over the combined teachings of Staab and Le Person.

This proposed rejection **is not adopted** for the reasons that follow.

As noted above, Staab anticipates or renders obvious claims 1-5, 10, 12-16, 21, 24, 25, 32, 44-46, 54, 55, 59, 63-70, 72-75, 78-84, 89, 91-95, 100, 103,

104, 111, 123-125, 133, 134, 138, 142-149, 151-154, 157-166, 171, 173-177, 182, 185, 186, 193, 205-207, 215, 216, 220, 224-231, 233-236, 239-242, 249-252, 254, 255, 257-260, 267-270, 272, 273, 275-278, 285-288, 290, 291 and 293-299. While it is acknowledged that Le Person further teaches, for example, the use of infrared drying (p. 258, col. 1), none of said claims is limited to this feature. Accordingly, the teachings of Le Person are not needed to reach the limitations of said claims, and thus, the proposed rejection of said claims over the combined teachings of Staab and Le Person is not adopted.

9. Claims 82, 89-91, 161, 171-173, 272-274 and 290-292 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Le Person.

The rejection of claims 82, 89-91, 161, 171-173, 272-274 and 290-292 under 35 USC 102(b) as anticipated by Le Person was proposed by Third Party Requester and **is adopted** for the reasons that follow. The rejection of claims 90, 172, 273 and 291 under 35 USC 103(a) as obvious over Le Person was proposed by Third Party Requester and **is adopted** for the reasons that follow. The 35 USC 103(a) rejection of claims 82, 89, 91, 161, 171, 173, 272, 274, 290 and 292 is Examiner initiated.

Le Person provides and compares several processes for the drying of pharmaceutical wet films including drying by convection, conduction, and infrared drying (see p. 258, first sentences of § 2.2). The films of Le Person contain an acrylic adhesive polymer, its solvents, which include water, and an active

substance which is a pharmaceutical or drug (see p. 258, line 5 and the first sentence of § 2.1; and Table 1). Le Person teaches that the constituents of the active phase, including the pharmaceutical or drug, in the matrix are homogeneously distributed (see p. 262, col. 2, lines 4-6). Le Person teaches that "[a]fter preparation, the coating mixture is spread on a web and submitted to drying in a tunnel or an oven. Frequently, impinging jets and Infra-red Radiation accomplish the work in a short drying time (100 s as an order of magnitude)." (See p. 257, col. 1, lines 10-14). Using a short infrared drying process, Le Person teaches that in 10 minutes, 99% of the initial water from a 100 μm thick coating is evaporated (see p. 260, col. 2, lines 12-14 and Fig. 5).

As noted above, Le Person teaches that the active substance is homogeneously distributed throughout the initially wet film (see p. 262, col. 2, lines 4-6). Le Person then studies the migration of the active material vertically, i.e. throughout the thickness, of the film throughout the drying process (see p. 262, col. 1, lines 11 to col. 2, line 3). Le Person discloses that after 5 min of the drying, "the polymeric network is not turgescent and the meshes are densely packed. The polymer skeleton acts as a filter for the active substance [i.e., pharmaceutical or drug] when the system reequilibrates." (See p. 262, col. 2, third full paragraph.) Le Person also teaches that "[b]etween the 5^{th} and 10^{th} min of drying the heavy solvent migrates... active substance, slowed down in its migration, stays in the bottom of the layer." (See the last four lines at page 262, col. 2). It is noted that the heavy solvent only accounts for 2% of the wet composition of the coating (see page 258, Table 1). As such, within 5-10

minutes, the solvent has been sufficiently evaporated such that, inherently, a substantial uniform distribution of the active is locked-in and migration is substantially prevented within the film, as here claimed. The active material homogenizes and a quasi-equilibrium is obtained for the components of the active phase, taking into account evaporation of the heavy solvent (p. 263, col. 1, lines 8-13), and thus, there is a variation of active content of less than 10%, as per claims 272, 273, 290 and 291.

As noted above, after 10 minutes of drying, 99% of the water has been evaporated (see p. 260, col. 2, lines 12-14 and Fig. 5). In fact, the water is intensely removed from the film in the first 3 minutes with the short infrared drying process (see p. 261, col. 2, lines 21-24 and 27-30). Also, as can be seen from Fig. 2 on p. 259, similar intense drying is seen using conduction, convention, etc. As seen in Fig. 5, after 4 minutes of drying, about 98% of the water has been evaporated. Since the mass of water is negligible at the 10 minute point, the film is inherently viscoelastic as here claimed.

While Le Person does not discuss viscoelasticity or that the films in its process have a "substantially uniform distribution of components" or disclose "locking-in or substantially preventing migration" of the active, Le Person, as cited above, discloses a process which reasonably appears to be either the same as or an obvious variation of the instantly claimed process. Accordingly, claims 82, 89-91, 161, 171-173, 272-274 and 290-292, if not anticipated under 35 USC 102(b), would be obvious under 35 USC 103(a).

With respect to claims 90 and 172, Le Person teaches that its coating mixture contains three light solvents (Sl_i) (see p. 258, section 2.1). Table 1 indicates that solvent Sl_2 has a molecular weight of 46, which is the molecular weight of ethanol. While dimethyl ether also has a molecular weight of 46, it cannot be used as a solvent due to its low boiling point of -24°C. Accordingly, the Le Person's light solvent of molecular weight 46 either anticipates or renders obvious ethanol as here claimed.

Le Person teaches that the films are used in patches for transdermal drug delivery (see Abstract and p. 257, col. 1). Thus, plural dosage units of the same size as per instant claims 273 and 291, e.g., plural transdermal patches of the same size, are anticipated or rendered obvious by Le Person.

With respect to claims 274 and 292, which require that the resulting film contains less than about 6% by weight solvent, the solvent content in Le Person's dried films is far under about 6% as evidenced by Figs. 2 and 5. Le Person teaches that using a short-infrared drying process, in 10 minutes 99% of the initial water content from a 100 µm thick coating is evaporated (see § 3.1 at pp. 260-261, in particular Fig. 5 and the second paragraph of right col. at page 260). In view of the water and heavy solvent content in Fig. 5, the total solvent content is well under about 6%.

10. Claims 92 and 174 are rejected under 35 U.S.C. 103(a) as being unpatentable over Le Person.

This rejection was proposed by Third Party Requester and **is adopted** for the reasons that follow.

Le Person, as relied upon for the reasons stated above in rejection No. 9, does not teach the pharmaceutical or drug active materials listed in claims 92 and 174. However, these materials are conventional pharmaceuticals and drugs.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have used the conventional pharmaceutical or drug materials here claimed as the pharmaceutical or drug material in Le Person's film so as to take advantage of the intended function of the pharmaceutical or drug, and because of a reasonable expectation of success.

11. Claims 1, 5, 7-10, 12-14, 23, 63, 64, 82, 84, 86-89, 91-93, 102, 142, 143, 161, 166, 168-171, 173-175, 184, 224, 225, 249, 254, 267, 272, 285 and 290 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Hortsmann.

The rejection of claims 1, 5, 7-10, 12-14, 23, 63, 64, 82, 84, 86-89, 91-93, 102, 142, 143, 161, 166, 168-171, 173-175, 184, 224, 225, 249, 254, 267, 272, 285 and 290 under 35 USC 102(b) as anticipated by Hortsmann was proposed by Third Party Requester and **is adopted** for the reasons that follow. The 35 USC 103(a) rejection of claims 1, 5, 7-10, 12-14, 23, 63, 64, 82, 84, 86-89, 91-93, 102, 142, 143, 161, 166, 168-171, 173-175, 184, 224, 225, 249, 254, 267, 272, 285 and 290 is Examiner initiated.

Horstmann teaches rapidly dissolvable films for delivery of individual dosage of drugs, cosmetics and the like (see Abstract, col. 3, lines 7-10 and 20-35). Horstmann teaches forming a masterbatch premix of components prior to adding the active material. In particular, in Examples 1, 3 and 4 at cols. 4-6, a masterbatch is formed containing a water soluble polymer, i.e. acetylated starch, and water; and then an active material, i.e., peppermint oil, is added to the premix to form a homogeneous, spreadable, i.e., flowable, polymer matrix (see also col. 3, lines 20-35; and col. 4, lines 19-26). Under the category of "Actives", the '080 patent teaches flavors such as mint oils (see col. 21, lines 35-63). Peppermint is also a breath freshener; and the '080 patent teaches that breath fresheners are drugs (col. 20, lines 35-38). In fact, peppermint has a high menthol content, and the '080 patent teaches menthol is a breath freshener (col. 21, lines 35-36). Horstmann teaches that the use of homogenizers to render the mixture more intimate or the application of a vacuum to remove air bubbles may be useful (see col. 4, lines 24-26).

The homogeneous mass is spread, i.e., casted, onto siliconized paper with a coating device, and the water is then evaporated (see col. 5, lines 1-3 and 51-53). In Horstmann's Example 3, the drying is for 10 minutes as here claimed at a temperature of 80°C (col. 3, lines 51-53), which is within the most desirable temperature range of 80°C or less taught at col. 27, lines 53-55 of the '080 patent. The resulting film in Example 3 is inherently viscoelastic since it can be removed, e.g., peeled from the paper (see col. 4, lines 46-51 and col. 5, lines 54-61). The films in Horstmann's Examples 1 and 4 are dried for 15 minutes at

80°C (see col. 5, lines 1-3 and col. 6, lines 12-14). It is the Examiner's position that the films of Examples 1 and 4 are inherently viscoelastic at 10 minutes or less of drying, the remaining time in the 15 minutes providing for a more dry viscoelastic film. Like the film of Example 3, the dried films of Examples 1 and 4 can be removed from the paper (see col. 4, lines 46-51 and col. 5, lines 4-12). The dried films in Examples 1, 3 and 4 are also viscoelastic since they are prepared using the same materials and process steps as here claimed.

The dried films of Horstmann's Examples 1, 3 and 4 inherently have a water content of 10% or less. The examples have the same components and use the same process steps as here claimed. Further, the examples in '080 patent specification start with more water than Examples 1, 3 and 4 of Horstmann, use the same or similar drying conditions as Horstmann, and result in dried films having well less than 10% water. For example, as noted above, Horstmann's Example 3 dries at 80° for 10 minutes (col. 5, lines 51-53). The total weight in Example 3 is (25 g acetylated starch +20 g sorbitol + 30 g calcium carbonate + 1 g titanium + 22 g water + 8 g glycerol + (0.5 mL peppermint oil x 0.9 g/mL estimated density of peppermint oil) = 106.45 g. Thus, the weight percent of water in Horstmann's Example 3 is (22/106.45) x 100 = 21%. In Example CI at col. 43-44 of the '080 patent, the water content before drying, based on the weights shown in Table 16, is about 65%. After drying for 10 minutes at 80°C the water content was either 3.52% or 3.95% (see col. 44, lines 2-5 of the '080 patent). Likewise Examples A-I (see Table 1) and BA-BI (see

Table 9) of the '080 patent start with much more water than Horstmann's Examples 1, 3 and 4 (see also col. 14, lines 55-59 of the '080 patent).

The claimed substantially uniform distribution of components and active, and locking-in or substantially preventing migration of active, and the variance of active content of 10% or less in dependent claims 254, 272 and 290 are also inherent in Horstmann's Examples 1, 3 and 4. In particular, Horstmann's films before drying are described as being uniform and homogeneous (see col. 3, line 11-19, 29-34 and 37-41; col. 5, lines 1 and 50), and as noted above, Horstmann uses the same components and process steps as here claimed. The '080 patent notes that Horstmann addressed the problem of self-aggregation and non-uniformity by increasing the viscosity of the film prior to drying in an effort to reduce aggregation of the components in the film (see col. 2, line 60 through col. 3, line 1). Further, ¶ 9 of the Cohen Declaration notes the following:

> 9. In general, as a homogeneous or completely dispersed coating mixture is dried, the solvent is removed, the viscosity increases and the active would be more firmly fixed in place. When working with a homogeneous or completely dissolved coating mixture, for example, it would be difficult for a person of ordinary skill in the thin film art not to obtain a film that has uniform content of active.

While Horstmann does not discuss viscoelasticity, water content of its dried films or that the films resulting from its process have a "substantially uniform distribution of components" or disclose "locking-in or substantially preventing migration" of the active, Horstmann, as cited above, discloses a process which reasonably appears to be either the same as or an obvious variation of the instantly claimed process. Accordingly, claims 1, 5, 7-10, 12-14,

23, 63, 64, 82, 84, 86-89, 91-93, 102, 142, 143, 161, 166, 168-171, 173-175, 184, 224, 225, 249, 254, 267, 272, 285 and 290, if not anticipated under 35 USC 102(b), would be obvious under 35 USC 103(a).

With respect to claims 5, 7-9, 84, 86-88, 166 and 168-170, Horstmann teaches that, besides starch and derivatives thereof, the gel former can be polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, polyacrylic acid, carrageenan, dextran, tragacanth, gums of vegetable origin, and polypeptides such as gelatin, albumin, collagen or egg white (see col. 3, line 62 through col. 4, line 6).

With respect to claims 12-14, 23, 63, 64, 91-93, 102, 142, 143, 173-175, 184, 224 and 225, as noted above, Horstmann's Examples 1, 3 and 4 have menthol in the form of peppermint oil, which reads on the instant drug. Horstmann expressly teaches that drugs can be included in its dosage units (see col. 3, lines 20-22). Another drug exemplified by Horstmann is glibenclamide, which is a well-known anti-diabetic drug (see col. 5, line 25). Horstmann further teaches that confectionaries, other food and cosmetics can be included in the films (see col. 3, lines 20-22). The active is "taste masked" due to the presence of honey, citric acid and/or sorbitol (see col. 4, lines 57-59; col. 5, line 40; and col. 6, line 9).

With respect to claims 249, 267 and 285, Horstmann teaches that its films disintegrate in the mouth within 10 minutes (see col. 3, lines 44-46).

Conclusion

The patent owner is reminded of the continuing responsibility under 37 CFR 1.985 to apprise the Office of any litigation activity, or other prior or concurrent proceeding, involving Patent No. 7,897,080 throughout the course of this reexamination proceeding. The third party requester is also reminded of the ability to similarly apprise the Office of any such activity or proceeding throughout the course of this reexamination proceeding. MPEP 2686.

In order to ensure full consideration of any amendments, affidavits or declarations, or other documents as evidence of patentability, such documents must be submitted in response to this Office action. Submissions after the next Office action, which is intended to be an Action Closing Prosecution (ACP), will be governed by 37 CFR 1.116(b) and (d), which will be strictly enforced.

All correspondence relating to this *inter partes* reexamination proceeding should be directed:

By EFS: Registered users may submit via the electronic filing system EFS-Web at https://efs.uspto.gov/efile/myportal/efs-registered

By Mail to: Attn: Mail Stop "Inter Partes Reexam"
Central Reexamination Unit
Commissioner for Patents
P. O. Box 1450
Alexandria VA 22313-1450

Please FAX any communications to:
(571) 273-9900
Central Reexamination Unit

Please hand-deliver any communications to:
Customer Service Window
Attn: Central Reexamination Unit
Randolph Building, Lobby Level

401 Dulany Street
Alexandria, VA 22314

Signed:

/Alan Diamond/
Patent Reexamination Specialist
Central Reexamination Unit 3991

/Jerry D. Johnson/
Patent Reexamination Specialist
Central Reexamination Unit 3991

/Deborah Jones/
Supervisory Patent Examiner
Central Reexamination Unit 3991

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	95002170	7897080
	Examiner	Art Unit
	ALAN DIAMOND	3991

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	10/08/2012								
	1	✓								
	2	✓								
	3	✓								
	4	✓								
	5	✓								
	6	✓								
	7	✓								
	8	✓								
	9	✓								
	10	✓								
	11	✓								
	12	✓								
	13	✓								
	14	✓								
	15	✓								
	16	✓								
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	22	✓								
	23	✓								
	24	✓								
	25	✓								
	26	✓								
	27	✓								
	28	✓								
	29	✓								
	30	✓								
	31	✓								
	32	✓								
	33	✓								
	34	✓								
	35	✓								
	36	✓								

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CLAIM		DATE								
Final	Original	10/08/2012								
	37	✓								
	38	✓								
	39	✓								
	40	✓								
	41	✓								
	42	✓								
	43	✓								
	44	✓								
	45	✓								
	46	✓								
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	63	✓								
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	65	✓								
	66	✓								
	67	✓								
	68	✓								
	69	✓								
	70	✓								
	71	✓								
	72	✓								

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CLAIM		DATE								
Final	Original	10/08/2012								
	73	✓								
	74	✓								
	75	✓								
	76	✓								
	77	✓								
	78	✓								
	79	✓								
	80	✓								
	81	✓								
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	101	✓								
	102	✓								
	103	✓								
	104	✓								
	105	✓								
	106	✓								
	107	✓								
	108	✓								

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CLAIM		DATE								
Final	Original	10/08/2012								
	109	✓								
	110	✓								
	111	✓								
	112	✓								
	113	✓								
	114	✓								
	115	✓								
	116	✓								
	117	✓								
	118	✓								
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	140	✓								
	141	✓								
	142	✓								
	143	✓								
	144	✓								

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CLAIM		DATE								
Final	Original	10/08/2012								
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	146	✓								
	147	✓								
	148	✓								
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	153	✓								
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	174	✓								
	175	✓								
	176	✓								
	177	✓								
	178	✓								
	179	✓								
	180	✓								

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CLAIM		DATE								
Final	Original	10/08/2012								
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	182	✓								
	183	✓								
	184	✓								
	185	✓								
	186	✓								
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	189	✓								
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	211	✓								
	212	✓								
	213	✓								
	214	✓								
	215	✓								
	216	✓								

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CLAIM		DATE								
Final	Original	10/08/2012								
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	218	✓								
	219	✓								
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	221	✓								
	222	✓								
	223	✓								
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	247	✓								
	248	✓								
	249	✓								
	250	✓								
	251	✓								
	252	✓								

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=	Allowed	÷	Restricted	I	Interference	O	Objected

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CLAIM		DATE								
Final	Original	10/08/2012								
	253	✓								
	254	✓								
	255	✓								
	256	✓								
	257	✓								
	258	✓								
	259	✓								
	260	✓								
	261	✓								
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	271	✓								
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	273	✓								
	274	✓								
	275	✓								
	276	✓								
	277	✓								
	278	✓								
	279	✓								
	280	✓								
	281	✓								
	282	✓								
	283	✓								
	284	✓								
	285	✓								
	286	✓								
	287	✓								
	288	✓								

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CLAIM		DATE								
Final	Original	10/08/2012								
	289	✓								
	290	✓								
	291	✓								
	292	✓								
	293	✓								
	294	✓								
	295	✓								
	296	✓								
	297	✓								
	298	✓								
	299	✓								

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
95/002,170	09/10/2012	7897080	117744-00023	6418

23869 7590 11/28/2012

Hoffmann & Baron LLP
6900 Jericho Turnpike
Syosset, NY 11791

EXAMINER	
DIAMOND, ALAN D	
ART UNIT	PAPER NUMBER
3991	
MAIL DATE	DELIVERY MODE
11/28/2012	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

DO NOT USE IN PALM PRINTER

(THIRD PARTY REQUESTER'S CORRESPONDENCE ADDRESS)

Danielle L. Herritt
McCARTER AND ENGLISH LLP
265 FRANKLIN STREET
BOSTON, MA 022110

Transmittal of Communication to Third Party Requester *Inter Partes* Reexamination

REEXAMINATION CONTROL NUMBER *95/002,170*.

PATENT NUMBER *7,897,080*.

TECHNOLOGY CENTER *3999*.

ART UNIT *3991*.

Enclosed is a copy of the latest communication from the United States Patent and Trademark Office in the above-identified reexamination proceeding. 37 CFR 1.903.

Prior to the filing of a Notice of Appeal, each time the patent owner responds to this communication, the third party requester of the *inter partes* reexamination may once file written comments within a period of 30 days from the date of service of the patent owner's response. This 30-day time period is statutory (35 U.S.C. 314(b)(2)), and, as such, it cannot be extended. See also 37 CFR 1.947.

If an *ex parte* reexamination has been merged with the *inter partes* reexamination, no responsive submission by any *ex parte* third party requester is permitted.

All correspondence relating to this inter partes reexamination proceeding should be directed to the **Central Reexamination Unit** at the mail, FAX, or hand-carry addresses given at the end of the communication enclosed with this transmittal.

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

HOFFMAN & BARON, LLP
6900 Jericho Turnpike
Syosset, New York 11791

(For Patent Owner)

Danielle L. Herritt
McCARTER AND ENGLISH LLP
265 Franklin Street
Boston, Massachusetts 022110

(For Third Party Requester)

In re: Yang et al.
Inter Partes: Reexamination Proceeding
Control No.: 95/002,170
For: U.S. Patent No.: 7,897,080

DECISION ON PETITION

This is a decision on a petition filed by the Patent Owner: a petition filed on November 26, 2012, entitled "PETITION AND REQUEST BY PATENTEE FOR RELIEF AVAILABLE TO PATENTEES AFFECTED BY HURRICANE SANDY".

In the petition Patent Owner requests that the Office Action in *Inter Partes* Reexamination 95/002,171, dated October 22, 2012, be reissued due to the effects of Hurricane Sandy. Patent Owner asserts that such relief is authorized pursuant to the memorandum signed by David J. Kappos on November 21, 2012, entitled *Emergency Notice of Relief Available to Patent and Trademark Applicant's, Patentees and Trademark Owners Affected by Hurricane Sandy.*

The petition is before the Director of the Central Reexamination Unit.

The petition is **Granted**.

REVIEW OF RELEVANT FACTS

- U.S. Patent No. 7,897,080 issued on March 1, 2011.
- A Request for *inter partes* reexamination was filed by third party requester on September 10, 2012 and assigned control no. 95/002,170.
- *Inter-Partes* reexamination was ordered on October 22, 2012.
- A Non-Final Office Action was mailed on October 22, 2012.
- David J. Kappos, Director of the United States Patent & Trademark Office issued a memorandum entitled *Emergency Notice of Relief Available to Patent and Trademark Applicant's, Patentees and Trademark Owners Affected by Hurricane Sandy* on November 21, 2012.
- Patent Owner filed the above identified petition on November 26, 2012 requesting that the October 22, 2012 Office Action be reissued.

DECISION

In the above identified petition, Patent Owner petitioner requests the October 12, 2012, Action be reissued in view of the memorandum issued on November 21, 2012, by David J. Kappos, Director of the United States Patent & Trademark Office entitled *Emergency Notice of Relief Available to Patent and Trademark Applicant's, Patentees and Trademark Owners Affected by Hurricane Sandy.*

Patent Owner has met the requirements for requesting such relief in that (1) Patent Owner has a reexamination proceeding pending as of October 29, 2012, (2) has a correspondence address in the region affected by Hurricane Sandy, (3) has an outstanding response due to a non-final Office Action which was pending as of October 29, 2012, (4) the non-statutory period for response has not expired, (5) the request for relief has been made prior to the expiration of the non-statutory period and (6) request for relief is accompanied by the copy of the November 21, 2012 notice of relief.

Since Patent Owner has met all requirements for requesting relief, Patent Owner's November 26, 2012 petition is hereby **granted**.

The non-final Office Action originally mailed October 22, 2012 is being re-mailed and the 2 month period for response is restarted.

CONCLUSION

1. The petition filed by Patent Owner on November 26, 2012, is **granted.**

2. Telephone inquiries related to this decision should be directed to Stephen Stein, Supervisory Patent Reexamination Specialist, at (571) 272-1544 or in his absence to the undersigned at (571) 272-0700.

Irem Yucel
Director, Central Reexamination Unit

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patentee:	Yang et al.	Examiner:	Diamond, Alan D.
Patent No.:	U.S. 7,897,080	Group Art Unit:	3991
Reexamination Control No.:	95/002,170	Confirmation No.	6418
Filed:	September 10, 2012	H&B Docket:	1199-26 RCE/CON/REX
Dated:	November 26, 2012	M&E Docket:	117744-00023

Mail Stop Petition
Commissioner for Patents
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

Certificate of EFS-Web Transmission
I hereby certify that this correspondence is being transmitted via the U.S. Patent and Trademark Office electronic filing system (EFS-Web) to the USPTO on November 26, 2012.
Signed: Michael I. Chakansky /Michael I Chakansky/

PETITION AND REQUEST BY PATENTEE FOR RELIEF AVAILABLE TO PATENTEES AFFECTED BY HURRICANE SANDY

Sir or Madame:

Patentee, in the above-captioned *Inter Partes* Reexamination, Control No. 95/002,170 ("*Inter Partes* Reexamination"), hereby petitions and requests that the US Patent and Trademark Office (PTO) withdraw the Office Action in the *Inter Partes* Reexamination dated October 22, 2012, which was outstanding on October 29, 2012, and for which a reply is currently due December 22, 2012, and reissue it on or before December 22, 2012. The need for reissuance of the Office Action is due to the effects of Hurricane Sandy in October and November 2012. Attached please find a copy of the Emergency Notice entitled Relief Available to Patent and Trademark Applicants, Patentees and Trademark Owners Affected by Hurricane Sandy and signed by David J. Kappos on November 21, 2012. Assignee/Patentee and the correspondence address are within the states affected by Hurricane Sandy.

Respectfully submitted,

/Daniel A. Scola, Jr./
Daniel A. Scola, Jr.
Registration No.: 29,855
Attorney for the Patentee

HOFFMANN & BARON, LLP
6900 Jericho Turnpike
Syosset, New York 11791
(973) 331-1700

CERTIFICATE OF FIRST CLASS SERVICE

It is certified that a copy of this **PETITION AND REQUEST BY PATENTEE FOR RELIEF AVAILABLE TO PATENTEES AFFECTED BY HURRICANE SANDY** has been served, by first class mail, on November 26, 2012, in its entirety on the third party requester as provided in 37 CFR § 1.903 and 37 CFR § 1.248 at the addess below.

DANIELLE L. HERRITT
McCARTER & ENGLISH LLP
265 FRANKLIN STREET
BOSTON, MASSACHUSETTS 02110

/Daniel A. Scola, Jr./
Daniel A. Scola, Jr.
Registration No.: 29,855
Attorney for the Patentee

Relief Available to Patent and Trademark Applicants, Patentees and Trademark Owners Affected by Hurricane Sandy

The United States Patent and Trademark Office (USPTO) considers the October and November 2012 effects of Hurricane Sandy in Connecticut, Delaware, Massachusetts, New Jersey, New York, North Carolina, Pennsylvania, Rhode Island, Maryland, Virginia, the District of Columbia, and the Appalachian region to be an "extraordinary situation" within the meaning of 37 CFR 1.183 and 37 CFR 2.146 for affected patent and trademark applicants, patentees, reexamination parties, and trademark owners.

For patent applications and reexamination proceedings pending in the USPTO as of October 29, 2012, having one or more inventors, an assignee, or a correspondence address in areas of Connecticut, Delaware, Massachusetts, New Jersey, New York, North Carolina, Pennsylvania, Rhode Island, Maryland, Virginia, the District of Columbia, and the Appalachian region affected by Hurricane Sandy, in which a reply or response to an Office action (final, non-final, or other), a notice of allowance, or other Office notice (hereinafter collectively referred to as "Office communication") is outstanding, and for which the statutory or non-statutory time period set for response has not yet expired, the USPTO will, on applicant's request, or a reexamination party's request, withdraw the Office communication and reissue it. The Office communication must have been outstanding on October 29, 2012. The request must be made prior to expiration of the statutory or non-statutory time period set for response and within sufficient time so that withdrawal and reissuance of the Office communication occur prior to expiration of the statutory or non-statutory time period (as permitted to be extended under 37 CFR 1.136(a), or as extended under 37 CFR 1.550(c) or 37 CFR 1.956). The request must be accompanied by a copy of this notice in order to permit the Office to quickly identify it as a request for relief and facilitate timely processing. The inclusion of a copy of this notice will be treated as a representation that the need for the reissuance of the Office communication was due to the effects of Hurricane Sandy in October and November 2012. The request should be sent via EFS-Web or by mail directed to Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

For patentees who were unable to timely pay a patent maintenance fee due to the effects of Hurricane Sandy in October and November 2012, the USPTO will waive the surcharge in 37 CFR 1.20(h) for paying a maintenance fee during the six-month grace period following the window to pay the maintenance fee and the surcharge in 37 CFR 1.20(i) for accepting a delayed maintenance fee payment when the patentee files the maintenance fee payment with a petition to accept a delayed maintenance fee under 37 CFR 1.378(c). *See* 37 CFR 1.183.

Patentees who seek to pay a maintenance fee during the six-month grace period following the window to pay the maintenance fee with a request to waive the surcharge in 37 CFR 1.20(h), must mail the payment and request to: Director of the United States Patent and

Trademark Office, Attn: Maintenance Fee, 2051 Jamieson Avenue, Suite 300, Alexandria, VA 22314; or via facsimile to: 571-273-6500.

The request must be accompanied by a copy of this notice in order to permit the Office to quickly identify it as a request for relief and facilitate timely processing. The inclusion of a copy of this notice with the payment of the maintenance fee during the grace period will be treated as a representation that the late payment of the fee was due to the effects of Hurricane Sandy in October and November 2012, and as a request for *sua sponte* waiver of the surcharge under 37 CFR 1.20(h). This waiver may only be appropriately requested where the original window of time to pay the maintenance fee without the surcharge required by 37 CFR 1.20(h) expired on or after October 29, 2012, and the delay in paying the fee was due to the effects of Hurricane Sandy in October and November 2012.

The USPTO advises patentees who need to file a petition to accept a delayed maintenance fee payment due to the effects of Hurricane Sandy in October and November 2012, where the maintenance fee payment was required to have been paid after October 28, 2012, to promptly file a petition under 37 CFR 1.378(c) (using USPTO form PTO/SB/66 – **Petition to Accept Unintentionally Delayed Payment of Maintenance Fee in an Expired Patent (37 CFR 1.378(c))** accompanied by the applicable maintenance fee payment (but not the surcharge under 37 CFR 1.20(i)) and a copy of this notice. The inclusion of a copy of this notice will be treated as a representation that the delay in payment of the maintenance fee was due to the effects of Hurricane Sandy in October and November 2012, and as a request for *sua sponte* waiver of the surcharge under 37 CFR 1.20(i). The petition must be filed by October 29, 2013, in order to be entitled to a waiver of the surcharge under 37 CFR 1.20(i).

Patentees are reminded that a petition to accept a delayed maintenance fee payment under 37 CFR 1.378(c) must be filed within twenty-four months from the expiration date of the patent. *See* 35 U.S.C. 41(c). A petition to accept a delayed maintenance fee payment under 37 CFR 1.378(c) due to the effects of Hurricane Sandy may be submitted via EFS-Web or by mail directed to Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450. A petition to accept a delayed maintenance fee payment filed later than twenty-four months after the expiration date of the patent must be filed under 37 CFR 1.378(b) and include a showing that the delay in payment was unavoidable. The USPTO will not waive the surcharge in 37 CFR 1.20(i) for accepting a delayed maintenance fee payment when the patentee files the maintenance fee payment with a petition to accept a delayed maintenance fee under 37 CFR 1.378(b).

For applicants who filed a nonprovisional application on or after October 29, 2012, and prior to November 30, 2012, without an executed oath or declaration or payment of the basic filing fee, search fee, and/or examination fee due to Hurricane Sandy in October and November 2012, the USPTO will waive the surcharge set forth in 37 CFR 1.16(f) for the late filing of the oath or declaration or basic filing fee, search fee, and/or examination fee. Patent applicants seeking waiver of the surcharge must include a copy of this notice, along with the executed oath or declaration or the basic filing fee, search fee, or examination fee, in order to permit the Office to quickly identify it as a request for relief

and facilitate timely processing. The inclusion of a copy of this notice will be treated as a representation that the late filing of the oath or declaration or the basic filing fee, search fee, or examination fee was due to the effects of Hurricane Sandy in October and November 2012, and as a request for *sua sponte* waiver of the surcharge under 37 CFR 1.16(f). The reply to the Notice to File Missing Parts requiring the oath or declaration or the filing fees may be submitted via EFS-Web or by mail directed to Mail Stop Missing Parts, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Patent-related inquiries concerning this notice may be directed to the Office of Patent Legal Administration at (571) 272-7704 ((571) 272-7703 for reexamination), or by e-mail to PatentPractice@uspto.gov.

For trademark applications and registrations with a correspondence or owner address in areas of Connecticut, Delaware, Massachusetts, New Jersey, New York, North Carolina, Pennsylvania, Rhode Island, Maryland, Virginia, the District of Columbia, and the Appalachian region affected by Hurricane Sandy in October and November 2012, in which an Office action (final, non-final, or other), a notice of allowance, or other Office notice requiring a response (hereinafter collectively referred to as "Office communication") is outstanding, the USPTO will, upon request, withdraw the Office communication and reissue it. The request must be made prior to the deadline for responding to the Office communication, and represent that the need for the reissuance of the Office communication is due to the effects of Hurricane Sandy in October and November 2012. The request should be sent via e-mail to TMFeedback@uspto.gov, or by mail to Commissioner for Trademarks, P.O. Box 1451, Alexandria, VA 22313-1451. If necessary, changes of correspondence address should be provided.

For trademark applications and registrations with a correspondence or owner address in areas of Connecticut, Delaware, Massachusetts, New Jersey, New York, North Carolina, Pennsylvania, Rhode Island, Maryland, Virginia, the District of Columbia, and the Appalachian region affected by Hurricane Sandy as of October 29, 2012, that were abandoned or cancelled due to inability to timely respond to a trademark-related Office communication due to the effects of Hurricane Sandy in October and November 2012, the USPTO will waive the petition fee (set by regulation, rather than statute) to revive the abandoned application or cancelled registration. Either a petition by regular mail to the address set forth in the preceding paragraph, or the Trademark Electronic Application System (TEAS) "Request for Reinstatement" form should be used, and must include a verified statement that the failure to respond to the Office communication was due to the effects of Hurricane Sandy.

Trademark-related inquiries concerning this notice may be directed to the Trademark Office of Petitions by telephone at (571) 272-8950, by facsimile at (571) 273-8950, or by e-mail at TMFeedback@uspto.gov.

The USPTO cannot grant waivers or extensions of dates or requirements set by statute. For example, the following patent-related time periods cannot be extended by the Director: (1) the period set forth in 35 U.S.C. 119(a)-(d) to file a nonprovisional patent

application claiming the benefit of a prior-filed foreign application; (2) the twelve-month time period set forth in 35 U.S.C. 119(e) during which a nonprovisional application claiming the benefit of a prior filed provisional application must be filed in order to obtain benefit of the provisional application's filing date; (3) the copendency requirement of 35 U.S.C. 120 between a parent application which issues as a patent and a later filed child application, which requires that the child application be filed prior to issuance of the parent application; (4) the three-month time period to pay the issue fee set forth in 35 U.S.C. 151; (5) the 35 U.S.C. 304 two-month time period from the date of patentee service, for a requester to file, in an *ex parte* reexamination, a reply to a statement filed by the patentee; and (6) the 35 U.S.C. 314(b)(2) thirty-day time period from the date of service, for a requester to file, in an *inter partes* reexamination, written comments addressing issues raised by an Office action or the patentee's response to the action. The following statutory trademark-related time periods cannot be extended and statutory fees cannot be waived by the Director: (1) the 36-month period set forth in 15 U.S.C. 1051(d) within which a statement of use must be filed and the associated fee(s); (2) the periods set forth in 15 U.S.C. 1058, 1141(k) for filing affidavits of continued use or excusable nonuse and the associated fee(s); (3) the period set forth in 15 U.S.C. 1059 for filing a renewal and the associated fee(s); and (4) the periods set forth in 15 U.S.C. 1063 and 1064 for filing an opposition or cancellation proceeding at the Trademark Trial and Appeal Board.

Date: 11/2/12

David J. Kappos
Under Secretary of Commerce for Intellectual Property and
Director of the United States Patent and Trademark Office

Electronic Acknowledgement Receipt

EFS ID:	14302035
Application Number:	95002170
International Application Number:	
Confirmation Number:	6418
Title of Invention:	POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM
First Named Inventor/Applicant Name:	7897080
Customer Number:	23869
Filer:	Michael I. Chakansky
Filer Authorized By:	
Attorney Docket Number:	117744-00023
Receipt Date:	26-NOV-2012
Filing Date:	10-SEP-2012
Time Stamp:	13:08:22
Application Type:	inter partes reexam

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Certification and Request for Disaster Relief	SandyRelief080.pdf	364262 34254f85fe2847871e5c44a8c7b288ca8073fca8	no	6

Warnings:	
Information:	

Total Files Size (in bytes):	364262

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
95/002,170	09/10/2012	7897080	117744-00023	6418

23869 7590 10/22/2012

Hoffmann & Baron LLP
6900 Jericho Turnpike
Syosset, NY 11791

EXAMINER	
DIAMOND, ALAN D	

ART UNIT	PAPER NUMBER
3991	

MAIL DATE	DELIVERY MODE
10/22/2012	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

ORDER GRANTING/DENYING REQUEST FOR* INTER PARTES *REEXAMINATION	**Control No.** 95/002,170	**Patent Under Reexamination** 7897080
	Examiner Alan Diamond	**Art Unit** 3991

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address. --

The request for *inter partes* reexamination has been considered. Identification of the claims, the references relied on, and the rationale supporting the determination are attached.

Attachment(s): ☒ PTO-892 ☒ PTO/SB/08 ☐ Other: _____

1. ☒ The request for *inter partes* reexamination is GRANTED.

☒ An Office action is attached with this order.

☐ An Office action will follow in due course.

2. ☐ The request for *inter partes* reexamination is DENIED.

This decision is not appealable. 35 U.S.C. 312(c). Requester may seek review of a denial by petition to the Director of the USPTO within ONE MONTH from the mailing date hereof. 37 CFR 1.927. EXTENSIONS OF TIME ONLY UNDER 37 CFR 1.183. In due course, a refund under 37 CFR 1.26(c) will be made to requester.

All correspondence relating to this *inter partes* reexamination proceeding should be directed to the **Central Reexamination Unit** at the mail, FAX, or hand-carry addresses given at the end of this Order.

Decision on Reexamination Request

The present request for inter partes reexamination establishes a reasonable likelihood that requester will prevail with respect to at least one claim of U.S. Patent 7,897,080 (hereafter "the '080 patent").

Art Cited in this Order

Chen et al, WO 00/42992, hereafter "Chen".

Staab, U.S. Patent 5,393,528.

Le Person et al, "Near infrared drying of pharmaceutical thin films: experimental analysis of internal mass transport," Chemical Engineering and Processing, Vol. 37, pp. 257-263, (1998), hereafter "Le Person".

Horstmann et al, U.S. Patent 5,629,003, hereafter "Horstmann".

U.S. Patent 7,666,337.

Reasonable Likelihood to Prevail (RLP)

RLPs based on Chen:

1. The request indicates that requester considers that claims 1, 4, 5, 8-18, 20-32, 34, 36-40, 44-47, 51, 53, 54, 59, 62-71, 82-84, 87-97, 99-111, 113, 115-119, 123-126, 130, 132, 133, 138, 141-150, 161-166, 169-179, 181-193, 195, 197-201, 205-208, 212, 214, 215, 220, 223-232, 243, 244, 246, 247, 249-262, 264, 265, 267-280, 282, 283 and 285-299 are anticipated by Chen.

2. The request indicates that requester considers that claims 2, 3, 6, 7, 19, 33, 35, 41-43, 48-50, 52, 55-58, 60, 61, 65-69, 71, 85, 86, 98, 112, 114, 120-122, 127-129, 131, 134-137, 139, 140, 144-148, 150, 167, 168, 180, 194, 196, 202-204, 209-211, 213, 216-219, 221, 222, 226-230, 232, 245, 248, 253, 263, 266, 271, 281, 284 and 289 are obvious over Chen.

3. The request indicates that requester considers that claims 1-3, 8, 9, 16, 17, 32, 55, 65-69, 71, 72-75, 78-82, 87, 88, 95, 96, 111, 134, 144-148, 150-154, 157-161, 169,

170, 177, 178, 193, 216, 226-230, 232-236, 239-242, 254, 255, 257-260, 272, 273, 275-278, 290, 291 and 293-299 are obvious over the combined teachings of Chen and Staab.

4. The request indicates that requester considers that claims 1, 8, 9, 17, 45, 53, 71, 82, 87, 88, 96, 124, 132, 150, 161, 169, 170, 178, 206, 214, 232, 254, 272 and 290 are obvious over the combined teachings of Chen and Le Person.

5. The request indicates that requester considers that claims 1, 4, 13, 15, 17, 45, 53, 71, 82, 83, 92, 94, 96, 124, 132, 150, 161, 165, 174, 176, 178, 206, 214 and 232 are obvious over the combined teachings of Chen and Horstmann.

Each of the above statement numbers 1 to 5, which assert a reasonable likelihood to prevail with respect to at least one claim of the '080 patent, relies at least in part on Chen. Accordingly, Chen is discussed below.

Chen teaches a dosage unit including a water-soluble hydrocolloid, mucosal surface-coat-forming film, such film including an effective dose of an active agent (see p. 3, lines 30-32). In Examples 5-8, Chen prepares hydroxypropyl methylcellulose (HPMC, i.e., "Methocel E5") based quick dissolving intraoral films containing active agents (see p. 20, lines 17-20 and Tables 5 and 7). In particular, the films in Examples 5-8 contain an active agent, e.g., nicotine, hydromorphone, oxybutynin or estradiol; HPMC; and a solvent, i.e., water (see Tables 5 and 7). Further, the film in Tables 7 and 8 of Chen uses sildenafil citrate as an active ingredient and is prepared using HPMC, i.e. "Methocel E15", and water as the solvent. The film in Chen's Example 1 contains HPMC; peppermint, citric acid and aspartame as actives; and water as the solvent (see Tables 1 to 4). The film in Chen's Example 2 contains "Pullalan (P-20) [sic, Pullulan (P-20)]" as the polymer; peppermint, citric acid and aspartame as actives; and water and ethanol as solvents (see Tables 1 and 2). Peppermint, citric acid and aspartame are

also actives in Chen's Examples 5-8, and peppermint and aspartame are actives in the film in Chen's Tables 7 and 8. Under the category of "Actives", the '080 patent teaches flavors such as mint oil, flavor enhancers such as citric acid, and sweeteners such as aspartame (see col. 21, lines 35-63 and col. 22, lines 9-13). Peppermint is also a breath freshener; and the '080 patent teaches that breath fresheners are drugs (col. 20, lines 35-38). In fact, peppermint has a high menthol content, and the '080 patent teaches menthol is a breath freshener (col. 21, lines 35-36). Other taste modifying agents, i.e., taste masking agents, are disclosed at p. 10, lines 7-14 of Chen.

The specific water-soluble polymer, solvent and actives exemplified in Chen are identical to those exemplified in the '080 patent. HPMC is employed in almost every example of the '080 patent. HPMC and pullulan are taught by the '080 patent as being water soluble (col. 15, lines 45-57). The same solvent, i.e., water is employed in almost every example in the '080 patent. Sildenafil is exemplified in Examples CI and FB of the '080 patent (see Tables 16 and 30). Likewise, peppermint oil and/or sweetener are used in numerous examples in the '080 patent, such as Examples A, B, C, D, F, G, H, BA, BB, BC, etc (see Tables 1 and 9).

The following is a list of hydrocolloid polymers, including said HPMC and pullulan, disclosed by Chen for forming the film (see p. 14, line 12 through page 15, line 3):

> In embodiments of the invention, the hydrocolloid may be a water soluble non-gelling (at room temperature) natural polysaccharide or derivatives including pectin and derivatives, guar gum arabic, tragacanth gum, xanthan gum, gellan sodium salt, propyleneglycol alginate, starches (amylose, amylopectin), modified starches, hydroxyethyl starch, pullulan, carboxymethyl starch, gum ghatti, okra gum, karaya gum, dextrans, dextrins and maltodextrins, konjac, acemannan from

aloe, locust bean gum, tara gum, quince seed gum, fenugreek seed gum, scleroglucan, gum arabic, psyllium seed gum, tamarind gum, oat gum, quince seed gum, carrageenans, scleraglucan, succinoglucan, larch arabinogalactan, flaxseed gum, chondroitin sulfates, hyaluronic acid, curdlan, chitosan, deacetylated konjac, and rhizobium gum.

In embodiments of the invention, the hydrocolloid may be a water soluble non-gelling polypeptide or protein exemplified by gelatins, albumins, milk proteins, soy protein, and whey proteins. The hydrocolloid may further be selected from a group of synthetic hydrocolloids exemplified by any of the following: polyethylene-imine, hydroxyethyl cellulose, sodium carboxymethyl cellulose, carboxymethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, methyl cellulose, ethyl cellulose, polyacrylic acids, low molecular weight polyacrylamides and their sodium salts (carbomers), polyvinylpyrollidone, polyethylene glycols, polyethylene oxides, polyvinyl alcohols, pluronics, tetronics, and other block co-polymers, carboxyvinyl polymers, and colloidal silicon dioxide. A preferred embodiment of the invention utilizes a hydroxypropyl methyl cellulose having a methoxy content of about 19-30% and hydroxypropyl content of 7-12% and a molecular weight of approximately 50,000-250,000 daltons (Table 9).

In addition to the specific active materials noted above, i.e., nicotine, hydromorphone, oxybutynin, estradiol, sildenafil citrate, peppermint, citric acid and aspartame, the following is a list of active agents disclosed by Chen (see p. 10, line 22 through page 11, line 12):

Active agents (for human and veterinary applications) include therapeutic agents, nutritional supplements and hygiene aids. The therapeutic agents are exemplified by analgesics, a-adrenergic receptor blockers, anti-Alzheimer's disease medication, antianginal, antianxiety, antiarrythmics, antiarthritics, antibiotics, anticoagulants/thrombolytics, anticonvulsants/anti-Parkinson medication, anti-depressants, anti-diabetics, anti-diarrheal, anti-epileptics, anti-fungal, anti-gout, anti-heartworm medication for dogs, anti-histamines, anti-hypertensives, anti-inflammatories, anti-infectives, antimigraines, anti-nasuants/anti-emetics, anti-neoplastics/anti-tumor active agents, anti-pruitics, anti-psychotics, anti-pyretics, anti-spasmodics, anti-virals, bronchial dilators/anti-asthmatics, calcium antagonists, cardiac agents, cardiotonics, central nervous system actives, contraceptives, coronary vasodilators, cough/cold remedies, dietary supplements, including vitamins and minerals, diuretics, fertility active agents, flea control agents for animals (Ivermectin), H_2 receptor antagonists,

> herbal actives, hormones, hypoglycemics, hypolipidemics, muscle relaxants, ovulation stimulators, peptide active agents, polypeptide active agents, proteins such as insulin, calcitonin, LHRH and the like. Sedatives and hypnotics, sexual dysfunction active agents, sleep aids, smoking cessation aids, steroids and steroidals, tranquilizers, laxatives, ophthalmic preparations, nutritional supplements, breath fresheners, breath deodorants, saliva substitutes, antigingivitis agents, anti-cavity agents, anti-plaque agents, diagnostic indicators, and local anesthetics. Also included are active agents for treatment of osteoporosis, hormone replacement, treatment of periodontal disease, antiseptics, corticosteroids, non steroidal anti-inflammatory agents, antiviral agents and vaccines.

In the method of preparation of the films, the HPMC or pullulan, which Chen teaches is a hydrocolloid, is dissolved in water under agitated mixing to form a uniform and viscous solution which reads on the instant masterbatch pre-mix, and the additional ingredients are added under agitated mixing until they are uniformly dispersed (i.e., suspended) or dissolved in the hydrocolloid (see p. 14, line 22 through p. 15, line 3; and p. 17, lines 6-19). The resultant mixture, i.e. the instant flowable polymer matrix, is degassed in a vacuum chamber until trapped air bubbles are removed, and then coated, i.e., casted as per step (b) of claims 82 and 161 and as per step (c) of claim 1, on the non-siliconized side of a polyester film (see p. 17, lines 13-15).

With respect to instant steps (c) and (d) of claims 82 and 161, and with respect to steps (d) and (e) of claim 1, Chen evaporates water from the cast matrix in 9 minutes of drying in a hot air circulating oven at 50°C (see p. 17, lines 13-15 and Fig. 2). As seen schematically in Chen's Fig. 2, the air flow is less direct at the film surface at the beginning of the drying and becomes more direct as the film proceeds through the drying oven, which has an aeration controller (see also p. 5, line 31 through p. 6, line 3). Chen's Example 1 starts with 74.42% water content and is dried to 1.7% water content

(see Tables 1 and 4). Chen's Examples 5 to 8 start with 73.03%, 71.51%, 70.72% and 72.94% water content and are dried to 2.93%, 2.42%, 2.32% and 2.31% water content, respectively. Chen's Example 2 starts with 10.6% ethanol and 67.025% water and, after drying for 9 minutes at 50°C, the water content is 8.5% (see Tables 1 and 2).

Chen's dried film product of Example 1 is cut into dosage units ready for packing (p. 17, lines 31-32) and has a weight of 0.028 ± 0.001 g/dosage film, a density of 1.0485 ± 0.009 g/cm^2, a water content of 1.7 ± 0.24%, and as noted above, a thickness of 2.1 ± 0.12 mil (see Table 4); and the dried films are glossy and substantially transparent (p. 17, line 15), i.e., they are visually free of aggregation. The 0.028 ± 0.001 g/dosage film has variation of (0.001/0.028) x 100 = 3.6%. The film weight rounded to two decimal places as in Table 2 at col. 31 of the '080 patent is 0.03 gram/dosage film with a variation of 0%.

Furthermore, as noted in the Rule 1.132 Declaration of Edward D. Cohen (hereafter "Cohen Declaration") submitted with the request, when working with a homogeneous or completely dissolved coating mixture as in Chen, it would be difficult for a person of ordinary skill in the film art not to obtain a film that has a uniform content of active, and the drying method disclosed in Chen would not be expected to create any agglomeration, aggregation or otherwise non-uniform content of active (see ¶¶ 8-10).

Chen thus teaches all the limitations of at least one claim of the '080 patent. Accordingly, Requester has shown a reasonable likelihood of prevailing with respect to at least one claim of the '080 patent.

RLPs based on Staab:

6. The request indicates that requester considers that claims 1-5, 10, 12-15, 21, 24, 25, 44-46, 54, 55, 59, 63-70, 72-75, 78-84, 89, 91-94, 100, 103, 104, 123-125, 133, 134, 138, 142-149, 151-154, 157-166, 171, 173-176, 182, 185, 186, 205-207, 215, 216, 220, 224-231, 233-236, 239-242, 249-252, 254, 255, 257-260, 267-270, 272, 273, 275-278, 285-288, 290, 291 and 293-299 are anticipated by Staab.

7. The request indicates that requester considers that claims 6-9, 16, 32, 76, 77, 85-88, 95, 111, 155, 156, 167-170, 177, 193, 237 and 238 are obvious over Staab.

8. The request indicates that requester considers that claims 1-5, 10, 12-16, 21, 24, 25, 32, 44-46, 54, 55, 59, 63-70, 72-75, 78-84, 89, 91-95, 100, 103, 104, 111, 123-125, 133, 134, 138, 142-149, 151-154, 157-166, 171, 173-177, 182, 185, 186, 193, 205-207, 215, 216, 220, 224-231, 233-236, 239-242, 249-252, 254, 255, 257-260, 267-270, 272, 273, 275-278, 285-288, 290, 291 and 293-299 are obvious over the combined teachings of Staab and Le Person.

Each of the above statement numbers 6-8, which assert a reasonable likelihood to prevail with respect to at least one claim of the '080 patent, relies at least in part on Staab. Accordingly, Staab is discussed below.

Staab teaches the preparation of a film for local administration of an active agent in an internal body area (see col. 2, lines 34-62). Staab teaches films made of dissolvable polymer material, e.g., PEO and/or HPMC, both of which are identified as water soluble polymers in the '080 patent at col. 15, lines 50-51, and Staab's film also contains a drug or medication as the active agent (see Abstract; and col. 2, lines 34-46). Staab teaches that "[t]he agent material is evenly distributed throughout the film, so as the film slowly dissolves, it releases the agent material in the proper dosage..." (See col. 5, line 68 through col. 6, line 3). Staab teaches that "the polymer solids, water, or other solvent, contraceptive [i.e., an active]…, are admixed in the proper concentrations and

the mixture heated to the appropriate temperature for dissolution and formation of a uniform blend to take place." (See col. 7, lines 37-41). In the Example at cols. 11-12, the ingredients are mixed together in a blender until just blended (see col. 11, lines 222-27). As such, Staab teaches formation of a flowable polymer matrix. A masterbatch pre-mix can be formed containing polymer and solvent, and the pre-mix is then transferred to a cooler vessel for addition of heat-sensitive pharmaceuticals or other agents (see col. 7, lines 37-51). Other polymers that can be used along with PEO and/or HPMC include polyvinyl alcohol (see col. 2, line 41; and col. 4, lines 22-61).

The active agents that can be used in Staab's film include spermicides for contraceptive use and/or drugs or medications (see col. 5, lines 66-68). The following is a list of active agents taught by Staab at col. 6, line 35 through col. 7, line 3:

(1) anti-infectives such as antibiotics, sulfonamides, antivirals, antifungals, antiprotozoan and antibacterials;

(2) anti-inflammatories, such as hydrocortisone, dexamethasone, triamcinolone, and various prednisolone compounds;

(3) estrogenic steroids, such as estrone;

(4) progestational agents, such as progesterone;

(5) prostaglandins;

(6) coronary vasodilators;

(7) antitussives;

(8) antihistamines;

(9) anesthetics and

(10) decongestants.

> Monoclonal antibodies [which are biological response modifiers] such as those useful against cell surface components or against pathogenic organisms such as the human-immuno-deficiency (HIV) family of viruses may be incorporated into the device of the present invention … . Other drugs include clotrimazole, miconazole, ticonazole, benzalkonium chloride, nystatin, dermally active steroids, hormones, benzocaine, sulfas, biologically prepared actives, decongestants, cough/cold remedies, psychotropics, nitroglycerine, etc.

Staab also teaches the use of flavors, fragrances and coloring agents (see col. 7, lines 28-29). Thus, Staab's active material can be taste-masked.

Staab also discloses that "[t]he device of the invention thus is composed of a biologically compatible material that has been blended homogeneously" with the drug (see col. 6, lines 5-10). In the Example at cols. 11-12, Staab prepares a four-foot wide film which is then cut into two inch by two inch films each weighing 190 mg and containing 19 mg of benzalkonium chloride as the active agent (see col. 11, line 52 through col. 12, line 3).

With respect to step (c) in claim 1 and with respect to step (b) in claims 82 and 161, Staab further discloses that "the mixture in liquid form will be poured or cast on to a plate or into a mold..." (See col. 5, lines 51-58 and the casting lines depicted in Fig. 5). In the Example at cols. 11-12, the blended mixture is poured onto a glass plate and spread to an even 3 mil thick film covering the surface of the glass (see col. 11, lines 41-44).

With respect to steps (d) and (e) in claim 1 and with respect to steps (c) and (d) in claims 82 and 161, Staab discloses drying the film in a temperature regulated oven for approximately 20 minutes at 160°F, i.e., 71°C, or for 20 to 40 minutes when using a continuously moving belt that enters a drier (see col. 11, lines 45 and 65). The

ingredients blended to prepare the film are 52.5% HPMC, 37.5% glycerin and 10.0% of a 50% aqueous solution of the benzalkonium chloride (see col. 11, lines 30-34). Accordingly, within 10 minutes or fewer (i.e. half the 20 minute drying time), at least a portion of the water has been evaporated to form the film. Since the water content before drying is 5% (i.e., half of the 10% of the 50% aqueous solution of benzalkonium chloride), the dried film must have a water content of 10% or less.

Staab thus teaches all the limitations of at least one claim of the '080 patent. Accordingly, Requester has shown a reasonable likelihood of prevailing with respect to at least one claim of the '080 patent.

RLP based on Le Person:

9. The request indicates that requester considers that claims 82, 89-91, 161, 171-173, 272-274 and 290-292 are anticipated by Le Person.

10. The request indicates that requester considers that claims 90, 92, 172, 174, 273 and 291 are obvious over Le Person.

Each of the above statement numbers 9 and 10, which assert a reasonable likelihood to prevail with respect to at least one claim of the '080 patent, relies on Le Person. Accordingly, Le Person is discussed below.

Le Person provides and compares several processes for the drying of pharmaceutical wet films including drying by convection, conduction, and infrared drying (see p. 258, first sentences of § 2.2). The films of Le Person contain an acrylic adhesive polymer, its solvents, which include water, and an active substance which is a pharmaceutical or drug (see p. 258, line 5 and the first sentence of § 2.1; and Table 1).

Le Person teaches that the constituents of the active phase, including the pharmaceutical or drug, in the matrix are homogeneously distributed (see p. 262, col. 2, lines 4-6). Le Person teaches that "[a]fter preparation, the coating mixture is spread on a web and submitted to drying in a tunnel or an oven. Frequently, impinging jets and Infra-red Radiation accomplish the work in a short drying time (100 s as an order of magnitude)." (See p. 257, col. 1, lines 10-14). Using a short infrared drying process, Le Person teaches that in 10 minutes, 99% of the initial water from a 100 µm thick coating is evaporated (see p. 260, col. 2, lines 12-14 and Fig. 5).

As noted above, Le Person teaches that the active substance is homogeneously distributed throughout the initially wet film (see p. 262, col. 2, lines 4-6). Le Person then studies the migration of the active material vertically, i.e. throughout the thickness, of the film throughout the drying process (see p. 262, col. 1, lines 11 to col. 2, line 3). Le Person discloses that after 5 min of drying, "the polymeric network is not turgescent and the meshes are densely packed. The polymer skeleton acts as a filter for the active substance [i.e., pharmaceutical or drug] when the system reequilibrates." (See p. 262, col. 2, third full paragraph.) Le Person also teaches that "[b]etween the 5^{th} and 10^{th} min of drying the heavy solvent migrates… active substance, slowed down in its migration, stays in the bottom of the layer." (See the last four lines at page 262, col. 2). It is noted that the heavy solvent only accounts for 2% of the wet composition of the coating (see page 258, Table 1). As such, within 5-10 minutes, the solvent has been sufficiently evaporated such that a substantial uniform distribution of the active is locked-in and migration is substantially prevented within the film. The active material homogenizes

and a quasi-equilibrium is obtained for the components of the active phase, taking into account evaporation of the heavy solvent (p. 263, col. 1, lines 8-13), and thus, there is a variation of active content of less than 10%, as per claims 272, 273, 290 and 291.

As noted above, after 10 minutes of drying, 99% of the water has been evaporated (see p. 260, col. 2, lines 12-14 and Fig. 5). In fact, the water is intensely removed from the film in the first 3 minutes with the short infrared drying process (see p. 261, col. 2, lines 21-24 and 27-30). Also, as can be seen from Fig. 2 on p. 259, similar intense drying is seen using conduction, convention, etc. As seen in Fig. 5, after 4 minutes of drying, about 98% of the water has been evaporated.

Le Person thus teaches all the limitations of at least one claim of the '080 patent. Accordingly, Requester has shown a reasonable likelihood of prevailing with respect to at least one claim of the '080 patent.

RLP based on Horstmann:

11. The request indicates that requester considers that claims 1, 5, 7-10, 12-14, 23, 63, 64, 82, 84, 86-89, 91-93, 102, 142, 143, 161, 166, 168-171, 173-175, 184, 224, 225, 249, 254, 267, 272, 285 and 290 are anticipated by Horstmann.

Horstmann teaches rapidly dissolvable films for delivery of individual dosage of drugs, cosmetics and the like (see Abstract, col. 3, lines 7-10 and 20-35). Horstmann teaches forming a masterbatch premix of components prior to adding the active material. In particular, in Examples 1, 3 and 4 at cols. 4-6, a masterbatch is formed containing a water soluble polymer, i.e. acetylated starch, and water; and then an active material, i.e., peppermint oil, is added to the premix to form a homogeneous,

spreadable, i.e., flowable, polymer matrix (see also col. 3, lines 20-35; and col. 4, lines 19-26). Under the category of "Actives", the '080 patent teaches flavors such as mint oils (see col. 21, lines 35-63). Peppermint is also a breath freshener; and the '080 patent teaches that breath fresheners are drugs (col. 20, lines 35-38). In fact, peppermint has a high menthol content, and the '080 patent teaches menthol is a breath freshener (col. 21, lines 35-36). Horstmann teaches that the use of homogenizers to render the mixture more intimate or the application of a vacuum to remove air bubbles may be useful (see col. 4, lines 24-26).

The homogeneous mass is spread, i.e., casted, onto siliconized paper with a coating device, and the water is then evaporated (see col. 5, lines 1-3 and 51-53). In Horstmann's Example 3, the drying is for 10 minutes as here claimed at a temperature of 80°C (col. 3, lines 51-53), which is within the most desirable temperature range of 80°C or less taught at col. 27, lines 53-55 of the '080 patent. The resulting film in Example 3 is viscoelastic since it can be removed, e.g., peeled from the paper (see col. 4, lines 46-51 and col. 5, lines 54-61). The films in Horstmann's Examples 1 and 4 are dried for 15 minutes at 80°C (see col. 5, lines 1-3 and col. 6, lines 12-14). It is the Examiner's position that the films of Examples 1 and 4 are viscoelastic at 10 minutes or less of drying, the remaining time in the 15 minutes providing for a more dry viscoelastic film. Like the film of Example 3, the dried films of Examples 1 and 4 can be removed from the paper (see col. 4, lines 46-51 and col. 5, lines 4-12). The dried films in Examples 1, 3 and 4 are also viscoelastic since they are prepared using the same materials and process steps as here claimed.

The dried films of Horstmann's Examples 1, 3 and 4 have a water content of 10% or less. The examples have the same components and use the same process steps as here claimed. Further, the examples in '080 patent specification start with more water than Examples 1, 3 and 4 of Horstmann, use the same or similar drying conditions as Horstmann, and result in dried films having well less than 10% water. For example, as noted above, Horstmann's Example 3 dries at 80° for 10 minutes (col. 5, lines 51-53). The total weight in Example 3 is (25 g acetylated starch +20 g sorbitol + 30 g calcium carbonate + 1 g titanium + 22 g water + 8 g glycerol + (0.5 mL peppermint oil x 0.9 g/mL estimated density of peppermint oil) = 106.45 g. Thus, the weight percent of water in Horstmann's Examples 3 is (22/106.45) x 100 = 21%. In Example CI at col. 43-44 of the '080 patent, the water content before drying, based on the weights shown in Table 16, is about 65%. After drying for 10 minutes at 80°C the water content was either 3.52% or 3.95% (see col. 44, lines 2-5 of the '080 patent). Likewise Examples A-I (see Table 1) and BA-BI (see Table 9) of the '080 patent start with much more water than Horstmann's Examples 1, 3 and 4 (see also col. 14, lines 55-59 of the '080 patent).

Horstmann's films before drying are described as being uniform and homogeneous (see col. 3, line 11-19, 29-34 and 37-41; col. 5, lines 1 and 50), and as noted above, Horstmann uses the same components and process steps as here claimed. The '080 patent notes that Horstmann addressed the problem of self-aggregation and non-uniformity by increasing the viscosity of the film prior to drying in an effort to reduce aggregation of the components in the film (see col. 2, line 60 through col. 3, line 1). Further, ¶ 9 of the Cohen Declaration notes the following:

> 9. In general, as a homogeneous or completely dispersed coating mixture is dried, the solvent is removed, the viscosity increases and the active would be more firmly fixed in place. When working with a homogeneous or completely dissolved coating mixture, for example, it would be difficult for a person of ordinary skill in the thin film art not to obtain a film that has uniform content of active.

Horstmann thus teaches all the limitations of at least one claim of the '080 patent. Accordingly, Requester has shown a reasonable likelihood of prevailing with respect to at least one claim of the '080 patent.

RLP and 35 USC 101 Double Patenting

12. The request indicates that requester considers that claim 82 should be rejected under 35 USC 101 double patenting over claim 25 of U.S. Patent 7,666,337 (hereafter the '337 patent).

For the following reasons, it is **not agreed** that requester has demonstrated a reasonable likelihood that requester will prevail with respect to at least one claim of the '080 patent.

Claim 82 of the '080 patent and claim 25 of the '337 patent are reproduced below:

82. A process for making a film having a substantially uniform distribution of components, comprising the steps of:

(a) forming a flowable polymer matrix comprising a polymer selected from the group consisting of a water-soluble polymer, a water swellable polymer and combinations thereof, a solvent and an active selected from the group consisting of bioactive actives, pharmaceutical actives, drugs, medicaments and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix;

(c) evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film within about 10 minutes or fewer to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film; and

(d) forming a resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained.

25. A process for making a film having a substantially uniform distribution of components, comprising the steps of:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and an active, said matrix having a uniform distribution of said active;

(b) casting said flowable polymer matrix;

(c) evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film within about 10 minutes or fewer to maintain said uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film; and

(d) forming a resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained.

Requester argues that the term “water soluble polymer” in claim 25 is coextensive with “water swellable polymer" in claim 82 and cites col. 15, lines 62-66 of the '080 patent (see p. 239 of the request). The ‘080 patent is a continuation of the '337 patent, and thus share the same disclosure. Col. 15, line 45 through col. 16, of the ‘080 patent is reproduced below:

> The polymer may be water soluble, water swellable, water insoluble, or a combination of one or more either water soluble, water swellable or water insoluble polymers. The polymer may include cellulose or a cellulose derivative. Specific examples of useful water soluble polymers include, but are not limited to, polyethylene oxide (PEO), pullulan, hydroxypropylmethyl cellulose (HPMC), hydroxyethyl cellulose (HPC), hydroxypropyl cellulose, polyvinyl pyrrolidone, carboxymethyl cellulose, polyvinyl alcohol, sodium aginate, polyethylene glycol, xanthan gum, tragancanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof. Specific examples of useful water insoluble polymers include, but are not limited to, ethyl cellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate and combinations thereof.

> As used herein the phrase "water soluble polymer" and variants thereof refer to a polymer that is at least partially soluble in water, and desirably fully or predominantly soluble in water, or absorbs water. Polymers that absorb water are often referred to as being water swellable polymers. The materials useful with the present invention may be water soluble or water swellable at room temperature and other temperatures, such as temperatures exceeding room temperature. Moreover, the materials may be water soluble or water swellable at pressures less than atmospheric pressure. Desirably, the water soluble polymers are water soluble or water swellable having at least 20 percent by weight water uptake. Water swellable polymers having a 25 or greater percent by weight water uptake are also useful. Films or dosage forms of the present invention formed from such water soluble polymers are desirably sufficiently water soluble to be dissolvable upon contact with bodily fluids.

The terms "water soluble polymer" and "water swellable polymer" are not coextensive. A water swellable polymer is not necessarily water soluble. For example, the '080 patent teaches that ethyl cellulose and hydroxypropyl ethyl cellulose (HPEC) are water insoluble (see col. 15, lines 56-60). However, it is well known that ethyl cellulose and HPEC are water swellable, as evidenced by the teachings in U.S. Patent 6,534,090, hereby made of record (see col. 2, lines 6-12 and col. 5, lines 41-45).

Requester further argues that the Markush group of actives in claim 82, i.e., "bioactive actives, pharmaceutical actives, drugs, medicaments and combinations thereof", is coextensive with the term "active" in claim 25 of the '337 patent (see p. 240 of the request).

This is unpersuasive. The '080 patent teaches the following at col. 19, lines 42-48:

> The active components that may be incorporated into the films of the present invention include, without limitation pharmaceutical and cosmetic actives, drugs, medicaments, proteins, antigens or allergens such as ragweed pollen, spores, microorganisms, seeds, mouthwash components, flavors, fragrances,

enzymes, preservatives, sweetening agents, colorants, spices, vitamins and combinations thereof.

The bioactive actives, pharmaceutical actives, drugs and medicaments (i.e., "medicating active ingredient") are discussed and exemplified at col. 19, line 49 through col. 21, line 31 of the '080 patent. This discussion does not include materials such as preservatives, fragrances, colorants, spices, vitamins, etc.

For example, cosmetic active ingredients such as flavors, fragrances, sweeteners and colors are subsequently discussed at col. 21, line 35 through col. 22, line 21 of the '080 patent. While some cosmetic actives such as breath fresheners are listed in the '080 patent as drugs and cosmetic actives (col. 20, line 38 and col. 21, line 35), there's nothing in the '080 patent teaching that materials such cherry, grape, beef or chicken flavor, color additives such as azo dyes or inorganic pigments, preservatives or fragrances are considered to be bioactive actives, pharmaceutical actives, drugs or medicaments.

Accordingly, the term "active" in claim 25 of the '337 patent is broader than the term "bioactive actives, pharmaceutical actives, drugs, medicaments and combinations thereof" in claim 82 of the '080 patent.

Furthermore, claims 25 and 82 are of different scope because step (a) of claim 25 requires that the matrix has "a uniform distribution of said active", whereas step (a) of claim 82 requires that the matrix has "a substantially uniform distribution of said active". The term "substantially" opens the claimed "uniform distribution" to

interpretation, and "substantially uniform distribution" in the matrix of claim 82 does not require a "uniform distribution" in the matrix as in claim 25.

Request argues that "uniform distribution of said active" and "substantially uniform distribution of said active" are coextensive. In particular, requester argues the following on pp. 241-242:

> First, no distinction between the terms "substantially uniform" and "uniform" as applied to active variation is made or defined by the '080 Patent specification. Other than appearing many times in the '080 Patent claims, the term "substantially uniform" only appears once in the specification in the Summary of the Invention. Col. 4, line 51.
>
> Second, Applicant has without ambiguity disavowed a claim scope - in both patents - where the uniformity of its films exceeds a 10% variation in its active content. Specifically, Applicant emphasizes, when distinguishing the inventive films from those in the prior art, that government regulatory agencies worldwide, including the U.S. Food and Drug Administration require no more than 10% variation in the amount of active present. See the '080 Patent, col. 2, lines 40-46; and the '337 Patent, col. 2, lines 38-44. "When applied to dosage units based on films, this virtually mandates that uniformity in the film be present." *Id.* Applicant chose to make these statements to distinguish the uniformity its films from the lack of uniformity of the prior art films. Col. 2, lines 7-47. "For this reason, dosage forms formed by processe[s] such as Fuchs, would not likely meet the stringent standards of government or regulatory agencies, such as the U.S. Federal Drug Administration (FDA) ...." Col. 2, lines 37-41. Applicant has clearly disavowed variance of more than 10% of active in distinguishing its inventive film from those in the art. Accordingly, the term "substantially uniform distribution of active" - recited in the claims - at best, means a variation of less than 10%, as the remaining scope has been disavowed. This is the broadest reasonable interpretation of the claims, as is required in a reexamination proceeding.
>
> At the same time, Applicant has also chosen to define what "uniformity" means when referring to distribution of active in the films of the present invention. It is defined as the presence of no more than 10% variance.
>
> > .... Furthermore, such consideration with proper material selection provides the compositions of the present invention, including a pharmaceutical and/or cosmetic dosage form or film product having no more than a 10% variance of a pharmaceutical and/or cosmetic active per

> unit area. **In other words, the uniformity of the present invention is determined by the presence of no more than a 10% by weight of pharmaceutical and/or cosmetic variance throughout the matrix.** Desirably, the variance is less than 5% by weight, less than 2% by weight, less than 1% by weight, or less than 0.5% by weight.
>
> The '080 Patent, col. 15, lines 32-42; and the '337 Patent, col. 15, lines 32-42 (emphasis added).

That is, under the broadest reasonable interpretation of the claims, the terms "uniformity" and "substantial uniformity" have both been defined and employed in the '080 Patent to mean less than 10% variation. These terms are co-extensive and there are no embodiments that fall within one claim and not the other.

Finally, it is noted that remaining steps (b), (c), and (d) are identical except for the same recitation of "substantially uniform" dealt with directly above.

These arguments are unpersuasive. The no more than 10% variance that requester cites to in the '080 patent is referring to the final film product. The "uniform distribution of said active" and "substantially uniform distribution of said active" at issue here is in the material that results from step (a), i.e., the matrix, which is an intermediate product, not the final product. This matrix has a uniform distribution of active material in claim 25, and a substantially uniform distribution of active material in claim 82.

In claim 25, the active is uniformly distributed (i.e., no variance of active) in the matrix, and then, after casting and solvent evaporation, the active has been locked in place or its migration has been substantially prevented such that the resulting dried film product has a substantially uniform distribution of the active, for example said no more than 10% variance. In claim 82, the active is substantially uniformly distributed in the matrix, i.e., the active is either uniformly distributed (i.e., no variance of active) or close to uniformly distributed in the matrix (e.g., no more than 10% variance), and then, after

casting and solvent evaporation, the active has been locked in place or its migration has been substantially prevented such that the resulting dried film product has a substantially uniform distribution of the active, for example said no more than 10% variance.

Accordingly, requester has not shown that claim 25 of the '337 demonstrates a reasonable likelihood that requester will prevail with respect to claim 82 of the '080 patent.

Duty to Disclose

The patent owner is reminded of the continuing responsibility under 37 CFR 1.565(a) to apprise the Office of any litigation activity, or other prior or concurrent proceeding, involving Patent No. 7,897,080 throughout the course of this reexamination proceeding. The third party requester is also reminded of the ability to similarly apprise the Office of any such activity or proceeding throughout the course of this reexamination proceeding.

All correspondence relating to this *inter partes* reexamination proceeding should be directed:

By EFS: Registered users may submit via the electronic filing system EFS-Web at https://efs.uspto.gov/efile/myportal/efs-registered

By Mail to: Attn: Mail Stop "Inter Partes Reexam"
Central Reexamination Unit
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Alexandria VA 22313-1450

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Central Reexamination Unit

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Customer Service Window
Attn: Central Reexamination Unit
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/Deborah Jones/
Supervisory Patent Examiner, Art Unit 3991

Notice of References Cited	Application/Control No. 95/002,170	Applicant(s)/Patent Under Reexamination 7897080	
	Examiner Alan Diamond	Art Unit 3991	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-6,534,090	03-2003	Puthli et al.	424/473
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
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*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

EXHIBIT Q

PTO/SB/08b (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	Not Yet Assigned
Filing Date	September 10, 2012
First Named Inventor	Robert K. Yang
Art Unit	Not Yet Assigned
Examiner Name	Not Yet Assigned
Attorney Docket Number	117744-00023

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
/A.D./	A1	5,393,528	02-28-1995	Staab et al.	
/A.D./	A2	5,629,003	05-13-1997	Horstmann et al.	
/A.D./	A3	7,666,337	02-23-2010	Yang et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
/A.D./	B1	WO2000/42992	07-27-2000	Chen et al.		

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
/A.D./	C1	LE PERSON et al., "Near infrared drying of pharmaceutical thin films: experimental analysis of internal mass transport", Chem. Eng. & Proc. 37:257-263 1998	

Examiner Signature	/Alan Diamond/ (10/15/2012)	Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. * CITE NO.: Those application(s) which are marked with an single asterisk (*) next to the Cite No. are not supplied (under 37 CFR 1.98(a)(2)(iii)) because that application was filed after June 30, 2003 or is available in the IFW. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with § 1.6(a)(4).

Dated: September 10, 2012
Electronic Signature for Danielle L. Herritt: /Danielle L. Herritt/

INTER PARTES REEXAMINATION COMMUNICATION	Control No.	Patent Under Reexamination
	95/002,170	7897080
	Examiner	Art Unit
	Alan Diamond	3991

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address. --

BELOW/ATTACHED YOU WILL FIND A COMMUNICATION FROM THE UNITED STATES PATENT AND TRADEMARK OFFICE OFFICIAL(S) IN CHARGE OF THE PRESENT REEXAMINATION PROCEEDING.

All correspondence relating to this *inter partes* reexamination proceeding should be directed to the **Central Reexamination Unit** at the mail, FAX, or hand-carry addresses given at the end of this communication.

Reexamination	Application/Control No. 95002170	Applicant(s)/Patent Under Reexamination 7897080
	Certificate Date	Certificate Number

Requester Correspondence Address:	☐ Patent Owner	☒ Third Party

Danielle L. Herrit
McCarter & English LLP
265 Franklin Street
Boston, MA 02110

LITIGATION REVIEW ☒	/AD/ (examiner initials)	09/13/2012 (date)
Case Name		Director Initials
None		

COPENDING OFFICE PROCEEDINGS	
TYPE OF PROCEEDING	NUMBER
1. None	

Transmittal of Communication to Third Party Requester *Inter Partes* Reexamination	Control No.	Patent Under Reexamination	
	95/002,170	7897080	
	Examiner	Art Unit	
	Alan Diamond	3991	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address. --

(THIRD PARTY REQUESTER'S CORRESPONDENCE ADDRESS)

Danielle L. Herritt
McCarter & English LLP
265 Franklin Street
Boston, MA 02110

Enclosed is a copy of the latest communication from the United States Patent and Trademark Office in the above-identified reexamination proceeding. 37 CFR 1.903.

Prior to the filing of a Notice of Appeal, each time the patent owner responds to this communication, the third party requester of the *inter partes* reexamination may once file written comments within a period of 30 days from the date of service of the patent owner's response. This 30-day time period is statutory (35 U.S.C. 314(b)(2)), and, as such, it cannot be extended. See also 37 CFR 1.947.

If an *ex parte* reexamination has been merged with the *inter partes* reexamination, no responsive submission by any *ex parte* third party requester is permitted.

All correspondence relating to this inter partes reexamination proceeding should be directed to the **Central Reexamination Unit** at the mail, FAX, or hand-carry addresses given at the end of the communication enclosed with this transmittal.

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	95002170	7897080
	Examiner	Art Unit
	ALAN DIAMOND	3991

SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
Reviewed parent Serial No. 12/614,928	10/02/2012	/AD/

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
95/002,170	09/10/2012	7897080	117744-00023	6418

23869 7590 10/22/2012

Hoffmann & Baron LLP
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EXAMINER
DIAMOND, ALAN D

ART UNIT	PAPER NUMBER
3991	

MAIL DATE	DELIVERY MODE
10/22/2012	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

OFFICE ACTION IN INTER PARTES *REEXAMINATION*	Control No.	Patent Under Reexamination
	95/002,170	7897080
	Examiner	Art Unit
	Alan Diamond	3991

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address. --

Responsive to the communication(s) filed by:
Patent Owner on _____
Third Party(ies) on _____

RESPONSE TIMES ARE SET TO EXPIRE AS FOLLOWS:

For Patent Owner's Response:
2 MONTH(S) from the mailing date of this action. 37 CFR 1.945. EXTENSIONS OF TIME ARE GOVERNED BY 37 CFR 1.956.
For Third Party Requester's Comments on the Patent Owner Response:
30 DAYS from the date of service of any patent owner's response. 37 CFR 1.947. NO EXTENSIONS OF TIME ARE PERMITTED. 35 U.S.C. 314(b)(2).

All correspondence relating to this inter partes reexamination proceeding should be directed to the **Central Reexamination Unit** at the mail, FAX, or hand-carry addresses given at the end of this Office action.

This action is not an Action Closing Prosecution under 37 CFR 1.949, nor is it a Right of Appeal Notice under 37 CFR 1.953.

PART I. THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892
2. ☐ Information Disclosure Citation, PTO/SB/08
3. ☐ _____

PART II. SUMMARY OF ACTION:

1a. ☒ Claims 1-299 are subject to reexamination.
1b. ☐ Claims _____ are not subject to reexamination.
2. ☐ Claims _____ have been canceled.
3. ☐ Claims _____ are confirmed. [Unamended patent claims]
4. ☐ Claims _____ are patentable. [Amended or new claims]
5. ☒ Claims 1-299 are rejected.
6. ☐ Claims _____ are objected to.
7. ☐ The drawings filed on _____ ☐ are acceptable ☐ are not acceptable.
8. ☐ The drawing correction request filed on _____ is: ☐ approved. ☐ disapproved.
9. ☐ Acknowledgment is made of the claim for priority under 35 U.S.C. 119 (a)-(d). The certified copy has: ☐ been received. ☐ not been received. ☐ been filed in Application/Control No _____.
10. ☐ Other _____

Summary of Proceedings

A Request pursuant to 37 CFR 1.913 for inter partes reexamination of claims 1-299 of U.S. Patent 7,897,080 (hereinafter "the '080 patent") was filed September 10, 2012 by Third Party Requester. An Order granting inter partes reexamination of claims 1-299 of the '080 patent accompanies the instant Office action. 37 CFR 1.935.

Art Cited in this Office Action

Chen et al, WO 00/42992, hereafter "Chen".

Staab, U.S. Patent 5,393,528.

Le Person et al, "Near infrared drying of pharmaceutical thin films: experimental analysis of internal mass transport," Chemical Engineering and Processing, Vol. 37, pp. 257-263, (1998), hereafter "Le Person".

Horstmann et al, U.S. Patent 5,629,003, hereafter "Horstmann".

Scope of Claims

In reexamination, patent claims are construed broadly. *In re Yamamoto*, 740 F.2d 1569, 1571, 222 USPQ 934, 936 (Fed. Cir. 1984) (claims given "their broadest reasonable interpretation consistent with the specification"). This reexamination proceeding contains claims 1-299 directed to a process for making a film having a substantially uniform distribution of components and to a process for making a film capable of being administered to a body surface having a substantially uniform distribution of components. Claims 1, 82 and 161 representative:

1. A process for making a film having a substantially uniform distribution of components, comprising the steps of:

(a) forming a masterbatch pre-mix comprising a solvent and a polymer selected from the group consisting of water-soluble polymers, water-swellable polymers and combinations thereof;

(b) adding an active to a pre-determined amount of said masterbatch pre-mix to form a flowable polymer matrix, said matrix having a substantially uniform distribution of said active;

(c) casting said flowable polymer matrix;

(d) evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film within about 10 minutes or fewer to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film; and

(e) forming a resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained.

82. A process for making a film having a substantially uniform distribution of components, comprising the steps of:

(a) forming a flowable polymer matrix comprising a polymer selected from the group consisting of a water-soluble polymer, a water swellable polymer and combinations thereof, a solvent and an active selected from the group consisting of bioactive actives, pharmaceutical actives, drugs, medicaments and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix;

(c) evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film within about 10 minutes or fewer to

maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film; and

(d) forming a resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained.

161. A process for making a film capable of being administered to a body surface having a substantially uniform distribution of components, comprising the steps of:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and an active, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix;

(c) evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film within about 10 minutes or fewer to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film;

(d) forming a resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained; and

(e) administering said resulting film to a body surface.

Claims 1, 82 and 161 recite a step of forming a flowable polymer matrix comprising a recited polymer, a solvent and an active, said matrix having a substantially uniform distribution of said active. With respect to the “matrix”, the ‘080 patent, for example, states the following:

> When the active is combined with the polymer in the solvent, the type of matrix that is formed depends on the solubilities of the active and the polymer. If the active and/or polymer are soluble in the selected solvent, this may form a solution. However, if the components are not soluble, the matrix may be classified as an emulsion, a colloid, or a suspension (see col. 22, lines 22-28).
>
> After the desired components are combined to form a multi-component matrix, including the polymer, water, and an active or other components as desired … (see col. 25, lines 55-57).

Accordingly, the "matrix" is taken to be the material that results from mixing the polymer, solvent and active.

With respect to viscoelasticity in steps (d) and (e) of claim 1 and in steps (c) and (d) of claims 82 and 161, it is noted that the matrix prior to evaporating the solvent (water) may be viscoelastic, and the viscoelasticity is present due, for example, to the fact that a hydrocolloid has been added. In particular, the '080 patent teaches the following (bold emphasis added):

> The viscosity of the liquid phase is critical and is desirably modified by customizing the liquid composition to a **viscoelastic** non-Newtonian fluid with low yield stress values .... Formation of a **viscoelastic** or a highly structured fluid phase provides additional resistive forces to particle sedimentation. (Col. 8, lines 32-38).
>
> The addition of hydrocolloids to the aqueous phase of the suspension increases viscosity, may produce **viscoelasticity**, and can impart stability depending on the type of **hydrocolloid**, its concentration and the particle composition, geometry, size and volume fraction. (Col. 8, lines 42-46).
>
> For **viscoelastic** fluid systems, a rheology that yields stable suspensions for extended time period, such as 24 hours, must be balanced with the requirements of high-speed film casting operations. (Col. 8, line 66 through Col. 9, line 2).
>
> The rheology requirements for the inventive compositions and films are quite severe. This is due to the need to produce a stable suspension of particles, for example 30-60 wt. %, in a **viscoelastic** fluid matrix with acceptable viscosity values throughout a broad shear rate range...

> In film casting or coating, rheology is also a defining factor with respect to the ability to form films with the desired uniformity. Shear viscosity, extensional viscosity, **viscoelasticity**, structural recovery will influence the quality of the film. (Col. 9, lines 9-20).
>
> Desirably, the films or film-forming compositions of the present invention have a very rapid structural recovery, i.e. as the film is formed during processing, it doesn't fall apart or become discontinuous in its structure and compositional uniformity. Such very rapid structural recovery retards particle settling and sedimentation. Moreover, the films or film-forming compositions of the present invention are desirably shear-thinning pseudoplastic fluids. Such fluids with consideration of properties, such as **viscosity and elasticity**, promote thin film formation and uniformity. (Col. 9, lines 31-40).
>
> Compositions P-R show the effects of **visco-elastic** properties on the ability to coat the film composition mixture onto the substrate for film formation .... This product coated the substrate but would not stay level due to the change in the **visco-elastic** properties of the wet foam. (Col. 35, lines 55-57, and 61-63).

While the '080 does not state what is an example of a hydrocolloid, a well-known hydrocolloid in the art is the water-soluble polymer hydroxypropyl methylcellulose (HPMC), which is used in most of the examples of the '080 patent. The Chen reference teaches that HPMC is a hydrocolloid (see p. 14, lines 22-27).

The preamble of claims 1, 82 and 161 recite "for making a film having a substantially uniform distribution of components". These claims later recite "locking-in or substantially preventing migration" of the active, and also recite that the matrix has a "substantially uniform distribution of the active". None of these terms is given a special definition in the '080 patent. However, the '080 patent teaches at col. 31, lines 37-44, that a "uniform distribution of components" can be

determined by examination by either the naked eye or under slight magnification, and that "by viewing the films it was apparent that they were substantially free of aggregation, i.e. the carrier and the actives remained substantially in place and did not move substantially from one portion of the film to another … [t]herefore, there was substantially no disparity among the amount of active in any portion of the film." An alternative means for evaluating uniformity is to cut the film into individual doses and measure the weight of the doses (col. 31, line 46 through col. 32, line 45). The '080 patent notes that "films of substantially similar size cut from different locations of the same film contain substantially the same amount of active." (col. 32, lines 37-39).

Claims 16 and 32 are identical. So are claims 95 and 111; and claims 177 and 193.

Proposed Claim Rejections - 35 USC § 102 and § 103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which

said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1. Claims 1, 4, 5, 8-18, 20-32, 34, 36-40, 44-47, 51, 53, 54, 59, 62-71, 82-84, 87-97, 99-111, 113, 115-119, 123-126, 130, 132, 133, 138, 141-150, 161-166, 169-179, 181-193, 195, 197-201, 205-208, 212, 214, 215, 220, 223-232, 243, 244, 246, 247, 249-262, 264, 265, 267-280, 282, 283 and 285-299 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Chen.

The rejection of claims 1, 4, 5, 8-18, 20-32, 34, 36-40, 44-47, 51, 53, 54, 59, 62-71, 82-84, 87-97, 99-111, 113, 115-119, 123-126, 130, 132, 133, 138, 141-150, 161-166, 169-179, 181-193, 195, 197-201, 205-208, 212, 214, 215, 220, 223-232, 243, 244, 246, 247, 249-262, 264, 265, 267-280, 282, 283 and 285-299 under 35 USC 102(b) over Chen and the rejection of claims 65-69, 71, 144-148, 150, 226-230, 232, 253, 271 and 289 under 35 USC 103(a) over Chen were proposed by Third Party Requester and **are adopted** for the reasons that follow. The rejection of claims 1, 4, 5, 8-18, 20-32, 34, 36-40, 44-47, 51, 53, 54, 59, 62-64, 70, 82-84, 87-97, 99-111, 113, 115-119, 123-126, 130, 132, 133, 138, 141-143, 149, 161-166, 169-179, 181-193, 195, 197-201, 205-208, 212, 214, 215, 220, 223-225, 231, 243, 244, 246, 247, 249-252, 254-262, 264, 265, 267-270, 272-280, 282, 283, 285-288 and 290-299 under 35 USC 103(a) over Chen is Examiner initiated.

Chen teaches a dosage unit including a water-soluble hydrocolloid, mucosal surface-coat-forming film, such film including an effective dose of an

active agent (see p. 3, lines 30-32). In Examples 5-8, Chen prepares hydroxypropyl methylcellulose (HPMC, i.e., “Methocel E5”) based quick dissolving intraoral films containing active agents (see p. 20, lines 17-20 and Tables 5 and 7). In particular, the films in Examples 5-8 contain an active agent, e.g., nicotine, hydromorphone, oxybutynin or estradiol; HPMC; and a solvent, i.e., water (see Tables 5 and 7). Further, the film in Tables 7 and 8 of Chen uses sildenafil citrate as an active ingredient and is prepared using HPMC, i.e. “Methocel E15”, and water as the solvent. The film in Chen’s Example 1 contains HPMC; peppermint, citric acid and aspartame as actives; and water as the solvent (see Tables 1 to 4). The film in Chen’s Example 2 contains "Pullalan (P-20) [sic, Pullulan (P-20)]” as the polymer; peppermint, citric acid and aspartame as actives; and water and ethanol as solvents (see Tables 1 and 2). Peppermint, citric acid and aspartame are also actives in Chen’s Examples 5-8, and peppermint and aspartame are actives in the film in Chen's Tables 7 and 8. Under the category of "Actives", the '080 patent teaches flavors such as mint oil, flavor enhancers such as citric acid, and sweeteners such as aspartame (see col. 21, lines 35-63 and col. 22, lines 9-13). Peppermint is also a breath freshener; and the ‘080 patent teaches that breath fresheners are drugs (col. 20, lines 35-38). Additionally, peppermint has a high menthol content, and the ‘080 patent teaches menthol is a breath freshener (col. 21, lines 35-36). Other taste modifying agents, i.e., taste masking agents, are disclosed at p. 10, lines 7-14 of Chen.

The specific water-soluble polymer, solvent and actives exemplified in Chen are identical to those exemplified in the '080 patent. HPMC is employed in almost every example of the '080 patent. HPMC and pullulan are taught by the '080 patent as being water soluble (col. 15, lines 45-57). The same solvent, i.e., water is employed in almost every example in the '080 patent. Sildenafil is exemplified in Examples CI and FB of the '080 patent (see Tables 16 and 30). Likewise, peppermint oil and/or sweetener are used in numerous examples in the '080 patent, such as Examples A, B, C, D, F, G, H, BA, BB, BC, etc (see Tables 1 and 9).

The following is a list of hydrocolloid polymers, including said HPMC and pullulan, disclosed by Chen for forming the film (see p. 14, line 12 through page 15, line 3):

> In embodiments of the invention, the hydrocolloid may be a water soluble non-gelling (at room temperature) natural polysaccharide or derivatives including pectin and derivatives, guar gum arabic, tragacanth gum, xanthan gum, gellan sodium salt, propyleneglycol alginate, starches (amylose, amylopectin), modified starches, hydroxyethyl starch, pullulan, carboxymethyl starch, gum ghatti, okra gum, karaya gum, dextrans, dextrins and maltodextrins, konjac, acemannan from aloe, locust bean gum, tara gum, quince seed gum, fenugreek seed gum, scleroglucan, gum arabic, psyllium seed gum, tamarind gum, oat gum, quince seed gum, carrageenans, scleraglucan, succinoglucan, larch arabinogalactan, flaxseed gum, chondroitin sulfates, hyaluronic acid, curdlan, chitosan, deacetylated konjac, and rhizobium gum.
>
> In embodiments of the invention, the hydrocolloid may be a water soluble non-gelling polypeptide or protein exemplified by gelatins, albumins, milk proteins, soy protein, and whey proteins. The hydrocolloid may further be selected from a group of synthetic hydrocolloids exemplified by any of the following: polyethylene-imine, hydroxyethyl cellulose, sodium carboxymethyl cellulose, carboxymethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, methyl cellulose, ethyl cellulose, polyacrylic acids, low molecular weight polyacrylamides

> and their sodium salts (carbomers), polyvinylpyrollidone, polyethylene glycols, polyethylene oxides, polyvinyl alcohols, pluronics, tetronics, and other block co-polymers, carboxyvinyl polymers, and colloidal silicon dioxide. A preferred embodiment of the invention utilizes a hydroxypropyl methyl cellulose having a methoxy content of about 19-30% and hydroxypropyl content of 7-12% and a molecular weight of approximately 50,000-250,000 daltons (Table 9).

In addition to the specific active materials noted above, i.e., nicotine, hydromorphone, oxybutynin, estradiol, sildenafil citrate, peppermint, citric acid and aspartame, the following is a list of active agents disclosed by Chen (see p. 10, line 22 through page 11, line 12):

> Active agents (for human and veterinary applications) include therapeutic agents, nutritional supplements and hygiene aids. The therapeutic agents are exemplified by analgesics, a-adrenergic receptor blockers, anti-Alzheimer's disease medication, antianginal, antianxiety, antiarrythmics, antiarthritics, antibiotics, anticoagulants/thrombolytics, anticonvulsants/anti-Parkinson medication, anti-depressants, anti-diabetics, anti-diarrheal, anti-epileptics, anti-fungal, anti-gout, anti-heartworm medication for dogs, anti-histamines, anti-hypertensives, anti-inflammatories, anti-infectives, antimigraines, anti-nasuants/anti-emetics, anti-neoplastics/anti-tumor active agents, anti-pruitics, anti-psychotics, anti-pyretics, anti-spasmodics, anti-virals, bronchial dilators/anti-asthmatics, calcium antagonists, cardiac agents, cardiotonics, central nervous system actives, contraceptives, coronary vasodilators, cough/cold remedies, dietary supplements, including vitamins and minerals, diuretics, fertility active agents, flea control agents for animals (Ivermectin), H_2 receptor antagonists, herbal actives, hormones, hypoglycemics, hypolipidemics, muscle relaxants, ovulation stimulators, peptide active agents, polypeptide active agents, proteins such as insulin, calcitonin, LHRH and the like. Sedatives and hypnotics, sexual dysfunction active agents, sleep aids, smoking cessation aids, steroids and steroidals, tranquilizers, laxatives, ophthalmic preparations, nutritional supplements, breath fresheners, breath deodorants, saliva substitutes, antigingivitis agents, anti-cavity agents, anti-plaque agents, diagnostic indicators, and local anesthetics. Also included are active agents for treatment of osteoporosis, hormone replacement, treatment of periodontal disease, antiseptics, corticosteroids, non steroidal anti-inflammatory agents, antiviral agents and vaccines.

In the method of preparation of the films, the HPMC or pullulan, which Chen teaches is a hydrocolloid, is dissolved in water under agitated mixing to form a uniform and viscous solution which reads on the instant masterbatch pre-mix, and the additional ingredients are added under agitated mixing until they are uniformly dispersed (i.e., suspended) or dissolved in the hydrocolloid (see p. 14, line 22 through p. 15, line 3; and p. 17, lines 6-19). The resultant mixture, i.e. the instant flowable polymer matrix, is degassed in a vacuum chamber until trapped air bubbles are removed, and then coated, i.e., casted as per step (b) of claims 82 and 161 and as per step (c) of claim 1, on the non-siliconized side of a polyester film (see p. 17, lines 13-15).

With respect to steps (c) and (d) of claims 82 and 161, and with respect to steps (d) and (e) of claim 1, Chen evaporates water from the cast matrix in 9 minutes of drying in a hot air circulating oven at 50°C (see p. 17, lines 13-15 and Fig. 2). As seen schematically in Chen's Fig. 2, the air flow is less direct at the film surface at the beginning of the drying and becomes more direct as the film proceeds through the drying oven, which has an aeration controller (see also p. 5, line 31 through p. 6, line 3). Chen's Example 1 starts with 74.42% water content and is dried to 1.7% water content (see Tables 1 and 4). Chen's Examples 5 to 8 start with 73.03%, 71.51%, 70.72% and 72.94% water content and are dried to 2.93%, 2.42%, 2.32% and 2.31% water content, respectively. Chen's Example 2 starts with 10.6% ethanol and 67.025% water and, after drying for 9 minutes at 50°C, the water content is 8.5% (see Tables 1 and 2).

The claimed "substantially uniform distribution of components" and "locking-in or substantially preventing migration" of the active in independent claims 1, 82 and 161, and the variation of active content of 10% or less in dependent claims 254-255, 272-273 and 290-291, are inherent in Chen's exemplified films and process. Inherency is based on the following: As discussed above, Chen uses the same materials and method as here claimed. Chen's ingredients are mixed until they are uniformly dispersed or dissolved in the hydrocolloid (p. 17, lines 8-11). Chen uses the same criteria discussed above with respect to the '080 patent in the Scope of Claims section for evaluation of substantial uniform distribution, i.e., weight of dosages and visual inspection. In particular, Chen's dried film product of Example 1 is cut into dosage units ready for packing (p. 17, lines 31-32) and has a weight of 0.028 $\pm$ 0.001 g/dosage film, a density of 1.0485 $\pm$ 0.009 g/cm^2, a water content of 1.7 $\pm$ 0.24%, and as noted above, a thickness of 2.1 $\pm$ 0.12 mil (see Table 4); and the dried films are glossy and substantially transparent (p. 17, line 15), i.e., they are visually free of aggregation. The 0.028 $\pm$ 0.001 g/dosage film has variation of (0.001/0.028) x 100 = 3.6%. When film weight is rounded to two decimal places as in Table 2 at col. 31 of the '080 patent, then the weight is 0.03 gram/dosage film with a variation of 0%.

Furthermore, as noted in the Rule 1.132 Declaration of Edward D. Cohen (hereafter "Cohen Declaration") submitted with the request, when working with a homogeneous or completely dissolved coating mixture as in Chen, it would be difficult for a person of ordinary skill in the film art not to obtain a film that has a

uniform content of active, and the drying method disclosed in Chen would not be expected to create any agglomeration, aggregation or otherwise non-uniform content of active (see ¶¶ 8-10).

Further with respect to steps (c) and (d) of claims 82 and 161 and steps (d) and (e) of claim 1, and with respect to viscoelasticity, either Chen's mixture before drying is viscoelastic and the resulting dried film also is viscoelastic, or alternatively, if Chen's mixture before drying is not viscoelastic, then it becomes viscoelastic as the drying proceeds.

In particular, as noted above, the '080 patent teaches that "[t]he addition of hydrocolloids to the aqueous phase of the suspension increases viscosity, may produce viscoelasticity, and can impart stability depending on the type of hydrocolloid, its concentration and the particle composition, geometry, size and volume fraction (see col. 8, lines 42-46). Chen adds the same hydrocolloid as in the '080 patent, i.e. said HPMC, to water, and Chen's wet matrix before drying has a viscosity of 500-15,000 cps (p. 15, line 26), which is within the '080 patent's disclosed range of about 400-100,000 cps and overlaps the most preferred range of about 1,000-40,000 cps (see the paragraph bridging cols. 16 and 17 of the '080 patent). Accordingly, Chen's films in Examples 1, 2 and 5-8 and the Example in Tables 7 and 8 are inherently viscoelastic before drying.

Alternatively, to the extent that Chen's wet film in Examples 1, 2, 5-8 and the example in Tables 7 and 8 before drying are not viscoelastic, then at some time during the 9 minutes of drying in the hot air circulating oven at 50°C, a viscoelastic film is inherently formed. In particular, in order to arrive at a dried

film product as in Chen, which is made using the same materials as disclosed in the '080 patent and the same basic process steps here claimed, wherein the dried film is glossy and substantially transparent and has the gram per dosage, thickness, density and water content noted above for Example 1, then a viscoelastic film is inherently formed during Chen's 9-minute drying.

While Chen does not discuss viscoelasticity or that the films resulting from its process have a "substantially uniform distribution of components" or disclose "locking-in or substantially preventing migration" of the active, Chen, as cited above, discloses a process which reasonably appears to be either the same as or an obvious variation of the instantly claimed process. Accordingly, claims 1, 4, 5, 8-18, 20-32, 34, 36-40, 44-47, 51, 53, 54, 59, 62-71, 82-84, 87-97, 99-111, 113, 115-119, 123-126, 130, 132, 133, 138, 141-150, 161-166, 169-179, 181-193, 195, 197-201, 205-208, 212, 214, 215, 220, 223-232, 243, 244, 246, 247, 249-262, 264, 265, 267-280, 282, 283 and 285-299, if not anticipated under 35 USC 102(b), would be obvious under 35 USC 103(a).

With respect to claims 16, 32, 95, 111, 177 and 193, which require that the active is a biological response modifier, it is noted that all of the actives listed by Chen at p. 10, line 22 through page 11, line 12 are biological response modifiers. Alternatively, biological response modifiers are well-known actives in the art. It would have been obvious to one of ordinary skill in the art to have used any well-known active, such as a biological response modifier, as the active in Chen's film with the resulting expectation of preparing a film for delivery of the agent and so as to take advantage of the agent's known function.

With respect to claims 25, 104 and 186, which require that the active is an anti-tussive, Chen, as noted above, teaches that its active can be a cough/cold remedy (see p. 10, line 32 through page 11, line 1). A cough/cold remedy encompasses and thus, anticipates or renders obvious an anti-tussive, i.e., cough relieving/depressing, agent.

With respect to claims 65-69, 144-148 and 226-230, which require that the active is coated with a controlled release composition, Chen discloses that its films may release the active agent over a period of time that is determined by a number of different factors (see page 6, line 30 through page 7, line 21). More specifically, Chen discloses: "Depending on the optimal program for a specific application of the invention, the disintegration time and the dissolution time can be controlled within a prescribed range by adjustment of the formulation and the thickness of the film. In some cases, it is desirable for release of the active agent to occur after dissolution of the film. For these applications, the active agent may be encapsulated in a material with dissolution properties that are different from those of the hydrocolloid. Encapsulation of the active agent may also be utilized to achieve masking of taste for active agents that are bitter. In some cases, two or more different active agents may be included in the film." (See page 9, lines 9-16). Slow release films are also discussed, e.g., at page 7, lines 16-21. Accordingly, immediate, delayed, sustained or sequential release of active as here claimed, if not anticipated by the teachings of Chen, would have been obvious so as to obtain a desired release of the active(s).

With respect to claims 70, 149, 231, 259, 260, 277, 278 and 295-297, Chen teaches that the active material can be in the form of a particle, e.g., a colloid particle or microencapsulated (see p. 7, lines 17-21). As noted above, Chen's polymers such as HPMC are hydrocolloids (p. 14, line 24-31), and Chen's matrix has the ingredients uniformly dispersed, i.e., suspended, in the hydrocolloid (p. 17, lines 6-11).

With respect to claims 71, 150 and 232, which require the addition of a degassing agent, as noted above Chen teaches peppermint (see p. 10, line 9; Examples 1-8 and the example in Tables 7 and 8). During prosecution US patent application Serial No. 11/858,214, Patent Owner admits that peppermint is a foam reducing flavoring agent which "act[s] to both flavor the film and prevent and/or remove air from the film-forming compositions." (See the last paragraph on p. 5 of the response filed 12/20/10 and claim 5 of the 11/858,214 application).

With respect to claims 162, 163, 249-252, 258, 267-270, 276, 285-288 and 294, Chen teaches that the films are suitable for administration of the active material through buccal, gingival, sublingual and mucosal surfaces (see p. 8, lines 4 and 9-10, and Fig. 1). With respect to claim 164, Chen teaches that the mucosal surface can be a wound (see p. 7, lines 31-32).

With respect to claim 253, 271 and 289, which require that the film provides administration of the active within the body of the individual during surgery, as noted above, Chen teaches that its films can be applied to a mucosal surface, which refers to any moist surface in the body, including a wound (see p. 7, lines 31-32 and p. 8, line 4). Accordingly, Chen's films can be administered at

any time, including surgery. Chen discloses several active agents that are highly suitable for use "during surgery", including sedatives, local anesthetics, antiseptics, anti-inflammatory agents, anti-viral agents, muscle relaxants, and steroids (see p. 10, line 29 through p. 11, line 12). Further, Chen teaches that "[e]mbodiments of the invention include .... for a quick dissolving film for local and systemic delivery of pharmaceutical agents to a mucosal surface in a subject .... The dosage unit of the invention may be applied to any mucosal surface as deemed appropriate for the systemic or local delivery of an active agent including vaginal, rectal and ocular surfaces ... [e]mbodiments [may be administered easily by] physicians, parents, patients ..." (*see* p. 8, lines 2-4, 6-10, and 19-20). Chen also teaches the application of films to a wound surface "where lymph fluid bathes the tissue surface" at p. 7, lines 32 through p. 8, line 1. Thus, Chen anticipates or renders obvious that its film “provides administration of said active to an individual by administration within the body of the individual during surgery” as here claimed.

2. Claims 2, 3, 6, 7, 19, 33, 35, 41-43, 48-50, 52, 55-58, 60, 61, 85, 86, 98, 112, 114, 120-122, 127-129, 131, 134-137, 139, 140, 167, 168, 180, 194, 196, 202-204, 209-211, 213, 216-219, 221, 222, 245, 248, 263, 266, 281 and 284 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen.

This rejection was proposed by Third Party Requester and **is adopted** for the reasons that follow.

Chen, as relied upon for the reasons stated above, teaches the limitations of the instant claims other than the differences discussed below.

With respect to claims 2 and 3, Chen does not specifically teach that its premix of polymer and solvent, i.e., instant masterbatch premix, is controllably fed via a first metering pump and a control valve to a first mixer and a second mixer, and that the first and second mixers are arranged in parallel, series or a combination thereof.

However, metering pumps, mixing vessels and control valves are standard equipment in the art, and so is their arrangement in parallel, series or a combination thereof. Accordingly, it would have been obvious to one of ordinary skill in the art at the time was made to have used metering pumps, mixing vessels and control valves when preparing Chen's wet film because such equipment is standard in the art, and so as to mix Chen's masterbatch premix and active.

With respect to claims 6, 7, 85, 86, 167 and 168, Chen does not specifically teach using combinations of its hydrocolloids, such as a mixture of the exemplified HPMC with any of the other hydrocolloids taught by Chen such as ethylcellulose, polyacrylic acid polymer, etc.

However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have used combinations of Chen's hydrocolloids in place of a single hydrocolloid with the expectation that a film for mucosal delivery of active agent would be obtained. The rationale to use a

combination of Chen's hydrocolloids flows logically from their each having been individually taught as useful as the hydrocolloid component of Chen's film.

The remaining claims in this rejection, i.e., claims 19, 33, 35, 41-43, 48-50, 52, 55-58, 60, 61, 98, 112, 114, 120-122, 127-129, 131, 134-137, 139, 140, 180, 194, 196, 202-204, 209-211, 213, 216-219, 221, 222, 245, 248, 263, 266, 281 and 284 are directed to particular active materials. These active agents are either well-known in the art or are species of the generic active agents taught by Chen at p. 10, line 22 through p. 11, line 12. See also the discussion of these claims in the claim chart of the request on pp. 77-82 and 84-89, which are hereby incorporated by reference.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have used the actives here claimed so as to prepare Chen's film because such actives are well-known in the art or are species of the generic active agents taught by Chen; the reasonable expectation of success in preparing a film for mucosal delivery of the active; and so as to take advantage of the active's known function.

3. Claims 2, 3, 16, 32, 55, 72-81, 95, 111, 134, 151-160, 177, 193, 216 and 233-242 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teaching of Chen and Staab.

On pages 89-105 of the request, Third Party Requester proposes that claims 1-3, 16, 32, 55, 65-69, 72-75, 78-82, 95, 111, 134, 144-148, 151-154, 157-161, 177, 193, 216, 226-230, 233-236, 239-242, 254, 255, 257-259, 272,

273, 275-277, 290, 291 and 293-295 be rejected under 35 USC 103(a) as being obvious over the combined teachings of Chen and Staab. Likewise, on pages 143-151 of the request, Third Party Requester proposes that claims 1, 8, 9, 17, 71, 82, 87, 88, 96, 150, 161, 169, 170, 178, 232, 260, 278 and 296-299 be rejected under 35 USC 103(a) as being obvious over the combined teachings of Chen and Staab. For the reasons that follow, the proposed rejection of claims 1, 8, 9, 17, 65-69, 71, 82, 87, 88, 96, 144-148, 150, 161, 169, 170, 178, 226-230, 232, 254, 255, 257-260, 272, 273, 275-278, 290, 291 and 293-299 **is not adopted**. For the reasons that follow, the proposed rejection of claims 2, 3, 16, 32, 55, 72-75, 78-81, 95, 111, 134, 151-154, 157-160, 177, 193, 216, 233-236 and 239-242 **is adopted**. The rejection of claims 76, 77, 155, 156, 237 and 238 is Examiner initiated.

As noted above, Chen anticipates or renders obvious claims 1, 8, 9, 17, 65-69, 71, 82, 87, 88, 96, 144-148, 150, 161, 169, 170, 178, 226-230, 232, 254, 255, 257-260, 272, 273, 275-278, 290, 291 and 293-299. Reliance on the teachings of Staab is not needed to reject these claims, and thus, the proposed rejection of claims 1, 8, 9, 17, 65-69, 71, 82, 87, 88, 96, 144-148, 150, 161, 169, 170, 178, 226-230, 232, 254, 255, 257-260, 272, 273, 275-278, 290, 291 and 293-299 over the combined teachings of Chen and Staab is not adopted.

With respect to claims 2 and 3, to the extent that Chen does not render obvious controllably feeding its master batch pre-mix via a metering pump and a control valve to a first mixer and a second mixer such that the first and second

mixer are arranged in parallel, series or a combination thereof, then such is rendered obvious in combination with the teachings of Staab.

Staab teaches films made of dissolvable polymer material and/or complex carbohydrate material which are food grade materials, wherein the films also contain an agent such as a drug or medication (see abstract). Staab teaches that "[t]he agent material is evenly distributed throughout the film, so as the film slowly dissolves, it releases the agent material in the proper dosage ...." (see col. 5, line 68 through col. 6, line 3). Staab also discloses that “[t]he device of the invention thus is composed of a biologically compatible material that has been blended homogeneously" with the drug (see col. 6, lines 6-10). Staab teaches forming a pre-mix including a water soluble polymer and water in proper concentrations at a first temperature in a first vessel and then transferring to another vessel of a cooler temperature (in series with the first vessel), and then stirring in heat sensitive ingredients (see col. 7, lines 37-48). Staab’s Fig. 5 depicts three mixing vessels that can readily be employed for practicing the claimed method, the top two vessels being in parallel with each other, the lower vessel being in series with the top two vessels. Any transfer from one vessel to another would inherently or obviously involve a metering pump and control valve. Arrangement of the vessels in parallel would accommodate a choice of heat sensitive ingredients, such as those disclosed in Staab (see col. 7, lines 37-51).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have prepared Chen’s matrix by forming a pre-mix including a water soluble polymer and water in proper concentrations at a first

temperature, then to have transferred the contents of the vessel to another vessel of a cooler temperature, and then to have stirred in heat sensitive ingredients, e.g., drug(s) as in Staab, so as to protect the drug(s), which is usually the most expensive component.

With respect to claims 16, 32, 95, 111, 177 and 193, to the extent that Chen does not teach or render obvious that its active can be a biological response modifier, then such is rendered obvious in combination with the teachings of Staab. Likewise, with respect to claims 55, 134 and 216, to the extent that Chen does not teach or render obvious that its active can be a decongestant, then such is rendered obvious in combination with the teachings of Staab.

Staab teaches that its active agent can be monoclonal antibodies, i.e., biological response modifiers, such as those useful against cell surface components or against pathogenic organisms such as HIV (see col. 6, lines 49-53). Likewise, Staab teaches that its active agent can be a decongestant (see col. 7, line 1).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have used a monoclonal antibody or decongestant for Chen's active because such actives are conventional in the art, as shown by Staab; so as to take advantage of the active material's known function; and the reasonable expectation of success.

With respect to claims 72-81, 151-160 and 233-242, Chen does not specifically teach providing a second film layer. Staab teaches that its film may

be a laminate of two or more layers (see col. 5, lines 30-31; col. 9, lines 28-43; and Fig. 2). Staab teaches that the laminates can be formed in the conventional manner, for example the mixture in liquid form is poured or cast onto a plate or into a mold and allowed to begin to set, at which time another liquid mixture with different composition is poured on the first mixture, and both mixtures are allowed to set up completely producing a laminate or layers of different materials (see col. 5, lines 51-58). The extruding and spraying of the second film in claims 76, 77, 155, 156, 237 and 238 are conventional methods that are obvious variants of the pouring and casting exemplified by Staab.

Staab teaches that the first and second layers can comprise an active. In particular, referring to Fig. 2, Staab teaches the following at col. 9, lines 28-43:

> A first film layer 13 is made of, for example, a faster dissolving polymer material for release of a drug material 14a. A second film layer 15 is made of slower dissolving polymer material for release of more drug or another drug material 14b in combination, for example, a spermicide and an anti-infective or anti-inflammatory medication. A third (and additional) layer(s) 16 with additional drug can also be employed for sustained release of the drug.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have laminated a second film to Chen's drug-containing film as per the teachings of Staab so as to control the release rate of the drug, provide for release of more drug, or provide for release of another drug in addition to the drug in Chen's film.

4. On pages 105-108 and 200-208 of the request, Third Party Requester proposes that claims 1, 8, 9, 17, 45, 53, 71, 82, 87, 88, 96, 124, 132, 150, 161, 169, 170, 178, 206, 214, 232, 254, 272 and 290 be rejected under 35 USC 103(a) as being obvious over the combined teachings of Chen and Le Person.

This proposed rejection **is not adopted** for the reasons that follow.

As noted above, Chen anticipates or renders obvious claims 1, 8, 9, 17, 45, 53, 71, 82, 87, 88, 96, 124, 132, 150, 161, 169, 170, 178, 206, 214, 232, 254, 272 and 290. While it is acknowledged that Le Person further teaches, for example, the use of infrared drying (p. 258, col. 1), none of said claims is limited to this feature. Accordingly, the teachings of Le Person are not needed to reach the limitations of said claims, and thus, the proposed rejection of said claims over the combined teachings of Chen and Le Person is not adopted.

5. On pages 227-236 of the request, Third Party Requester proposes that claims 1, 4, 13, 15, 17, 45, 53, 71, 82, 83, 92, 94, 96, 124, 132, 150, 161, 165, 174, 176, 178, 206, 214 and 232 be rejected under 35 USC 103(a) as being obvious over the combined teachings of Chen and Horstmann.

This proposed rejection **is not adopted** for the reasons that follow.

As noted above, Chen anticipates or renders obvious claims 1, 4, 13, 15, 17, 45, 53, 71, 82, 83, 92, 94, 96, 124, 132, 150, 161, 165, 174, 176, 178, 206, 214 and 232. While it is acknowledged that Horstmann teaches, for example, forming a homogeneous mixture (col. 5, lines 1 and 44; and col. 6, line 9), so

does Chen (p. 17, lines 6-11). Accordingly, reliance on the teachings of Horstmann is not needed, and thus, the proposed rejection of said claims over the combined teachings of Chen and Horstmann is not adopted.

6. Claims 1-5, 10, 12-16, 21, 24, 25, 32, 44-46, 54, 55, 59, 63-70, 72-75, 78-84, 89, 91-95, 100, 103, 104, 111, 123-125, 133, 134, 138, 142-149, 151-154, 157-166, 171, 173-177, 182, 185, 186, 193, 205-207, 215, 216, 220, 224-231, 233-236, 239-242, 249-252, 254, 255, 257-260, 267-270, 272, 273, 275-278, 285-288, 290, 291 and 293-299 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Staab.

The rejection of claims 1-5, 10, 12-15, 21, 24, 25, 44-46, 54, 55, 59, 63-70, 72-75, 78-84, 89, 91-94, 100, 103, 104, 123-125, 133, 134, 138, 142-149, 151-154, 157-166, 171, 173-176, 182, 185, 186, 205-207, 215, 216, 220, 224-231, 233-236, 239-242, 249-252, 254, 255, 257-260, 267-270, 272, 273, 275-278, 285-288, 290, 291 and 293-299 under 35 USC 102(b) as anticipated by Staab and the rejection of claims 16, 32, 95, 111, 177 and 193 under 35 USC 103(a) as being obvious over Staab were proposed by Third Party Requester and **are adopted** for the reasons that follow. The 35 USC 102(b) rejection of claims 16, 32, 95, 111, 177 and 193 and the 35 USC 103(a) rejection of claims 1-5, 10, 12-15, 21, 24, 25, 44-46, 54, 55, 59, 63-70, 72-75, 78-84, 89, 91-94, 100, 103, 104, 123-125, 133, 134, 138, 142-149, 151-154, 157-166, 171, 173-176, 182, 185, 186, 205-207, 215, 216, 220, 224-231, 233-236, 239-242, 249-252,

254, 255, 257-260, 267-270, 272, 273, 275-278, 285-288, 290, 291 and 293-299 are Examiner initiated.

Staab teaches the preparation of a film for local administration of an active agent in an internal body area (see col. 2, lines 34-62). Staab teaches films made of dissolvable polymer material, e.g., PEO and/or HPMC, both of which are identified as water soluble polymers in the '080 patent at col. 15, lines 50-51, and Staab's film also contains a drug or medication as the active agent (see Abstract; and col. 2, lines 34-46). Staab teaches that "[t]he agent material is evenly distributed throughout the film, so as the film slowly dissolves, it releases the agent material in the proper dosage..." (See col. 5, line 68 through col. 6, line 3). Staab teaches that "the polymer solids, water, or other solvent, contraceptive [i.e., an active]…, are admixed in the proper concentrations and the mixture heated to the appropriate temperature for dissolution and formation of a uniform blend to take place." (See col. 7, lines 37-41). In the Example at cols. 11-12, the ingredients are mixed together in a blender until just blended (see col. 11, lines 222-27). As such, Staab teaches formation of a flowable polymer matrix. A masterbatch pre-mix as in instant claim 1 can be formed containing polymer and solvent, and the pre-mix is then transferred to a cooler vessel for addition of heat-sensitive pharmaceuticals or other agents (see col. 7, lines 37-51). Other polymers that can be used along with PEO and/or HPMC include polyvinyl alcohol (see col. 2, line 41; and col. 4, lines 22-61).

The active agents that can be used in Staab's film include spermicides for contraceptive use and/or drugs or medications (see col. 5, lines 66-68). The

following is a list of active agents taught by Staab at col. 6, line 35 through col. 7, line 3:

> (1) anti-infectives such as antibiotics, sulfonamides, antivirals, antifungals, antiprotozoan and antibacterials;
>
> (2) anti-inflammatories, such as hydrocortisone, dexamethasone, triamcinolone, and various prednisolone compounds;
>
> (3) estrogenic steroids, such as estrone;
>
> (4) progestational agents, such as progesterone;
>
> (5) prostaglandins;
>
> (6) coronary vasodilators;
>
> (7) antitussives;
>
> (8) antihistamines;
>
> (9) anesthetics and
>
> (10) decongestants.
>
> Monoclonal antibodies [which are biological response modifiers] such as those useful against cell surface components or against pathogenic organisms such as the human-immuno-deficiency (HIV) family of viruses may be incorporated into the device of the present invention … . Other drugs include clotrimazole, miconazole, ticonazole, benzalkonium chloride, nystatin, dermally active steroids, hormones, benzocaine, sulfas, biologically prepared actives, decongestants, cough/cold remedies, psychotropics, nitroglycerine, etc.

Staab also teaches the use of flavors, fragrances and coloring agents (see col. 7, lines 28-29). Thus, Staab's active material can be taste-masked.

Staab also discloses that "[t]he device of the invention thus is composed of a biologically compatible material that has been blended homogeneously" with the drug (see col. 6, lines 5-10). In the Example at cols. 11-12, Staab prepares a

four-foot wide film which is then cut into two inch by two inch films each weighing 190 mg and containing 19 mg of benzalkonium chloride as the active agent (see col. 11, line 52 through col. 12, line 3). Accordingly, Staab's films inherently have the instantly claimed substantially uniform distribution of components and active. Also, in view of the fact that each film contains 19 mg of benzalkonium chloride and in view of said homogeneous blending, the variation of active in the dosage units is 0%, as per claims 254, 255, 272, 273, 290 and 291.

With respect to step (c) in claim 1 and with respect to step (b) in claims 82 and 161, Staab further discloses that "the mixture in liquid form will be poured or cast on to a plate or into a mold..." (See col. 5, lines 51-58 and the casting lines depicted in Fig. 5). In the Example at cols. 11-12, the blended mixture is poured onto a glass plate and spread to an even 3 mil thick film covering the surface of the glass (see col. 11, lines 41-44).

With respect to steps (d) and (e) in claim 1 and with respect to steps (c) and (d) in claims 82 and 161, Staab discloses drying the film in a temperature regulated oven for approximately 20 minutes at 160°F, i.e., 71°C, or for 20 to 40 minutes when using a continuously moving belt that enters a drier (see col. 11, lines 45 and 65). The ingredients blended to prepare the film are 52.5% HPMC, 37.5% glycerin and 10.0% of a 50% aqueous solution of the benzalkonium chloride (see col. 11, lines 30-34). Accordingly, within 10 minutes or fewer (i.e. half the 20 minute drying time), at least a portion of the water has been evaporated to form the film. Since the water content before drying is 5% (i.e.,

half of the 10% of the 50% aqueous solution of benzalkonium chloride), the dried film must have a water content of 10% or less as here claimed.

Further, either Staab's mixture in the Example at cols. 11-12 before drying is viscoelastic and the resulting dried film also is viscoelastic, or alternatively, if the blended mixture before drying is not viscoelastic, then it becomes viscoelastic as the drying proceeds.

In particular, as noted above, the '080 patent teaches that "[t]he addition of hydrocolloids to the aqueous phase of the suspension increases viscosity, may produce viscoelasticity, and can impart stability depending on the type of hydrocolloid, its concentration and the particle composition, geometry, size and volume fraction (see col. 8, lines 42-46). Staab uses the same hydrocolloid as in the '080 patent, i.e. said HPMC. Accordingly, Staab's film in the Example at cols. 11-12 is inherently viscoelastic before drying. Accordingly, after drying for about 10 minutes, a viscoelastic film having less water that before drying is formed.

Alternatively, to the extent that Staab's blended mixture before drying is not viscoelastic, then within about 10 minutes of the drying, a viscoelastic film is inherently formed. In particular, in order to arrive at a dried film product as in Staab, which is made using the same materials as disclosed in the '080 patent and the same basic process steps here claimed and having a substantially uniform distribution of components as discussed above, then a viscoelastic film is inherently formed within about 10 minutes of the drying.

While Staab does not discuss viscoelasticity or that the films resulting from its process have a "substantially uniform distribution of components" or disclose

"locking-in or substantially preventing migration" of the active, Staab, as cited above, discloses a process which reasonably appears to be either the same as or an obvious variation of the instantly claimed process. Accordingly, claims 1-5, 10, 12-16, 21, 24, 25, 32, 44-46, 54, 55, 59, 63-70, 72-75, 78-84, 89, 91-95, 100, 103, 104, 111, 123-125, 133, 134, 138, 142-149, 151-154, 157-166, 171, 173-177, 182, 185, 186, 193, 205-207, 215, 216, 220, 224-231, 233-236, 239-242, 249-252, 254, 255, 257-260, 267-270, 272, 273, 275-278, 285-288, 290, 291 and 293-299, if not anticipated under 35 USC 102(b), would be obvious under 35 USC 103(a).

Further, with respect to claims 2 and 3, as noted above, Staab teaches a masterbatch pre-mix can be formed containing polymer and solvent, and the pre-mix is then transferred to a cooler vessel, i.e., a second vessel in series, for addition of heat-sensitive pharmaceuticals or other agents (see col. 7, lines 37-51). Staab's Fig. 5 depicts three mixing vessels, the top two vessels being in parallel with each other, the lower vessel being in series with the top two vessels. Any transfer from one vessel to another would inherently or obviously involve a metering pump and control valve.

With respect to claims 65-69, 144-148 and 226-230 which require that the active is coated with a controlled release composition, and with respect to claims 72-75, 78-81, 151-154, 157-160, 233-236 and 239-242 which require providing a second film layer, Staab teaches that its film may be a laminate of two or more layers (see col. 5, lines 30-31; col. 9, lines 28-43; and Fig. 2). Staab teaches that the laminates can be formed in the conventional manner, for example the mixture

in liquid form is poured or cast onto a plate or into a mold and allowed to begin to set, at which time another liquid mixture with different composition is poured on the first mixture, and both mixtures are allowed to set up completely producing a laminate or layers of different materials (see col. 5, lines 51-58). Staab teaches that the first and second film can comprise an active. In particular, referring to Fig. 2, Staab teaches the following at col. 9, lines 28-43:

> A first film layer 13 is made of, for example, a faster dissolving polymer material for release of a drug material 14a. A second film layer 15 is made of slower dissolving polymer material for release of more drug or another drug material 14b in combination, for example, a spermicide and an anti-infective or anti-inflammatory medication. A third (and additional) layer(s) 16 with additional drug can also be employed for sustained release of the drug.

Thus, the layers provide for controlled release of the drug material, i.e., a fast and slow release, and thus a sequential release, and also a sustained release. Staab also teaches immediate release since Staab teaches that "in case of medications to be administered via the oral cavity, it is advantageous that dissolution take place fairly rapidly." (See col. 4, lines 59-61). Immediate release and sustained release are also exemplified at col. 13, lines 13-41.

With respect to claims 70, 149, 231, 259, 260, 277, 278 and 295-297, Staab teaches many actives that are particulate, such as monoclonal antibodies (see col. 5, lines 49-53). The particulate monoclonal antibodies would be dispersed, i.e., suspended, in the matrix during the uniform blending (see col. 6, lines 5-10; col. 7, line 41; and col. 11, lines 26-35). Also, it is noted that polymers such as said PEO and HPMC are hydrocolloids.

With respect to claims 162, 163, 249-252, 258, 267-270, 276, 285-288 and 294, Staab teaches that if the drug can be applied on or in a moist area of the body, such as the mouth, vagina, rectum or eye, then the film can be used to deliver the drug effectively (see col. 7, lines 3-8). Application on or in the mouth either anticipates or renders obvious gingival, sublingual and buccal application. With respect to claim 164, Staab teaches the treatment of burn wounds with its films (see col. 7, lines 7-9).

7. Claims 8, 9, 76, 77, 87, 88, 155, 156, 169, 170, 237 and 238 are rejected under 35 U.S.C. 103(a) as being unpatentable over Staab.

On pages 135-143 of the request, Third Party Requester proposes that claims 6-9, 76, 77, 85-88, 155, 156, 167-170, 237 and 238 be rejected under 35 USC 103(a) as being obvious over Staab. The proposed rejection of claims 6, 7, 85, 86, 167 and 168 **is not adopted** for the reasons that follow. The proposed rejection of claims 8, 9, 76, 77, 87, 88, 155, 156, 169, 170, 237 and 238 **is adopted** for the reasons that follow.

With respect to claims 6, 7, 85, 86, 167 and 168, Staab does not teach or render obvious the combination of polymers required in these claims. Claims 6, 85 and 167 require, in addition to a material such as HPMC, the further presence of a particular water-insoluble polymer. Staab teaches dissolvable polymers such as PEO, polyvinyl alcohol, and/or a complex carbohydrate such as HPMC (col. 4, line 6 through col. 5, line 29), but does not teach or render obvious the further inclusion of a water-insoluble polymer. The further polymers set forth in

claims 7, 86 and 168 are also not taught by Staab, and the combination of these further polymers with, for example, HPMC or polyvinyl alcohol is not rendered obvious by Staab.

Staab is relied upon for the reasons stated above in rejection No. 6.

With respect to claims 8, 9, 87, 88, 169, and 170, Staab teaches that its polymer can be a dissolvable complex carbohydrate (col. 4, line 6 through col. 5, line 29), but does not specifically teach the complex carbohydrates here claimed, such as sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum and starch. However, these are conventional dissolvable polymers in the art. Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have used sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum and/or starch for the dissolvable complex carbohydrate to prepare Staab's film because these are conventional, dissolvable complex carbohydrates in the art and the reasonable expectation of success in preparing Staab's film.

With respect to claims 76, 77, 155, 156, 237 and 238, Staab does not specifically teach that its second film layer is extruded or sprayed onto its first film layer. As noted above, Staab teaches that the laminates can be formed in the conventional manner, for example the mixture in liquid form is poured or cast onto a plate or into a mold and allowed to begin to set, at which time another liquid mixture with different composition is poured on the first mixture, and both mixtures are allowed to set up completely producing a laminate or layers of different materials (see col. 5, lines 51-58). The instantly claimed extrusion and

spraying are well known alternative techniques to coating and casting for forming a layer.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have used extrusion or spraying in place of coating and casting to form Staab's second film layer because extrusion and spraying are well known alternative techniques to coating and casting, and the resulting reasonable expectation of success in preparing Staab's second film layer.

8. On pages 163-199 of the request, Third Party Requester proposes that claims 1-5, 10, 12-16, 21, 24, 25, 32, 44-46, 54, 55, 59, 63-70, 72-75, 78-84, 89, 91-95, 100, 103, 104, 111, 123-125, 133, 134, 138, 142-149, 151-154, 157-166, 171, 173-177, 182, 185, 186, 193, 205-207, 215, 216, 220, 224-231, 233-236, 239-242, 249-252, 254, 255, 257-260, 267-270, 272, 273, 275-278, 285-288, 290, 291 and 293-299 be rejected under 35 USC 103(a) as being obvious over the combined teachings of Staab and Le Person.

This proposed rejection **is not adopted** for the reasons that follow.

As noted above, Staab anticipates or renders obvious claims 1-5, 10, 12-16, 21, 24, 25, 32, 44-46, 54, 55, 59, 63-70, 72-75, 78-84, 89, 91-95, 100, 103, 104, 111, 123-125, 133, 134, 138, 142-149, 151-154, 157-166, 171, 173-177, 182, 185, 186, 193, 205-207, 215, 216, 220, 224-231, 233-236, 239-242, 249-252, 254, 255, 257-260, 267-270, 272, 273, 275-278, 285-288, 290, 291 and 293-299. While it is acknowledged that Le Person further teaches, for example,

the use of infrared drying (p. 258, col. 1), none of said claims is limited to this feature. Accordingly, the teachings of Le Person are not needed to reach the limitations of said claims, and thus, the proposed rejection of said claims over the combined teachings of Staab and Le Person is not adopted.

9. Claims 82, 89-91, 161, 171-173, 272-274 and 290-292 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Le Person.

The rejection of claims 82, 89-91, 161, 171-173, 272-274 and 290-292 under 35 USC 102(b) as anticipated by Le Person was proposed by Third Party Requester and **is adopted** for the reasons that follow. The rejection of claims 90, 172, 273 and 291 under 35 USC 103(a) as obvious over Le Person was proposed by Third Party Requester and **is adopted** for the reasons that follow. The 35 USC 103(a) rejection of claims 82, 89, 91, 161, 171, 173, 272, 274, 290 and 292 is Examiner initiated.

Le Person provides and compares several processes for the drying of pharmaceutical wet films including drying by convection, conduction, and infrared drying (see p. 258, first sentences of § 2.2). The films of Le Person contain an acrylic adhesive polymer, its solvents, which include water, and an active substance which is a pharmaceutical or drug (see p. 258, line 5 and the first sentence of § 2.1; and Table 1). Le Person teaches that the constituents of the active phase, including the pharmaceutical or drug, in the matrix are homogeneously distributed (see p. 262, col. 2, lines 4-6). Le Person teaches that

"[a]fter preparation, the coating mixture is spread on a web and submitted to drying in a tunnel or an oven. Frequently, impinging jets and Infra-red Radiation accomplish the work in a short drying time (100 s as an order of magnitude)." (See p. 257, col. 1, lines 10-14). Using a short infrared drying process, Le Person teaches that in 10 minutes, 99% of the initial water from a 100 µm thick coating is evaporated (see p. 260, col. 2, lines 12-14 and Fig. 5).

As noted above, Le Person teaches that the active substance is homogeneously distributed throughout the initially wet film (see p. 262, col. 2, lines 4-6). Le Person then studies the migration of the active material vertically, i.e. throughout the thickness, of the film throughout the drying process (see p. 262, col. 1, lines 11 to col. 2, line 3). Le Person discloses that after 5 min of the drying, "the polymeric network is not turgescent and the meshes are densely packed. The polymer skeleton acts as a filter for the active substance [i.e., pharmaceutical or drug] when the system reequilibrates." (See p. 262, col. 2, third full paragraph.) Le Person also teaches that "[b]etween the 5^{th} and 10^{th} min of drying the heavy solvent migrates… active substance, slowed down in its migration, stays in the bottom of the layer." (See the last four lines at page 262, col. 2). It is noted that the heavy solvent only accounts for 2% of the wet composition of the coating (see page 258, Table 1). As such, within 5-10 minutes, the solvent has been sufficiently evaporated such that, inherently, a substantial uniform distribution of the active is locked-in and migration is substantially prevented within the film, as here claimed. The active material homogenizes and a quasi-equilibrium is obtained for the components of the

active phase, taking into account evaporation of the heavy solvent (p. 263, col. 1, lines 8-13), and thus, there is a variation of active content of less than 10%, as per claims 272, 273, 290 and 291.

As noted above, after 10 minutes of drying, 99% of the water has been evaporated (see p. 260, col. 2, lines 12-14 and Fig. 5). In fact, the water is intensely removed from the film in the first 3 minutes with the short infrared drying process (see p. 261, col. 2, lines 21-24 and 27-30). Also, as can be seen from Fig. 2 on p. 259, similar intense drying is seen using conduction, convention, etc. As seen in Fig. 5, after 4 minutes of drying, about 98% of the water has been evaporated. Since the mass of water is negligible at the 10 minute point, the film is inherently viscoelastic as here claimed.

While Le Person does not discuss viscoelasticity or that the films in its process have a “substantially uniform distribution of components” or disclose "locking-in or substantially preventing migration" of the active, Le Person, as cited above, discloses a process which reasonably appears to be either the same as or an obvious variation of the instantly claimed process. Accordingly, claims 82, 89-91, 161, 171-173, 272-274 and 290-292, if not anticipated under 35 USC 102(b), would be obvious under 35 USC 103(a).

With respect to claims 90 and 172, Le Person teaches that its coating mixture contains three light solvents (Sl_i) (see p. 258, section 2.1). Table 1 indicates that solvent Sl_2 has a molecular weight of 46, which is the molecular weight of ethanol. While dimethyl ether also has a molecular weight of 46, it cannot be used as a solvent due to its low boiling point of -24°C. Accordingly,

the Le Person's light solvent of molecular weight 46 either anticipates or renders obvious ethanol as here claimed.

Le Person teaches that the films are used in patches for transdermal drug delivery (see Abstract and p. 257, col. 1). Thus, plural dosage units of the same size as per instant claims 273 and 291, e.g., plural transdermal patches of the same size, are anticipated or rendered obvious by Le Person.

With respect to claims 274 and 292, which require that the resulting film contains less than about 6% by weight solvent, the solvent content in Le Person's dried films is far under about 6% as evidenced by Figs. 2 and 5. Le Person teaches that using a short-infrared drying process, in 10 minutes 99% of the initial water content from a 100 µm thick coating is evaporated (see § 3.1 at pp. 260-261, in particular Fig. 5 and the second paragraph of right col. at page 260). In view of the water and heavy solvent content in Fig. 5, the total solvent content is well under about 6%.

10. Claims 92 and 174 are rejected under 35 U.S.C. 103(a) as being unpatentable over Le Person.

This rejection was proposed by Third Party Requester and **is adopted** for the reasons that follow.

Le Person, as relied upon for the reasons stated above in rejection No. 9, does not teach the pharmaceutical or drug active materials listed in claims 92 and 174. However, these materials are conventional pharmaceuticals and drugs.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have used the conventional pharmaceutical or drug materials here claimed as the pharmaceutical or drug material in Le Person's film so as to take advantage of the intended function of the pharmaceutical or drug, and because of a reasonable expectation of success.

11. Claims 1, 5, 7-10, 12-14, 23, 63, 64, 82, 84, 86-89, 91-93, 102, 142, 143, 161, 166, 168-171, 173-175, 184, 224, 225, 249, 254, 267, 272, 285 and 290 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Hortsmann.

The rejection of claims 1, 5, 7-10, 12-14, 23, 63, 64, 82, 84, 86-89, 91-93, 102, 142, 143, 161, 166, 168-171, 173-175, 184, 224, 225, 249, 254, 267, 272, 285 and 290 under 35 USC 102(b) as anticipated by Hortsmann was proposed by Third Party Requester and **is adopted** for the reasons that follow. The 35 USC 103(a) rejection of claims 1, 5, 7-10, 12-14, 23, 63, 64, 82, 84, 86-89, 91-93, 102, 142, 143, 161, 166, 168-171, 173-175, 184, 224, 225, 249, 254, 267, 272, 285 and 290 is Examiner initiated.

Horstmann teaches rapidly dissolvable films for delivery of individual dosage of drugs, cosmetics and the like (see Abstract, col. 3, lines 7-10 and 20-35). Horstmann teaches forming a masterbatch premix of components prior to adding the active material. In particular, in Examples 1, 3 and 4 at cols. 4-6, a masterbatch is formed containing a water soluble polymer, i.e. acetylated starch,

and water; and then an active material, i.e., peppermint oil, is added to the premix to form a homogeneous, spreadable, i.e., flowable, polymer matrix (see also col. 3, lines 20-35; and col. 4, lines 19-26). Under the category of "Actives", the '080 patent teaches flavors such as mint oils (see col. 21, lines 35-63). Peppermint is also a breath freshener; and the '080 patent teaches that breath fresheners are drugs (col. 20, lines 35-38). In fact, peppermint has a high menthol content, and the '080 patent teaches menthol is a breath freshener (col. 21, lines 35-36). Horstmann teaches that the use of homogenizers to render the mixture more intimate or the application of a vacuum to remove air bubbles may be useful (see col. 4, lines 24-26).

The homogeneous mass is spread, i.e., casted, onto siliconized paper with a coating device, and the water is then evaporated (see col. 5, lines 1-3 and 51-53). In Horstmann's Example 3, the drying is for 10 minutes as here claimed at a temperature of 80°C (col. 3, lines 51-53), which is within the most desirable temperature range of 80°C or less taught at col. 27, lines 53-55 of the '080 patent. The resulting film in Example 3 is inherently viscoelastic since it can be removed, e.g., peeled from the paper (see col. 4, lines 46-51 and col. 5, lines 54-61). The films in Horstmann's Examples 1 and 4 are dried for 15 minutes at 80°C (see col. 5, lines 1-3 and col. 6, lines 12-14). It is the Examiner's position that the films of Examples 1 and 4 are inherently viscoelastic at 10 minutes or less of drying, the remaining time in the 15 minutes providing for a more dry viscoelastic film. Like the film of Example 3, the dried films of Examples 1 and 4 can be removed from the paper (see col. 4, lines 46-51 and col. 5, lines 4-12).

The dried films in Examples 1, 3 and 4 are also viscoelastic since they are prepared using the same materials and process steps as here claimed.

The dried films of Horstmann's Examples 1, 3 and 4 inherently have a water content of 10% or less. The examples have the same components and use the same process steps as here claimed. Further, the examples in '080 patent specification start with more water than Examples 1, 3 and 4 of Horstmann, use the same or similar drying conditions as Horstmann, and result in dried films having well less than 10% water. For example, as noted above, Horstmann's Example 3 dries at 80° for 10 minutes (col. 5, lines 51-53). The total weight in Example 3 is (25 g acetylated starch +20 g sorbitol + 30 g calcium carbonate + 1 g titanium + 22 g water + 8 g glycerol + (0.5 mL peppermint oil x 0.9 g/mL estimated density of peppermint oil) = 106.45 g. Thus, the weight percent of water in Horstmann's Example 3 is (22/106.45) x 100 = 21%. In Example CI at col. 43-44 of the '080 patent, the water content before drying, based on the weights shown in Table 16, is about 65%. After drying for 10 minutes at 80°C the water content was either 3.52% or 3.95% (see col. 44, lines 2-5 of the '080 patent). Likewise Examples A-I (see Table 1) and BA-BI (see Table 9) of the '080 patent start with much more water than Horstmann's Examples 1, 3 and 4 (see also col. 14, lines 55-59 of the '080 patent).

The claimed substantially uniform distribution of components and active, and locking-in or substantially preventing migration of active, and the variance of active content of 10% or less in dependent claims 254, 272 and 290 are also inherent in Horstmann's Examples 1, 3 and 4. In particular, Horstmann's films

before drying are described as being uniform and homogeneous (see col. 3, line 11-19, 29-34 and 37-41; col. 5, lines 1 and 50), and as noted above, Horstmann uses the same components and process steps as here claimed. The '080 patent notes that Horstmann addressed the problem of self-aggregation and non-uniformity by increasing the viscosity of the film prior to drying in an effort to reduce aggregation of the components in the film (see col. 2, line 60 through col. 3, line 1). Further, ¶ 9 of the Cohen Declaration notes the following:

> 9. In general, as a homogeneous or completely dispersed coating mixture is dried, the solvent is removed, the viscosity increases and the active would be more firmly fixed in place. When working with a homogeneous or completely dissolved coating mixture, for example, it would be difficult for a person of ordinary skill in the thin film art not to obtain a film that has uniform content of active.

While Horstmann does not discuss viscoelasticity, water content of its dried films or that the films resulting from its process have a "substantially uniform distribution of components" or disclose "locking-in or substantially preventing migration" of the active, Horstmann, as cited above, discloses a process which reasonably appears to be either the same as or an obvious variation of the instantly claimed process. Accordingly, claims 1, 5, 7-10, 12-14, 23, 63, 64, 82, 84, 86-89, 91-93, 102, 142, 143, 161, 166, 168-171, 173-175, 184, 224, 225, 249, 254, 267, 272, 285 and 290, if not anticipated under 35 USC 102(b), would be obvious under 35 USC 103(a).

With respect to claims 5, 7-9, 84, 86-88, 166 and 168-170, Horstmann teaches that, besides starch and derivatives thereof, the gel former can be polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, polyacrylic acid,

carrageenan, dextran, tragacanth, gums of vegetable origin, and polypeptides such as gelatin, albumin, collagen or egg white (see col. 3, line 62 through col. 4, line 6).

With respect to claims 12-14, 23, 63, 64, 91-93, 102, 142, 143, 173-175, 184, 224 and 225, as noted above, Horstmann's Examples 1, 3 and 4 have menthol in the form of peppermint oil, which reads on the instant drug. Horstmann expressly teaches that drugs can be included in its dosage units (see col. 3, lines 20-22). Another drug exemplified by Horstmann is glibenclamide, which is a well-known anti-diabetic drug (see col. 5, line 25). Horstmann further teaches that confectionaries, other food and cosmetics can be included in the films (see col. 3, lines 20-22). The active is “taste masked” due to the presence of honey, citric acid and/or sorbitol (see col. 4, lines 57-59; col. 5, line 40; and col. 6, line 9).

With respect to claims 249, 267 and 285, Horstmann teaches that its films disintegrate in the mouth within 10 minutes (see col. 3, lines 44-46).

Conclusion

The patent owner is reminded of the continuing responsibility under 37 CFR 1.985 to apprise the Office of any litigation activity, or other prior or concurrent proceeding, involving Patent No. 7,897,080 throughout the course of this reexamination proceeding. The third party requester is also reminded of the ability to similarly apprise the Office of any such activity or proceeding throughout the course of this reexamination proceeding. MPEP 2686.

In order to ensure full consideration of any amendments, affidavits or declarations, or other documents as evidence of patentability, such documents must be submitted in response to this Office action. Submissions after the next Office action, which is intended to be an Action Closing Prosecution (ACP), will be governed by 37 CFR 1.116(b) and (d), which will be strictly enforced.

All correspondence relating to this *inter partes* reexamination proceeding should be directed:

By EFS: Registered users may submit via the electronic filing system EFS-Web at https://efs.uspto.gov/efile/myportal/efs-registered

By Mail to: Attn: Mail Stop "Inter Partes Reexam"
Central Reexamination Unit
Commissioner for Patents
P. O. Box 1450
Alexandria VA 22313-1450

Please FAX any communications to:
(571) 273-9900
Central Reexamination Unit

Please hand-deliver any communications to:
Customer Service Window
Attn: Central Reexamination Unit
Randolph Building, Lobby Level
401 Dulany Street
Alexandria, VA 22314

Signed:

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Central Reexamination Unit 3991

/Jerry D. Johnson/
Patent Reexamination Specialist
Central Reexamination Unit 3991

/Deborah Jones/

Supervisory Patent Examiner, Art Unit 3991

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	95002170	7897080
	Examiner	Art Unit
	ALAN DIAMOND	3991

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
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Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
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	Examiner	Art Unit
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Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
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	Examiner	Art Unit
	ALAN DIAMOND	3991

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	299	✓								

Transmittal of Communication to Third Party Requester *Inter Partes* Reexamination	Control No.	Patent Under Reexamination	
	95/002,170	7897080	
	Examiner	Art Unit	
	Alan Diamond	3991	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address. --

(THIRD PARTY REQUESTER'S CORRESPONDENCE ADDRESS)

Danielle L. Herrit
McCarter & English LLP
265 Franklin Street
Boston, MA 02110

Enclosed is a copy of the latest communication from the United States Patent and Trademark Office in the above-identified reexamination proceeding. 37 CFR 1.903.

Prior to the filing of a Notice of Appeal, each time the patent owner responds to this communication, the third party requester of the *inter partes* reexamination may once file written comments within a period of 30 days from the date of service of the patent owner's response. This 30-day time period is statutory (35 U.S.C. 314(b)(2)), and, as such, it cannot be extended. See also 37 CFR 1.947.

If an *ex parte* reexamination has been merged with the *inter partes* reexamination, no responsive submission by any *ex parte* third party requester is permitted.

All correspondence relating to this inter partes reexamination proceeding should be directed to the **Central Reexamination Unit** at the mail, FAX, or hand-carry addresses given at the end of the communication enclosed with this transmittal.

INTER PARTES REEXAMINATION COMMUNICATION	Control No.	Patent Under Reexamination
	95/002,170	7897080
	Examiner	Art Unit
	Alan Diamond	3991

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address. --

BELOW/ATTACHED YOU WILL FIND A COMMUNICATION FROM THE UNITED STATES PATENT AND TRADEMARK OFFICE OFFICIAL(S) IN CHARGE OF THE PRESENT REEXAMINATION PROCEEDING.

All correspondence relating to this *inter partes* reexamination proceeding should be directed to the **Central Reexamination Unit** at the mail, FAX, or hand-carry addresses given at the end of this communication.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

REEXAM CONTROL NUMBER	FILING OR 371 (c) DATE	PATENT NUMBER
95/002,170	09/10/2012	7897080

CONFIRMATION NO. 6418
ASSIGNMENT NOTICE

23869
Hoffmann & Baron LLP
6900 Jericho Turnpike
Syosset, NY 11791

OC000000056562272

Date Mailed: 09/17/2012

NOTICE OF ASSIGNMENT OF *INTER PARTES* REEXAMINATION REQUEST

The above-identified request for *inter partes* reexamination has been assigned to Art Unit 3991. All future correspondence in this proceeding should be identified by the control number listed above and directed to: Mail Stop Inter Partes Reexam, Commissioner for Patents, P.O. Box 1450, Alexandria VA 22313-1450.

A copy of this Notice is being sent to the latest attorney or agent of record in the patent file or, if none is of record, to all owners of record. (See 37 CFR 1.33(c).) If the addressee is not, or does not represent, the current owner, he or she is required to forward all communications regarding this proceeding to the current owner(s)

(MPEP 2222). An attorney or agent receiving this communication who does not represent the current owner(s) may wish to seek to withdraw pursuant to 37 CFR 1.36 in order to avoid receiving future communications. If the address of the current owner(s) is unknown, this communication should be returned with the request to withdraw pursuant to Section 1.36.

cc: Third Party Requester
DANIELLE L. HERRITT
MCCARTER & ENGLISH LLP,
265 FRANKLIN STREET
BOSTON, MA 02110

/sdstevenson/

Legal Instruments Examiner
Central Reexamination Unit 571-272-7705; FAX No. 571-273-9900

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

REEXAM CONTROL NUMBER	FILING OR 371 (c) DATE	PATENT NUMBER
95/002,170	09/10/2012	7897080

CONFIRMATION NO. 6418

REEXAM ASSIGNMENT NOTICE

DANIELLE L. HERRITT
MCCARTER & ENGLISH LLP,
265 FRANKLIN STREET
BOSTON, MA 02110

OC000000056562271

Date Mailed: 09/17/2012

NOTICE OF *INTER PARTES* REEXAMINATION REQUEST FILING DATE

Requester is hereby notified that the filing date of the request for *inter partes* reexamination is 09/10/2012, the date that the filing requirements of 37 CFR § 1.915 were received.

A decision on the request for *inter partes* reexamination will be mailed within three months from the filing date of the request for *inter partes* reexamination. (See 37 CFR 1.923.)

A copy of this Notice is being sent to the person identified by the requestor as the patent owner. Further patent owner correspondence will be with the latest attorney or agent of record in the patent file. (See 37 CFR 1.33.) Any paper filed should include a reference to the present request for *inter partes* reexamination (by Reexamination Control Number) and should be addressed to: Mail Stop Inter Partes Reexam, Commissioner for Patents, P.O. Box 1450, Alexandria VA 22313-1450.

cc: Patent Owner
23869
Hoffmann & Baron LLP
6900 Jericho Turnpike
Syosset, NY 11791

/sdstevenson/

Legal Instruments Examiner
Central Reexamination Unit 571-272-7705; FAX No. 571-273-9900

REEXAMINATION TITLE REPORT (AKA PATENT ASSIGNMENT ABSTRACT OF TITLE)

TYPE OF REEXAMINATION: EX PARTE X *INTER PARTES*

REEXAM CONTROL NO.: 95/002170

SERIAL NUMBER : 12/614928 FILING DATE: 09/10/12

PATENT NUMBER: 7897080 ISSUE DATE: 03/01/11

FIRST *THREE* INVENTORS' NAMES: ROBERT K. YANG; RICHARD C. FUISZ; GARY L. MYERS

ET. AL?: X Y N

CONTINUITY DATA (IF ANY) :

__ THIS IS (OR) A __CON __ DIV, CIP, A _PROVISIONAL APPLICATION __ OTHER OF SERIAL NUMBER , FILED ON . STATUS: PATENTED WITH PATENT NUMBER OR__PENDING, OR __ABANDONED (*EXPIRED* FOR PROVISIONALS).

__ WHICH IS A _ CON , _ DIV, _CIP , A_PROVISIONAL APPLICATION, ___ OTHER, OF SERIAL NUMBER FILED ON . STATUS: PATENTED, WITH PATENT NUMBER. AND SERIAL NUMBER FILED PENDING, OR ABANDONED.

__ WHICH IS A_CON, _DIV, _CIP, A _PROVISIONAL APPLICATION, ___ OTHER OF SERIAL NUMBER FILED ON . STATUS: PATENTED WITH PATENT NUMBER OR__PENDING, OR ABANDONED.

__ WHICH IS A _ CON, DIV, _CIP A PROVISIONAL APPLICATION, ___OTHER OF SERIAL NUMBER FILED ON. STATUS: PATENTED WITH PATENT NUMBER: OR__PENDING, OR ABANDONED.

__ WHICH IS A CON, DIV, _CIP A PROVISIONAL APPLICATION, ___OTHER OF SERIAL NUMBER FILED ON. STATUS: PATENTED WITH PATENT NUMBER: OR__PENDING, OR ABANDONED.

__WHICH IS A CIP OF SERIAL NUMBER FILED ON. STATUS: PATENTED, WITH PATENT NUMBER.

ET AL

ASSIGNMENT RECORD DATA

THE ASSIGNMENT RECORDS REVEAL THAT THE TITLE REPORT APPEARS TO BE VESTED IN:

xxxINVENTOR(S) ROBERT K. YANG; RICHARD C. FUISZ; GARY L. MYERS; JOSEPH M. FUISZ

___AS ENDORSED:

___AS THE RECORD STANDS, THE PATENT WHEN GRANTED WILL ISSUE IN THE NAME OF THE INVENTOR(S)

___LEGAL REPRESENTATIVE:

___SECURITY ASSIGNMENT/LICENSEE(PLEASE NOTE THAT THE OWNERSHIP OF THE PATENT IS STILL REFLECTED IN THE *ASSIGNOR*. THE *ASSIGNEE* IN THIS CASE CANNOT OWN THE PATENT. (SEE ACCOMPANYING PAGES, IF ANY.)

___WHEN THE ASSIGNMENT IS RECORDED, THE PATENT SHOULD BELONG TO:

___OTHER: REEL NO: FRAME NO.: DATE RECORDED: // COMPANY NAME: CITY AND STATE OR COUNTRY: .

___NOTES/COMMENTS: Please see section 306 of the Manual of Patent Examining Procedure regarding the *Assignment of a Division, Continuation, Substitute, and Continuation-in-Part in Relation to Parent Application.*

EXAMINED UP TO AND INCLUDING THIS CERTIFICATE DATED AND SIGNED: 09/14/12

LEGAL INSTRUMENTS EXMR., OFFICE OF PATENT LEGAL ADMIN., CENTRAL REEXAMINATION UNIT

TO ANY PRINTERS: THE REEXAMINATION TITLE REPORT DOES NOT HAVE TO HAVE THE STREET ADDRESS OF THE OWNER(S). IF THERE IS ANY INQUIRY, PLEASE NOTIFY THE PERSON ABOVE.

Litigation Search Report CRU 3999

Reexam Control No 95/002,170

TO: Examiner **Location: CRU** **Art Unit: 3991** **Date: 09/13/12** **Case Serial Number: 95/002,170**	**From: Tredelle Jackson** **Location: CRU 3999** **MDE 5D30** **Phone: (571) 272-2783** **Tredelle.Jackson@uspto.gov**

Search Notes

Litigation Search for U.S. Patent Number 7,897,080.

Sources:

1) I performed a KeyCite Search in Westlaw, which retrieves all history on the patent including any litigation.

2) I performed a search on the patent in Lexis CourtLink for any open dockets or closed cases.

3) I performed a search in Lexis in the Federal Courts and Administrative Materials databases for any cases found.

4) I performed a search in Lexis in the IP Journal and Periodicals database for any articles on the patent.

5) I performed a search in Lexis in the news databases for any articles about the patent or any articles about litigation on this patent.

Westlaw.

Date of Printing: Sep 13, 2012

KEYCITE

C US PAT 7897080 POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM, Assignee: MonoSol Rx, LLC (Mar 01, 2011)

History

Direct History

=> 1 **POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM,** US PAT 7897080, 2011 WL 693980 (U.S. PTO Utility Mar 01, 2011)

Patent Family

2 INGESTIBLE WATER-SOLUBLE DELIVERY SYSTEM IN THE FORM OF A FILM COMPOSITION USEFUL FOR THE PREPARATION OF A DRIED FILM COMPRISES GLUCAN AND A WATER-SOLUBLE POLYMER, Derwent World Patents Legal 2003-430230+

Prior Art (Coverage Begins 1976)

C 3 BIOADHESIVE HOT-MELT EXTRUDED FILM FOR TOPICAL AND MUCOSAL ADHESION APPLICATIONS AND DRUG DELIVERY AND PROCESS FOR PREPARATION THEREOF, US PAT 6375963 (U.S. PTO Utility 2002)

C 4 BIOERODABLE FILM FOR DELIVERY OF PHARMACEUTICAL COMPOUNDS TO MUCOSAL SURFACES, US PAT 5800832Assignee: Virotex Corporation, (U.S. PTO Utility 1998)

C 5 DERMAL BANDAGE AND DERMAL PREPARATION, US PAT 4880416Assignee: Nitto Electric Industrial Co., Ltd., (U.S. PTO Utility 1989)

C 6 DRUG LOADED POLYMERIC MATERIAL AND METHOD OF MANUFACTURE, US PAT 5605696Assignee: Advanced Cardiovascular Systems, Inc., (U.S. PTO Utility 1997)

C 7 DRYING PROCESS, US PAT 4872270Assignee: Eastman Kodak Company, (U.S. PTO Utility 1989)

C 8 EXTRUDABLE COMPOSITIONS FOR TOPICAL OR TRANSDERMAL DRUG DELIVERY, US PAT 6072100Assignee: Johnson & Johnson Consumer Products,, (U.S. PTO Utility 2000)

C 9 MEDICAMENT CARRIERS IN THE FORM OF FILM HAVING ACTIVE SUBSTANCE INCORPORATED THEREIN, US PAT 4136145Assignee: Schering Aktiengesellschaft, (U.S. PTO Utility 1979)

C 10 METHOD AND APPARATUS FOR DRYING FRUIT PULP AND THE LIKE, US PAT 4631837 (U.S. PTO Utility 1986)

C 11 METHOD AND SYSTEM FOR PRODUCING SEALED PACKAGES OF A FILM WHICH IS DISSOLVED IN A BODY FLUID, US PAT 5806284Assignee: Apothecus Pharmaceutical Corp., (U.S. PTO Utility 1998)

C 12 METHOD FOR PRODUCING FILM-TYPE DOSAGE, US PAT 6800329Assignee: LTS Lohmann Therapie-Systeme AG, (U.S. PTO Utility 2004)

C 13 METHOD OF FORMING AN EDIBLE MEDICINAL WAFER STRIP PACKAGE, US PAT 3007848 (U.S. PTO Utility 1961)

C 14 METHODS FOR CONVERSION OF PROTEIN ISOFORMS, US PAT 6281337Assignee: Schering Corporation, (U.S. PTO Utility 2001)

C 15 METHODS FOR MANUFACTURING ARTICLES FROM SHEETS OF UNHARDENED HYDRAULICALLY SETTABLE COMPOSITIONS, US PAT 5766525Assignee: E. Khashoggi Industries, (U.S. PTO Utility 1998)

C 16 PHARMACEUTICAL CARRIER DEVICE SUITABLE FOR DELIVERY OF PHARMACEUTICAL COMPOUNDS TO MUCOSAL SURFACES, US PAT 7579019Assignee: Arius Two, Inc., (U.S. PTO Utility 2009)

C 17 POLYETHYLENE OXIDE-BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM, US PAT 7666337Assignee: MonoSol Rx, LLC, (U.S. PTO Utility 2010)

C 18 POLYETHYLENE OXIDE-BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM, US PAT APP 20050037055Assignee: MonoSolRx LLC., (U.S. PTO Application 2005)

C 19 PROCESS FOR MAKING AN INGESTIBLE FILM, US PAT 7357891Assignee: MonoSol Rx, LLC, (U.S. PTO Utility 2008)

C 20 PROCESS FOR MANUFACTURING THIN FILM STRIPS, US PAT 6824829Assignee: Acupac Packaging, Inc., (U.S. PTO Utility 2004)

C 21 PROCESS FOR PRODUCING AN ADMINISTRATION OR DOSAGE FORM FOR DRUGS, REAGENTS OR OTHER ACTIVE INGREDIENTS, US PAT 4849246 (U.S. PTO Utility 1989)

C 22 RAPIDLY DISINTEGRATING SHEET-LIKE PRESENTATIONS OF MULTIPLE DOSAGE UNITS, US PAT 5629003Assignee: LTS Lohmann Therapie-Systeme GmbH &, (U.S. PTO Utility 1997)

C 23 TEXTURED-FOAM COATED URETHANE WALL AND CEILING COVERING AND METHOD OF MAKING THE SAME, US PAT 4049848Assignee: United Foam Corporation, (U.S. PTO Utility 1977)

C 24 THIN FILM WITH NON-SELF-AGGREGATING UNIFORM HETEROGENEITY AND DRUG DELIVERY SYSTEMS MADE THEREFROM, US PAT APP 20040258896Assignee: MonoSolRx LLC., (U.S. PTO Application 2004)

C 25 THIN FILM WITH NON-SELF-AGGREGATING UNIFORM HETEROGENEITY AND DRUG DELIVERY SYSTEMS MADE THEREFROM, US PAT APP 20030107149Assignee: INTERNATIONAL FLUIDICS., (U.S. PTO Application 2003)

C 26 VETERINARY DELIVERY SYSTEMS AND METHODS OF DELIVERING EFFECTIVE AGENTS TO ANIMALS, US PAT 7005142 (U.S. PTO Utility 2006)

C 27 WATER SOLUBLE FILM FOR ORAL ADMINISTRATION WITH INSTANT WETTABILITY, US PAT 5948430Assignee: LTS Lohmann Therapie-Systeme GmbH, (U.S. PTO Utility 1999)

Patent Search 7897080 9/13/2012

No cases found.

Return to Search

(Charges for search still apply)

1. US Fed News, March 5, 2011 Saturday 12:06 PM EST, , 245 words, US Patent Issued to MonoSol Rx on March 1 for "Polyethylene-Oxide Based Films and Drug Delivery Systems Made Therefrom" (District Of Columbia, New York, Virginia, Tennessee Inventors), ALEXANDRIA, Va.

   ... r=1&f=G&l=50&co1=AND&d=PTXT&s1=**7897080**&OS=**7897080**&RS=**7897080**
   For any query with respect to this article or any other content requirement, please ...

2. Tendersinfo News, July 28, 2011 Thursday 6:30 AM EST, , 128 words, ITALY : Edil CO. SRL wins contract of 5 080 915 Euros

   ... di Bari - ripartizione contratti ed appalti, Italy has issued the contract of 5 **080** 915 Euros to Edil CO. SRL, Italy for execution of restoration work. This ...
   ... per open procedure method. Initial estimated total value of the contract was 8 **897** 000 EUR and the final contract award value was 5 **080** 915 EUR. Total 11 number of offers received for this tender. GPA has ...

3. TendersInfo, July 28, 2011 Thursday, 107 words, ITALY : Edil CO. SRL wins contract of 5 080 915 Euros, Tejas98

   ... di Bari - ripartizione contratti ed appalti, Italy has issued the contract of 5 **080** 915 Euros to Edil CO. SRL, Italy for execution of restoration work. This ...
   ... per open procedure method. Initial estimated total value of the contract was 8 **897** 000 EUR and the final contract award value was 5 **080** 915 EUR. Total 11 number of offers received for this tender. GPA has ...

4. Financial Law Reporter, April 5, 2011, 253317030, 897 words, Cross Refrence Citation Name : 1981 SCMR 198 SUPREME-COURT.

   ... Versus MUNIR HUSSAIN AND 2 OTHERS-Respondents Civil Petition No. 285 of **080,** decided on 8th April, 1980. (On appeal from the judgment and order dated ...
   April **7,** 2011

5. News Bites US Markets, May 7, 2011 Saturday, 418 words, Weekly: Sinovac Biotech price 7.1% below volume weighted price

   ... turnover rate in the 12 months to date was 155.3% (or a turnover period of **7** months). Rises to Falls: In the last six months the number of falls outnumbered ...
   ... value of US$1,000 invested thirteen weeks ago is US$**897** [vs US$1,022 for the NASDAQ-100 index] for a ...
   ... SVA $1US,000 $**897** $1US,619
   Total NASDAQ Market $1US,017 $1US,**080** $1US,675 ...
   May **7,** 2011

6. Plus NEWS, March 5, 2011, 250627097, 79 words, World Stock Reports: Casablanca Stock Exchange Ltd Best 10 capitalisation: 05-03-2011.

   ... ITISSALAT AL-MAGHRIB 138 **897** 063 720,00 ...
   ... CGI 30 097 **080** 000,00 ...

7. News Bites US Markets, November 10, 2010 Wednesday, 1052 words, American Independence Corp. closes at 4.0% above VWP but at 26.0% discount to 52-week high

   ... Volatility: the stock traded between an intraday low of US$4.73 and **seven**-day high of US$4.85, suggesting a trading opportunity between ...
   ... strength of 40 which means it has underperformed 60.0% of the market. Volume and turnover period: there were **897** shares worth US$4,350 traded. The volume was

0.4 times average ...
... in the 12 months to date was 7.3% (or a turnover period of 13 years **7** months). % Discount to high: the last price is at a discount of 26.0% to the ...
... Insurance $1US,**080** $23US,097
NASDAQ-100 $1US,**080** $1US,238 ...

8. News Bites US Markets, November 5, 2010 Friday, 931 words, Cardium Therapeutics gains 4.3% on low volume

   ... value of US$1,000 invested a month ago is US$**897** [vs US$1,048 for the NYSE U.S. 100 index], for ...
   ... CXM $**897** $731
   Health Care $1US,039 $1US,**080** ...
   November **7,** 2010

9. News Bites US Markets, May 7, 2011 Saturday, 618 words, Weekly: Cornerstone Financial slides 5.3% on thin volume

   ... value of US$1,000 invested thirteen weeks ago is US$**897** [vs US$1,019 for the NASDAQ-100 index] for a ...
   ... CFIC $**897** $1US,**080** ...
   May **7,** 2011

10. News Bites US Markets, November 5, 2010 Friday, 1259 words, Overland Storage closes at 5.4% below VWP but at 6.6% premium to 52-week low

    ... value of US$1,000 invested a month ago is US$**897** [vs US$1,081 for the NASDAQ-100 index], for a ...
    ... OVRL $**897** $549
    Computers & Electronics $1US,**080** $1US,256 ...
    November **7,** 2010

Source: **Combined Source Set 4** [i] **- News, Most Recent Two Years (English, Full Text)**
Terms: **7897080 or 7,897,080** (Suggest Terms for My Search | Feedback on Your Search)
View: Cite
Date/Time: Thursday, September 13, 2012 - 3:56 PM EDT

614928 (12) 7897080 March 1, 2011

UNITED STATES PATENT AND TRADEMARK OFFICE GRANTED PATENT

7897080

Get Drawing Sheet 1 of 34
Access PDF of Official Patent *
Order Patent File History / Wrapper from REEDFAX®
Link to Claims Section

March 1, 2011

Polyethylene-oxide based films and drug delivery systems made therefrom

INVENTOR: Yang, Robert K. - Flushing, New York, United States of America (US), United States of America () ; Fuisz, Richard C. - McLean, Virginia, United States of America (US), United States of America () ; Myers, Gary L. - Kingsport, Tennessee, United States of America (US), United States of America () ; Fuisz, Joseph M. - Washington, District of Columbia, United States of America (US), United States of America ()

APPL-NO: 614928 (12)

FILED-DATE: November 9, 2009

GRANTED-DATE: March 1, 2011

CORE TERMS: film, composition, drying, polymer, dried, desirably, particle, coating, flavor, viscosity, ingredient, mixing, uniformity, dosage, heat, drop, simethicone, moisture, cellulose, minutes, mixture, acid, calcium, solvent, oven, film-forming, carbonate, soluble, zone, vacuum

ENGLISH-ABST:

The invention relates to the film products and methods of their preparation that demonstrate a non-self-aggregating uniform heterogeneity. Desirably, the films disintegrate in water and may be formed by a controlled drying process, or other process that maintains the required uniformity of the film. The films contain a polymer component, which includes polyethylene oxide optionally blended with hydrophilic cellulosic polymers. Desirably, the films also contain a pharmaceutical and/or cosmetic active agent with no more than a 10% variance of the active agent pharmaceutical and/or cosmetic active agent per unit area of the film.

PTO/SB/58 (02-12)
Approved for use through 02/28/2013. OMB 0651-0033
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

(Also referred to as FORM PTO-1465)

REQUEST FOR *INTER PARTES* REEXAMINATION TRANSMITTAL FORM

Address to:
Mail Stop *Inter Partes* Reexam
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Attorney Docket No.: 117744-00023

Date: September 10, 2012

1. ☒ This is a request for *inter partes* reexamination pursuant to 37 CFR 1.913 of patent number 7,897,080 issued 03/01/2011. The request is made by a third party requester, identified herein below.

2. ☒ a. The name and address of the person requesting reexamination is:

Danielle L. Herritt

McCarter & English LLP, 265 Franklin Street

Boston, MA 02110

b. The real party in interest (37 CFR 1.915(b)(8)) is: BioDelivery Sciences International, 801 Corporate Center Drive, Suite 210, Raleigh, NC 27607

3. ☐ a. A check in the amount of $_____ is enclosed to cover the reexamination fee, 37 CFR 1.20(c)(2);

☒ b. The Director is hereby authorized to charge the fee as set forth in 37 CFR 1.20(c)(2) to Deposit Account No. 50-4876; **or**

☐ c. Payment by credit card. Form PTO-2038 is attached.

4. ☒ Any refund should be made by ☐ check or ☒ credit to Deposit Account No. 50-4876. 37 CFR 1 .26(c). If payment is made by credit card, refund must be made to credit card account.

5. ☒ A copy of the patent to be reexamined having a double column format on one side of a separate paper is enclosed. 37 CFR 1 .915(b)(5)

6. ☐ CD-ROM or CD-R in duplicate, Computer Program (Appendix) or large table
☐ Landscape Table on CD

7. ☐ Nucleotide and/or Amino Acid Sequence Submission
If applicable, items a. - c. are required.

a. ☐ Computer Readable Form (CRF)
b. Specification Sequence Listing on:
i ☐ CD-ROM (2 copies) or CD-R (2 copies); **or**
ii ☐ paper
c. ☐ Statements verifying identity of above copies

8. ☒ A copy of any disclaimer, certificate of correction or reexamination certificate issued in the patent is included. (None)

9. ☒ Reexamination of claim(s) 1-299 is requested.

10. ☒ A copy of every patent or printed publication relied upon is submitted herewith including a listing thereof on Form PTO/SB/08, PTO-1449, or equivalent.

11. ☐ An English language translation of all necessary and pertinent non-English language patents and/or printed publications is included.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

12. ☒ The attached detailed request includes at least the following items:

a A listing of the grounds that the requester asserts to raise a showing of a reasonable likelihood that the requester will prevail with respect to at least one of the claims challenged in the request. 37 CFR 1.915(b)(3).
b. For each ground listed, an identification of every claim to which the showing applies, and a detailed explanation of the pertinency and manner of applying the patents and printed publications to every claim which is identified for that ground. 37 CFR 1.915(b)(3).

13. ☒ It is certified that the estoppel provisions of 37 CFR 1.907 do not prohibit this reexamination. 37 CFR 1.915(b)(7).

14. ☒ a. It is certified that a copy of this request has been served in its entirety on the patent owner as provided in 37 CFR 1.33(c).
The name and address of the party served and the date of service are:

Daniel A. Scola, Jr.

HOFFMANN & BARON, LLP

6900 Jericho Turnpike, Syosset, NY

Date of Service: September 10, 2012; **or**

☐ b. A duplicate copy is enclosed because service on patent owner was not possible. An explanation of the efforts made to serve patent owner **is attached.** See MPEP 2620.

15. Third Party Requester Correspondence Address: Direct all communications about the reexamination to:

☐ The address associated with Customer Number:

OR

☒ Firm or Individual Name Danielle L. Herritt

Address

McCarter & English LLP, 265 Franklin Street

City	State	Zip
Boston	MA	02110

Country
U.S.A.

Telephone	Email
617-449-6500	dherritt@mccarter.com

16. ☐ The patent is currently the subject of the following concurrent proceeding(s):

☐ a. Copending reissue Application No. _____
☐ b. Copending reexamination Control No. _____
☐ c. Copending Interference No. _____
☐ d. Copending litigation styled:

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

/Danielle L. Herritt/ — Authorized Signature
September 10, 2012 — Date

Danielle L. Herritt — Typed/Printed Name
43,670 — Registration Number, if applicable

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re *Inter Partes* Reexamination of:	)	
US Patent No. 7,897,080	)	
Issued: March 1, 2011	)	
Named Inventor: Robert K. Yang *et al.*	)	Group Art Unit: To Be Assigned
Control No.: To Be Assigned	)	Examiner: To Be Assigned
Filed: September 10, 2012	)	
Title: Polyethylene-oxide based films and drug delivery systems made therefrom	)	

Mail Stop *Inter Partes* Reexam
Attn: Central Reexamination Unit
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST FOR *INTER PARTES* REEXAMINATION

This is a request for *inter partes* reexamination of the 299 claims of U.S. Patent No. 7,897,080 ("the '080 Patent"), which issued on March 1, 2011, to Robert K Yang *et al.* A copy of the '080 Patent is attached hereto and made a part hereof as Exhibit A. This patent is assigned to Monosol RX, LLC ("Monosol"). Third party Requester, BioDelivery Sciences International, Inc. ("BDSI"), submits this request.

Requester respectfully seeks the entry of an Office Action on the merits, as soon as the resources of the US Patent and Trademark Office (hereinafter "the Patent Office") permit. In this regard, Requester understands that under the applicable rules and practices, an order granting reexamination will usually be accompanied by the initial Office Action on the merits. 37 C.F.R.

§ 1.935; MPEP § 2660. Requester respectfully seeks the entry of an initial Office Action with the order granting reexamination and has done and will do whatever it can to help the Office achieve that goal.

To assist the Examiner in the consideration of the issues presented in this request, Requester has prepared a Table of Contents and included sections meant to help the Examiner understand and decide the issues. Requester has presented the specific rejections that it believes should be applied in a form that can readily be imported into an Office action, should the Examiner agree.

As the MPEP explains, the Examiner may, when appropriate, **cut and paste the claim chart or other material within the request to incorporate it within the body of an Office Action. Requester, therefore, through the undersigned counsel, stands ready to provide the Examiner with an electronic copy of this request, or any portion of it, in response to a request by email or phone.** Requester also understands that the Examiner may, in appropriate circumstances, set forth specific rejections in an Office Action and incorporate by reference Requester's reasons for the rejections, when the Examiner agrees with the proposed rejections and reasons supporting them.

Requester is also willing to provide any other appropriate assistance it can to permit the Examiner to address and decide the issues presented by this Request.

TABLE OF CONTENTS

I. Introduction

A. Request for *Inter Partes* Reexamination and Certification

Requester respectfully requests *inter partes* reexamination of claims 1-299 of U.S. Patent No. 7,897,080 ("the '080 Patent") owned by Monosol ("Applicant"). As explained in detail below, the claims at issue are unpatentable over the prior art patents and publications identified and applied in this Request.

For the convenience of the Patent Office, and in accordance with its Best Practices Guide, Requester identifies the *inter partes* reexamination filing date requirements as set forth in 71 Fed. Reg. 44219, 44221, with separate headings:

1. The complete reexamination fee.

Pursuant to 37 CFR §§ 1.915(a) and 1.20(c)(2), Requester is submitting a fee of $8,800.00. To the extent that any additional fees are required to complete this Request for Reexamination, the Patent Office is hereby authorized by the undersigned to charge Deposit Account No. 50-4876 for such fees.

2. An identification of every claim for which reexamination is requested.

Pursuant to 37 CFR § 1.915(b)(1), the patent for which reexamination is requested is U.S. Patent No. 7,897,080, and reexamination of claims 1-299 is requested. A copy of the claims is provided. (Exhibit B).

3. A citation of the patents and printed publications presented to provide a showing of a reasonable likelihood that the requester will prevail.

Pursuant to 37 CFR § 1.915(b)(2), Requester submits, in a separate paper (PTO/SB/08A Form) (Exhibit Q), a citation of the patents and printed publications that show a reasonable likelihood that the requester will prevail with respect to at least one of the claims challenged in the request. *See* 76 Fed. Reg. 59056 (final rule amending Rule 1.915(b)(2) with respect to requests filed between September 16, 2011 and September 16, 2012).

4. A showing of a reasonable likelihood that the requester will prevail with respect to at least one of the challenged claims based on the cited patents and publications.

Pursuant to 37 CFR § 1.915(b)(3), a statement pointing out, based on the cited patents and printed publications, each showing of a reasonable likelihood that the requester will prevail with respect to at least one of the claims challenged in the request is provided in Section III of this Request. *See* 76 Fed. Reg. 59056 (final rule amending Rule 1.915(b)(3) and the standard for ordering an *inter partes* reexamination with respect to requests filed between September 16, 2011 and September 16, 2012).

5. A detailed explanation of how all of the cited documents are applied to the claims for which reexamination is requested.

Pursuant to 37 CFR § 1.915(b)(3), a detailed explanation of the pertinency and manner of applying the patents and printed publications to each claim for which reexamination is requested, is provided in Section IV of this Request.

6. A legible copy of every patent or printed publication relied upon or referred to in the request.

Pursuant to 37 CFR § 1.915(b)(4), a copy of every patent or printed publication relied upon or referred to is provided (Exhibits C-F). Because all cited patents and patent publications are written in the English language, no translations are provided.

7. A legible copy of the entire patent to be reexamined.

Pursuant to 37 CFR § 1.915(b)(5), a legible single-sided copy of the entire patent for which reexamination is requested is provided (Exhibit A).

8. A legible copy of any disclaimer, certificate of correction, or reexamination certificate issued for the patent.

Pursuant to 37 CFR § 1.915(b)(5), a legible copy of the terminal disclaimer on record for the '080 Patent is provided (Exhibit G). To Requester's knowledge, no certificate of correction

on record for the '080 Patent. To Requester's knowledge, no other reexamination proceedings have been initiated as of today's date, and no reexamination certificates have issued.

9. A certificate of service on the patent owner at the address as provided for in §1.33(c).

Pursuant to 37 CFR § 1.915(b)(6), Requester attaches a Certificate of Service certifying that a copy of the request is being served in its entirety on the patent owner at the address provided for in 37 CFR § 1.33(c), and indicating the name and address of the party served (Exhibit R).

10. A certification by the requester that the estoppel provisions of § 1.907 do not prohibit the *inter partes* reexamination being requested.

Pursuant to 37 CFR § 1.915(b)(7), Requester certifies that the estoppel provisions of 37 CFR § 1.907 do not prohibit this *inter partes* reexamination.

11. A statement identifying the real party in interest for whom (on whose behalf) the request is being filed.

Pursuant to 37 CFR § 1.915(b)(8), Requester states that the real party in interest is BioDelivery Sciences International, Inc. ("BDSI").

12. If the request is filed by an attorney acting in a representative capacity pursuant to § 1.34.

Pursuant to 37 CFR § 1.915(c), attorneys for BDSI, acting in a representative capacity pursuant to 37 CFR § 1.34, have filed this Request.

B. The '080 Patent is Not in Litigation

Pursuant to 37 C.F.R. § 1.985, Requester confirms that there is no litigation proceeding where the '080 Patent has been asserted as of today's date.

II. The '080 Patent Claims

A. Claims for Which Reexamination is Requested

Requester seeks reexamination of claims 1-299 of the '080 Patent. This patent has three independent claims: 1, 82, and 161. All are very similar. Claim 82 is the broadest:

> 82. A process for making a film having a substantially uniform distribution of components, comprising the steps of:
>
> (a) forming a flowable polymer matrix comprising a polymer selected from the group consisting of a water-soluble polymer, a water swellable polymer and combinations thereof, a solvent and an active selected from the group consisting of bioactive actives, pharmaceutical actives, drugs, medicaments and combinations thereof, said matrix having a substantially uniform distribution of said active;
>
> (b) casting said flowable polymer matrix;
>
> (c) evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film within about 10 minutes or fewer to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film; and
>
> (d) forming a resulting film from said visco-elastic film,
>
> wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained.

In light of the similarities between independent claim 82 and the other two independent claims (*i.e.*, claims 1 and 161), redlined versions of claims 1 and 161 (comparing them to claim 82) are provided below for convenience. In comparison to claim 82, claim 1 additionally recites a masterbatch premix step:

> ~~82.~~1. A process for making a film having a substantially uniform distribution of components, comprising the steps of:
>
> (a) forming a ~~flowable polymer matrix~~ masterbatch pre-mix comprising a solvent and a polymer selected from the group consisting of ~~a~~ water soluble polymers, water swellable polymers and combinations thereof ~~a solvent and~~;
>
> (b) adding an active ~~selected from the group consisting~~ to a pre-determined amount of ~~bioactive actives, pharmaceutical actives, drugs, medicaments and combinations~~

~~thereof~~ said masterbatch pre-mix to form a flowable polymer matrix, said matrix having a substantially uniform distribution of said active;

~~(b)~~(c) casting said flowable polymer matrix;

~~(c)~~(d) evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film within about 10 minutes or fewer to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film; and

~~(d)~~ (e) forming a resulting film from said visco-elastic film,

wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking in or substantially preventing migration of said active is maintained.

In comparison to claim 82, claim 161 additionally recites an administration step:

~~82.~~161. A process for making a film capable of being administered to a body surface having a substantially uniform distribution of components, comprising the steps of:

(a) forming a flowable polymer matrix comprising ~~a polymer selected from the group consisting of~~ a water soluble polymer, ~~a water swellable polymer and combinations thereof,~~ a solvent and an active ~~selected from the group consisting of bioactive actives, pharmaceutical actives, drugs, medicaments and combinations thereof~~, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix;

(c) evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film within about 10 minutes or fewer to maintain said substantially uniform distribution of said active by locking in or substantially preventing migration of said active within said visco-elastic film; ~~and~~

(d) forming a resulting film from said visco-elastic film,

wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained; and

(e) administering said resulting film to a body surface.

Due to the unusually large number of claims in the '080 Patent, the dependent claims are recited in their entirety in the claim charts below rather than reciting them multiple times in this Request. For the Examiner's convenience, a copy of the claims is attached (Exhibit B). Although each of the independent claims is directed to a process, the vast majority of these

dependent claims recite product limitations – *e.g.*, a large number of active species or various desired properties of the film.

B. The Claims Must be Given Their Broadest Reasonable Construction

Under MPEP §§ 2258 (I)(G) and 2658 (I), the claims during reexamination are given their broadest reasonable interpretation consistent with the specification. Moreover, limitations in the specification are not read into the claims. "[R]eading a claim in light of the specification, to thereby interpret limitations explicitly recited in the claim, is a quite different thing from 'reading limitations of the specification into a claim,' to thereby narrow the scope of the claim by implicitly adding disclosed limitations which have no express basis in the claim." MPEP § 2111 (citation omitted). The requirement and reasoning for giving the claims the broadest reasonable construction is explained in MPEP § 2111. For example, when the claims are before the Patent Office, giving the claims the broadest reasonable interpretation is appropriate because the applicant has the opportunity to amend the claims during prosecution. The application of the broadest reasonable interpretation by the Examiner reduces the possibility that a claim, once issued, will be interpreted more broadly than is justified. Thus, during examination, the pending claims must be "given their broadest reasonable interpretation consistent with the specification." MPEP § 2111, *quoting*, *Phillips v. AWH Corp.*, 415 F.3d 1303, 75 USPQ2d 1321 (Fed. Cir. 2005) (*en banc*).

C. Requester Expressly Reserves its Right to Challenge the Claims of the '080 Patent under 35 U.S.C. § 112

Requester understands that 37 C.F.R. § 1.906 prevents it from raising § 112 invalidity issues in an *inter partes* reexamination. Requester hereby expressly reserves the right to challenge the claims under 35 U.S.C. § 112 in the event that Applicant asserts this patent against Requester. Requester also expressly reserves its right to challenge priority in the event that Applicant asserts this patent against Requester.

III. Statement of Reasonable Likelihood of Prevailing

Under 35 U.S.C. §§ 312 and 313, an order for *inter partes* reexamination of a patent is granted by the Patent Office if the information presented in this Request shows that there is a reasonable likelihood that Requester will prevail with respect to at least one of the claims challenged in the Request. Requester respectfully submits that cited references – *Chen*, *Staab*, *Le Person*, and *Horstmann* – alone or in proper combination, present a reasonable likelihood of prevailing with respect to claims 1-299 of the '080 Patent in that they anticipate and/or render obvious each and every claim of this patent. Requester provides a detailed explanation of how the cited references apply to the claims in Section IV.

A. Related Patent Family Members in Reexamination

For the Examiner's reference, Requester brings to the Examiner's attention that three members of the same patent family are currently being reexamined or have recently concluded reexamination. There is currently an ongoing *Inter Partes* Reexamination in related US Patent No. 7,824,588 ("the '588 Patent"), filed on September 12, 2011, and identified by Control No. 95/001,753. Additionally, related US Patent No. 7,357,891 ("the '891 Patent") and US Patent No. 7,425,292 ("the '292 Patent") were reexamined in *ex parte* reexamination proceedings in the last year and reexamination certificates have issued with amended claims. The three foregoing patents share with the '080 Patent both a priority claim to US Patent Application Serial No. 60/328,868, filed October 12, 2001, and claims to substantially similar subject matter. The Examiner in the '080 Patent deemed the two reexamined patents (*i.e.*, the '891 Patent and the '292 Patent), the '080 Patent, and US Patent No. 7,666,337 ("the '337 Patent", the parent of the '080 Patent) have claims so similar that they were patentably indistinguishable. See the terminal disclaimer (Exhibit G). The '588, '891, and '292 Patents have been asserted by the Patent Owner in the US District Court, District of New Jersey on November 2, 2010. The action is captioned Monosol RX, LLC v. BioDelivery Sciences International, Inc., MEDA Pharmaceuticals, Inc. and Aveva Drug Delivery Systems, Inc., Civil Action No. 10-cv-5695. Additionally, Requester, is also requesting *Inter Partes* reexamination of US Patent No. 7,666,337 (the '337 Patent), which is a continuation-in-part of the '891 Patent, and the parent of

the instant patent. For the Examiner's convenience, Requester submits a patent chart (Exhibit H) indicating the relationship among the above patents and where these patents have been the subject of nonstatutory obvious-type double patenting rejections and reexaminations. Please note that this chart is not exhaustive.

B. Brief Overview of Prosecution History

The '080 Patent application was filed with 242 original process claims. In prosecution there was only one Office Action mailed on September 29, 2010. A copy of the Office Action is attached as Exhibit I. In the Office Action, the Examiner rejected the claims on the ground of nonstatutory obvious-type double patenting in view of US Application Serial Nos. 12/411,505 and 12/171,692, and US Patent Nos. 7,357,891, 7,425,292, and 7,666,337. The Examiner did not raise any substantive rejections.

On November 16, 2010, Applicant filed an Amendment and Response, together with an Information Disclosure Statement. A copy of the Amendment and Response, as well as the Information Disclosure Statement is attached as Exhibit J. In the Amendment and Response, Applicant amended the pending claims to recite that distribution of active is "substantially uniform" instead of "uniform" and added 57 additional claims. Applicant also submitted a terminal disclaimer (Exhibit G) to obviate each of the nonstatutory obvious-type double patenting rejections. Following the Amendment and Response, the Examiner issued the Notice of Allowance on January 14, 2011 to allow all 299 claims, without identifying any reasons for allowance.

With respect to the Information Disclosure Statement, Applicant did not disclose several highly relevant references that were disclosed in the prosecution of the parent US Patent No. 7,666,337 ("the '337 Patent").[1] Specifically, Applicant did not disclose either *Chen* or *Staab*, which anticipate and render obvious the '080 Patent claims as set forth in detail in Tables 1-4 and 6-8. Applicant disclosed these two references to the Patent Office during the previous

[1] Applicant cited 171 references in the '337 patent prosecution. It disclosed only 31 references in the '080 Patent prosecution.

prosecution of the parent '337 Patent. *Staab* was cited by the Examiner against the claims of the parent '337 Patent. *Chen* is another important reference. It has been cited by the Examiners in US Application Serial No. 12/171,692, which was considered to have claims that were not patentably distisguished from the instant claims and, accordingly, was the subject of a nonstatutory obvious-type double patenting rejection. Also, *Chen* was cited as an "X" reference in priority PCT Application No. PCT/US02/32594, and its US equivalent was cited as anticipatory to claims in US 7,425,292, which was deemed by the Examiner to also have patentably indistinguishable claims. A terminal disclaimer was filed to overcome this rejection. See Exhibit G for the relationship of these applications and patents.

In short, during the original examination of the '080 Patent, the Examiner lacked a complete picture of what was known in the art at the relevant time.

C. The Cited References Demonstrate A Reasonable Likelihood of Prevailing

1. <u>The recited method steps of the '080 Patent claims</u>

The '080 Patent claims recite a general film-forming process that includes four basic steps:

a) mixing a water soluble or swellable polymer (*e.g.,* hydroxypropyl methyl cellulose (HPMC)) [2], a solvent (*e.g.,* water), and an active to form a flowable polymer matrix;
b) casting the matrix;
c) evaporating at least a portion of the solvent to form a visco-elastic film within about 10 minutes; and
d) forming a resulting film from the visco-elastic film (to the extent that this step is distinct from step c).

The foregoing steps are the steps in independent claim 82. Claim 1 additionally recites a premix step. Claim 161 additionally recites administration of the film to a body surface.

[2] HPMC is identified as a water soluble polymer in the '080 patent at col. 15, lines 49-51, and used in the majority of its examples, *e.g.*, Examples P-Z.

Applicant also recites a number of desired properties (*e.g.*, substantial uniformity) and scientific explanations or theories (*e.g.*, locking-in of the active) in its claims, but not the steps for achieving them. Although we later show these features are anticipated by the art, as correctly stated by the Examiner of the related '588 Patent, the recitation of a desired property:

> is a mere obvious matter of choice dependent on the desired final product *and of little patentable consequence to the claimed process since it is not a manipulative feature or step of the claimed process.* Furthermore the claimed product limitations are well-known in the ingestible or insertable film art.
>
> The '588 Patent File History, February 4, 2010 Office Action at p. 5 (Exhibit K) (emphasis added) (referring to, *e.g.*, wherein the self-supporting therapeutic active-containing film has a variation of active content of less than 10% per unit film).

Indeed, desired properties and scientific theories or explanations are not entitled to patentable weight as has been made clear by the US Supreme Court. "A claim covers and secures a process, a machine, a manufacture, a composition of matter, or a design, but *never the function or result of either, nor the scientific explanation of their operation*." *Markman v. Westview Instruments, Inc.*, 517 US 370, 373 (1996)(emphasis added). Specifically with respect to process claims, the Federal Circuit clarifies that a "whereby clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited...." *Minton v. Nat'l Ass'n of Securities Dealers, Inc.*, 336 F.3d 1373, 1381, 67 USPQ2d 1614, 1620 (Fed. Cir. 2003) citing *Texas Instruments v. USITC*, 988 F.3d 1165, 1172 (Fed. Cir. 1993). (*See e.g.,* MPEP 2111.04). In present claims, the process steps required to achieve the recited properties aren't even positively recited. The "elements" of a method claim are, and must be, *acts* or *manipulative steps* that are performed upon an article or chemical substance. Simply reciting desired features of a film, *e.g.,* substantial uniformity, and/or a scientific explanation of how uniformity is maintained, are of little patentable consequence in process claims. Rather, Applicant must properly recite the manipulative steps that result in the desired properties.

2. The drying steps of the '080 Patent claims

Requester observes that steps (c) and (d) only appear to require "evaporating at least a portion of the solvent within about 10 minutes." Specifically, while both steps recite "form[ing] a visco-elastic film" and "forming a resulting film", these do not further distinguish the film from the film cast in step (b).

As to step (c) (*i.e.*, "evaporating at least a portion of said solvent. . . to form a visco-elastic film within about 10 minutes or fewer. . ."), the '080 Patent describes both the matrix and wet film prior to drying as being viscoelastic. That is, the matrix and wet film are viscoelastic prior to step (c):

> The viscosity of the liquid phase is critical and is desirably modified by customizing the liquid composition to a **viscoelastic** non-Newtonian fluid with low yield stress values. … Formation of a **viscoelastic** or a highly structured fluid phase provides additional resistive forces to particle sedimentation. (Col. 8, lines 32-38, emphasis added).
>
> The addition of hydrocolloids to the aqueous phase of the suspension increases viscosity, may produce **viscoelasticity**, and can impart stability depending on the type of hydrocolloid, its concentration and the particle composition, geometry, size and volume fraction. (Col. 8, lines 42-46, emphasis added).
>
> For **viscoelastic** fluid systems, a rheology that yields stable suspensions for extended time period, such as 24 hours, must be balanced with the requirements of high-speed film casting operations. (Col. 8, line 66 through Col. 9, line 2, emphasis added).
>
> The rheology requirements for the inventive compositions and films are quite severe. This is due to the need to produce a stable suspension of particles, for example 30-60 wt. %, in a **viscoelastic** fluid matrix with acceptable viscosity values throughout a broad shear rate range. . .
>
> In film casting or coating, rheology is also a defining factor with respect to the ability to form films with the desired uniformity. Shear viscosity, extensional viscosity, **viscoelasticity**, structural recovery will influence the quality of the film." (Col. 9, lines 9-20, emphasis added).

> Desirably, the films or film-forming compositions of the present invention have a very rapid structural recovery, *i.e.* as the film is formed during processing, it doesn't fall apart or become discontinuous in its structure and compositional uniformity. Such very rapid structural recovery retards particle settling and sedimentation. Moreover, the films or film-forming compositions of the present invention are desirably shear-thinning pseudoplastic fluids. Such fluids with consideration of properties, such as **viscosity and elasticity**, promote thin film formation and uniformity. (Col. 9, lines 32-41, emphasis added).
>
> Compositions P-R show the effects of **visco-elastic** properties on the ability to coat the film composition mixture onto the substrate for film formation. … This product coated the substrate but would not stay level due to the change in the **visco-elastic** properties of the wet foam. (Col. 35, lines 55-57, and 61-63, emphasis added).

Requester submits that if the wet film is a visco-elastic film **prior to drying** (as repeatedly taught by Applicant in its own specification), there is no further limitation represented by this recitation other than that at least a portion of the solvent be evaporated in less than about 10 minutes. Furthermore, there is no significant limitation recited in step (d). Resulting films are also described as viscoelastic. *See e.g.*, col. 13, lines 53-54. Reciting a moisture range (*e.g.*, a water content of 10% or less) also does not distinguish the film from the films of the previous steps since no original moisture range is claimed to differentiate it. For example, the matrix could start out with only 10% water such that it meets this limitation prior to any drying steps.

3. The actual drying step as taught in the '080 Patent

Requester notes that the '080 Patent specification recites visco-elastic fourteen times in total. Nine times (as shown above) all relate to the matrix and wet film **prior to drying**. Five times (as shown below) are referring to the result of the "drying process of the present invention". Specifically, the '080 Patent teaches that such a visco-elastic film is a result of bottom drying with substantially no air flow present across the top of the film, which is **NOT** recited in the claims at issue.

> Desirably, the film is dried from the bottom of the film to the top of the film. Desirably, substantially no air flow is present across the top of the film during its initial setting period, during which a solid, **visco-elastic** structure is

> formed. This can take place within the first few minutes, *e.g.* about the first 0.5 to about 4.0 minutes of the drying process. (Col 27, lines 33-38, emphasis added).
>
> As mentioned above, the controlled drying process of the present invention allows for uniform drying to occur, whereby evaporative cooling and thermal mixing contribute to the rapid formation of **viscoelastic** film and the "locking-in" of uniformity of content throughout the film. One of the additional advantages of the present invention is that the film composition reaches its **viscoelastic** state, and even the fully dried state, without exposing the components of the composition to temperatures which will cause them to be altered or unusable for their intended purpose. (Col. 44, lines 9-18, emphasis added).
>
> FIG. 8 is a sequential representation of the drying process of the present invention. After mechanical mixing, the film may be placed on a conveyor for continued thermal mixing during the drying process. At the outset of the drying process, depicted in Section A, the film 1 preferably is heated from the bottom 10 as it is travels via conveyor (not shown). Heat may be supplied to the film by a heating mechanism, such as, but not limited to, the dryer depicted in FIG. 7 [FIG. 7 depicts a bottom only drying apparatus]. As the film is heated, the liquid carrier, or volatile ("V"), begins to evaporate, as shown by upward arrow 50. Thermal mixing also initiates as hotter liquid, depicted by arrow 30, rises and cooler liquid, depicted by arrow 40, takes its place. Because no skin forms on the top surface 20 of the film 1, as shown in Section B the volatile liquid continues to evaporate 50 and thermal mixing 30/40 continues to distribute thermal energy throughout the film. Once a sufficient amount of the volatile liquid has evaporated, thermal mixing has produced uniform heat diffusion throughout the film 1. The resulting dried film 1 is a **visco-elastic** solid, as depicted in Section C. The components desirably are locked into a uniform distribution throughout the film. Although minor amounts of liquid carrier, *i.e.*, water, may remain subsequent to formation of the **visco-elastic**, the film, may be dried further without movement of the particles, if desired. (Col. 13, lines 36-59, emphasis added).

Instead of reciting bottom drying with substantially no air flow present across the top of the film, Applicant has recited "evaporating at least a portion of said solvent" which would happen to some extent even at room temperature, and a property – viscoelastic – which its films possessed even prior to drying.

Accordingly, the acts or manipulative steps of the '080 Patent as represented in claim 82 can be summarized as shown below in redline format where desired results and scientific theories (which are not entitled to patentable weight in methods claims) and non-limiting recitations are indicated in strike-through:

82. A process for making a film ~~having a substantially uniform distribution of components~~[3], comprising the steps of:

(a) forming a flowable polymer matrix comprising a polymer selected from the group consisting of a water-soluble polymer, a water swellable polymer and combinations thereof, a solvent and an active selected from the group consisting of bioactive actives, pharmaceutical actives, drugs, medicaments and combinations thereof, ~~said matrix having a substantially uniform distribution of said active~~[4];

(b) casting said flowable polymer matrix;

(c) evaporating at least a portion of said solvent from said flowable polymer matrix ~~to form a visco-elastic film~~[5] within about 10 minutes or fewer ~~to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film~~[6]; and

(d) forming a resulting film from said visco-elastic film,

~~wherein said resulting film has a water content of 10% or less~~[7] ~~and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained~~[8].

---

[3] Desired result recited in preamble.
[4] Desired result not entitled to patentable weight in differentiating the claimed process from the methods of the prior art according to the United States Supreme Court under *Markman v. Westview Instruments, Inc.*, 517 US 370, 373 (1996).
[5] Fails to define a method step since the matrix and wet film is already viscoelastic *prior to drying* as admitted in the '080 Patent specification.
[6] Scientific theory and desired result not entitled to patentable weight in differentiating the claimed process from the methods of the prior art according to the United States Supreme Court under *Markman v. Westview Instruments, Inc.*, 517 US 370, 373 (1996).
[7] Desired result that also fails to define a process step as the matrix can begin with less than 10% water.
[8] Scientific theory and desired result not entitled to patentable weight in differentiating the claimed process from the methods of the prior art according to the United States Supreme Court under *Markman v. Westview Instruments, Inc.*, 517 US 370, 373 (1996). *See also*, MPEP § 2111.04.

4. ***Chen*** International Application Pub. No. WO2000/42992 (Exhibit C)

Chen, entitled "Compositions and Methods for Mucosal Delivery," was published on July 27, 2000, which is more than one year before the October 12, 2001 priority date of the '080 Patent. Accordingly, *Chen* qualifies as prior art under 35 U.S.C. § 102(b). As mentioned in the Brief Overview of Prosecution History (Section III.B) of this Request, Applicant failed to submit this reference to the Patent Office during the prosecution of the '080 Patent, even though it was disclosed in its parent application.

As explained in detail in Table 1 below, *Chen* anticipates independent claims 1, 82, and 161, and a large number of dependent claims. Since *Chen* teaches each and every step of the independent claims and many dependent claims, it raises a reasonable likelihood of prevailing with respect to at least one of the '080 Patent claims as either the sole or primary reference.

Specifically, with respect to the recited steps of claim 82, *Chen* teaches:

a) mixing a water soluble polymer (*e.g.*, HPMC), a solvent (*e.g.*, water), and an active (*e.g.*, hydroxymorphone) to form a flowable polymer matrix (*i.e.*, a uniform and viscous solution). (*See* p. 17, lines 6-11, Example 6 at p. 20, lines 17-20 and Table 5);

b) casting the matrix (*Id.* and p. 17, lines 13-15);

c) evaporating at least a portion of the solvent to form a visco-elastic film within about 10 minutes, *e.g.*, 9 minutes (*See* p. 17, lines 13-15); and

d) forming a resulting film from the visco-elastic film (to the extent that this step is distinct from step c, *Id.* and p. 17, lines 15-19 and Table 6).

Chen even teaches the desired properties recited in claim 82. The resulting films of *Chen* have less than 10% water. *See e.g.,* Example 6, Table 6 wherein the resulting film has 2.42% water. Since the films exemplified in *Chen* are dried to solid, flexible films in 9 minutes, at this point, the desired properties of steps (c) and (d) are met in the films of *Chen*. That is, *Chen* discloses a visco-elastic film formed within about 10 minutes, which maintains the substantially uniform distribution of the active by locking-in or substantially preventing migration of said active within

said visco-elastic film (since it is a solid flexible film), and a resulting film formed from the viscoelastic film. Moreover, even the wherein clause of claim 82 is taught by *Chen* since the resulting film of *Chen* has 2.42% water (which is "a water content of 10% or less") and is a solid, flexible film (the "substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained").

Additionally, the uniformity of active throughout the film preparation is also described and demonstrated. *Chen* demonstrates the uniformity of its films employing the same criteria set forth in the '080 Patent, and indeed appears to demonstrate a higher degree of uniformity in some instances. The Examiner needs to look no further than Applicant's own specification to immediately understand that the films of *Chen* are as uniform as those of Applicant, if not more so.

First, the '080 Patent employs the criteria of unit dosage weight to demonstrate the uniformity of its films in the opening Examples A-I:

> Uniformity was also measured by first cutting the film into individual dosage forms. ... Then eight of these dosage forms were randomly selected and additively weighed. ... The individual dosages were consistently 0.04 gm, which shows that the distribution of the components within the film was consistent and uniform. This is based on the simple principal that each component has a unique density. Therefore, when the components of different densities are combined in a uniform manner in a film, as in the present invention, individual dosages forms from the same film of substantially equal dimensions, will contain the same mass.
>
> The '080 Patent, col.31, line 46 through col. 32, line 34 (emphasis added).

As shown in Table 2, all films of Examples A-I were reported to be consistently 0.04 g/unit dosage. The '080 Patent, col. 32, lines 26-28.

Chen demonstrates the uniformity of its films to at least the same degree as the films of the '080 Patent by consistent unit dosage weight. For example, *Chen* demonstrates the uniformity of its films in Table 4 where the films of Example 1 are reported to have a consistent weight of 0.028 ± 0.001 grams per unit dosage. Any argument by Applicant that weight is

unrelated to the content of the product let alone any uniformity of content of the product is contrary to the teachings of Applicant's own Specification. The '080 Patent employs this very measurement to demonstrate the uniformity of their films. Indeed, the film weights of *Chen* are consistent out to the second decimal place, whereas the films of the '080 Patent are rounded to the second decimal place and could vary as much as 25%. Accordingly, the films of *Chen* are as uniform as those disclosed and claimed in the '080 Patent.

Any argument by the Applicant that the uniformity of the films of Example 1-3 would not be present in the films of Examples 5-8 because there is no disclosure of homogeneous mixing of the active must disregard *Chen*'s clear disclosure that the additional ingredients in Examples 1-8 were added "under agitated mixing until they were uniformly dispersed or dissolved in the hydrocolloid." *See Chen* p. 17, lines 6-11. Even more importantly, any such argument must also disregard the data shown in *Chen*'s Figure 5. Figure 5 shows not only the release rates, but also the total amount of active released by each dosage unit in Examples 5-8. At the last time noted, 10 minutes, all measurements of active appear approximately within ± 10% of 100 percent. There are many factors involved in release rate, some of which may account for the modest variation in percentage release. Although not a direct measurement, Figure 5 evidences that the films of *Chen* have substantial uniformity of content per dosage unit.

Second, the '080 Patent specification identifies visual inspection as yet another alternative for demonstrating uniformity:

> The uniform distribution of the components within the film was apparent by examination by either the naked eye or under slight magnification. By viewing the films it was apparent that they were substantially free of aggregation, *i.e.* the carrier and the actives remained substantially in place and did not move substantially from one portion of the film to another. Therefore, there was substantially no disparity among the amount of active found in any portion of the film.
>
> The '080 Patent, col. 31, lines 37-45 (emphasis added).

Chen explicitly describes its films as "glossy, substantially transparent", *i.e.*, visually free of aggregation. *See e.g., Chen*, p. 17, line 15. *Chen* applies the same standard to demonstrate uniformity of its films as Applicant did in the '080 Patent specification. Both the '080 Patent and *Chen* employ and meet identical standards.

Third, the '080 Patent specification states that uniformity is maintained during drying by avoiding drying conditions that cause surface disruption or mottle:

> When a controlled or rapid drying process is desired, this may be through a variety of methods. A variety of methods may be used including those that require the application of heat. The liquid carriers are removed from the film in a manner such that the uniformity, or more specifically, the non-self-aggregating uniform heterogeneity, that is obtained in the wet film is maintained.
>
> Desirably, the film is dried from the bottom of the film to the top of the film. Substantially no air flow is present across the top of the film during its initial setting period, during which a solid, visco-elastic structure is formed. This can take place within the first few minutes, *e.g.* about the first 0.5 to about 4.0 minutes of the drying process. Controlling the drying in this manner, prevents the destruction and reformation of the film's top surface, which results from conventional drying methods. This is accomplished by….
>
> The '080 Patent, col. 27, lines 26-42 (emphasis added).

Chen also maintains its uniformity during drying by avoiding drying conditions that cause surface disruption or mottle. *Chen* discloses films that are glossy and substantially transparent and the drying parameters for doing so. *See e.g.*, *Chen*, p. 17, lines 13-16, Figure 2 (showing controlled drying).

Finally, Requester submits a Declaration by Dr. Edward D. Cohen ("The Cohen Declaration, Exhibit L). Dr. Cohen, an independent expert in the coating and drying field, confirms that a homogeneous coating mixture, such as those in *Chen*, would be expected to yield a film having uniform content of active per dosage unit. More specifically, as stated in the Cohen Declaration:

> *Chen* provides coating mixtures containing active that are described as "homogeneous", "completely dissolved", or "completely dispersed". Drying such hydrocolloid coating mixtures would be expected to yield films with substantially uniform content of active per unit of film, where the unit of film is a typical dosage unit or per sheet of uncut film. It is my opinion that *Chen* teaches films with substantially uniform content of active per unit of film, where the unit of film is, for example, a dosage unit or an uncut sheet of film.
>
> In general, as a homogeneous or completely dispersed coating mixture is dried, the solvent is removed, the viscosity increases and the active would be more firmly fixed in place. *When working with a homogeneous or completely dissolved coating mixture, for example, it would be difficult for a person of ordinary skill in the thin film art not to obtain a film that has uniform content of active*.
>
> The Cohen Declaration, p. 2-3, ¶¶ 8-9 (emphasis added).

In sum, as shown at page 17, lines 6-19 and Example 6 in Table 6 at page 22, *Chen* anticipates all the three independent claims and many dependent claims of the '080 Patent. As such, *Chen* raises a reasonable likelihood of prevailing with respect to at least one of the '080 Patent claims as either the sole or primary reference.

5. ***Staab*** US Patent No. 5,393,528 (Exhibit D)

Staab, entitled "Dissolvable Device for Contraception or Delivery of Medication," issued in 1995, which is more than one year before the October 12, 2001 priority date of the '080 Patent. Accordingly, *Staab* qualifies as prior art under 35 U.S.C. § 102(b). The Examiner cited *Staab* against the claims of the '337 Patent, the parent application of the '080 Patent. However, Applicant did not disclose this reference to the Patent Office during the prosecution of the '080 Patent.

Staab also discloses the same basic steps recited in the '080 Patent claims:

a) mixing a water soluble or swellable polymer (*e.g.*, HPMC), a solvent (*e.g.*, water), and an active (*e.g.*, contraceptive) to form a flowable polymer matrix (*i.e.*, a uniform blend). (*See* col. 4, lines 7-10; col. 5, lines 23-25; and col. 7, lines 37-42);

b) casting the matrix (*See* col. 7, lines 37-42; col. 10, lines 28-31; and Figure 5);

c) evaporating at least a portion of the solvent to form a visco-elastic film within about 10 minutes (*See* col. 10, line 66 – col. 11, line 6 and lines 44-45 where drying occurs in 20 minutes); and

d) forming a resulting film from the visco-elastic film (to the extent that this step is distinct from step c, *See id.*).

Even the desired properties are all anticipated by *Staab,* including, *e.g.*, that the active is evenly distributed throughout its films. *See* col. 9, lines 11-13. *See also* the Example showing that the methods of *Staab* resulted in two inch square films each containing 19 mg benzalkonium chloride and weighing about 190 mg. Col. 11, lines 49-51. Additionally, these films have less than 10% water in them, since they at most start with only 5% water in them. *See* col. 11, lines 30-33 where the wet film, prior to drying, comprises 10.0% benzalkonium chloride (50% aqueous). So, although not entitled to patentable weight, the recited properties are also anticipated by *Staab*.

Applicant made three assertions about *Staab* during the prosecution of the '337 Patent (the parent application of the '080 Patent):

1. Nowhere in *Staab* is it disclosed, taught or suggested to utilize a water-soluble polymer composition, a solvent, and remove at least a portion of the liquid solvent to provide a visco-elastic film that maintains a uniform distribution of the active component in the resulting film product.
2. Nowhere in *Staab* is it disclosed, taught or suggested to maintain the uniform distribution of active components by locking-in or substantially preventing migration of the active components within the visco-elastic film and resulting film product.
3. Moreover, *Staab* fails to disclose or suggest that the visco-elastic film must be formed within a 10 minute time period and the resulting film present has a 10% water content.

See the Response in the prosecution of the '337 Patent, filed September 4, 2009, page 10, first full paragraph (Exhibit M).

Applicant's assertions are untenable. As to the first assertion, *Staab* teaches using a water soluble polymer (*e.g.*, HPMC) and its solvent (*e.g.*, water). *See* col. 4, lines 7-10; col. 5, line 15-25; and col. 7, lines 37-41. *See also* the example where HMPC, water and active are homogeneously blended and cast. Col. 11, lines 22-44. *Staab* teaches evaporating the solvent (*i.e.*, drying its film) in an oven. *See* col. 11, line 44-46. *Staab* also teaches that the film prepared in Example 1 each contains 19 mg benzalkonium chloride and about 190 mg in weight. *See* col. 11, lines 49-51. Thus, *Staab* discloses and demonstrates that its films are formed while maintaining the substantially uniform distribution of active.

With respect to the second assertion, neither the '337 Patent nor its continuation (the '080 Patent) explains what the term "locking-in" refers to. It is, at best, only a scientific theory for an existing means of achieving a result (*i.e.*, uniform distribution). As discussed in Section III.C.1. above, a scientific theory of how uniformity is possibly maintained, is of little patentable consequence in process claims. Rather, Applicant must properly recite the manipulative steps that result in the desired properties. Nonetheless, *Staab* discloses that the active is evenly distributed throughout the film. *See* col. 5, line 68 through col. 6, line 1. The active would, of course, be "locked-in" the resulting dried films of *Staab,* and "substantially prevent[ed from] migration".

Turning to the third assertion, *Staab* discloses that in Example 1, 10% wt. of the premix is benzalkonium chloride solution (50% aqueous). *See* col. 11, lines 27-35. In other words, the premix contains 5% wt. water. As such, the final product of *Staab* has a water content of 10% or less.

Moreover, as established in Section III.B, Requester submits that if the wet film is a viscoelastic film *prior to drying* (as repeatedly taught by Applicant in its own specification), there is no further limitation represented by this recitation other than that at least a portion of the solvent be evaporated in less than about 10 minutes. Notwithstanding the foregoing, *Staab* anticipates the feature of "forming a visco-elastic film within a 10 minute time period and the resulting film present has a water content of 10% or less" for reasons provided below.

As set forth in MPEP 2112.01 (I): "[w]here the claimed and prior art products are identical or substantially identical in structure or composition, or **are produced by identical or substantially identical processes**, a prima facie case of either anticipation or obviousness has been established." (emphasis added). First, *Staab*'s films are made using the same solvent (*e.g.*, water) and the same polymer (*e.g.*, HPMC), which is disclosed and claimed in the '080 Patent as a suitable film forming polymer (*See* the '080 Patent, col. 15, lines 44-51) and used in a majority of its examples (*See* Examples P-AA). Second, *Staab*'s films are also formed from a blend mixture of evenly distributed ingredients (*See* col. 7, lines 37-41). Third, *Staab*'s films (*e.g.*, in Example 1), have only 5% water in HPMC prior to drying. Thus, even though *Staab* discloses drying its films in approximately 20 minutes (*See* col. 11, line 45), within about 10 minutes or fewer, its films would be as viscoelastic as the films of the '080 Patent, as they are **produced by identical or substantially identical processes** as claimed in the '080 Patent. As such, *Staab* anticipates the recited feature.

Staab also discloses the premix steps of claim 1. *See e.g.*, col. 7, lines 37-47 and Figure 5. Regarding claim 161, it further discloses applying its films to a body surface. *See e.g.*, col. 7, lines 3-7.

In sum, as shown in col. 7, lines 37-51 and col. 10, line 66 through col. 11, line 45, *Staab* anticipates all the three independent claims and many dependent claims of the '080 Patent. As such, *Staab* raises a reasonable likelihood of prevailing with respect to at least one of the '080 Patent claims as either the sole or primary reference.

6. ***Le Person*** *Le Person et al.* CHEM ENG & PROC 37:257-263 1998 (Exhibit E)

Le Person, entitled "Near Infrared Drying of Pharmaceutical Thin Films: Experimental Analysis of Internal Mass Transport," was published in 1998, which is more than one year before the October 12, 2001 priority date of the '080 Patent. Thus, *Le Person* qualifies as prior art under 35 U.S.C. § 102(b). Also, this reference was not considered during prosecution. *Le Person* is a detailed experimental analysis of internal mass transport during the drying of pharmaceutical wet films, focusing on uniformity of active throughout the film. *See* the Title

and Introduction at page 257. *Le Person* discloses the same basic steps recited in the '080 Patent claim 82:

a) mixing a water soluble or swellable polymer (*e.g.*, an acrylic adhesive polymer), a solvent (*e.g.*, water), and an active (*e.g.*, a pharmaceutical active substance) to form a flowable polymer matrix (*i.e.*, a uniform blend) (*See* page 258, col. 1, § 2.1; page 262, col. 2, lines 4-6);

b) casting the matrix (*See* page 257, col. 1, lines 10-11);

c) evaporating at least a portion of the solvent to form a visco-elastic film within 10 minutes (*See* page 260, col. 2, line 12-14 and Figure 5); and

d) forming a resulting film from the visco-elastic film (to the extent that this step is distinct from step c, *See id.*).

Le Person also anticipates the desired results recited in the claims. *Le Person* teaches that in 10 minutes, 99% of the initial water from a 100 μm thick coating is evaporated. *See* page 260, col. 2, line 12-14 and Figure 5. Accordingly, in less than about 10 minutes, the films of *Le Person* have less than 10% water, are viscoelastic, and the uniformity is "locked-in" and migration of active prevented and maintained since the dried films are solid at this point. The films of *Le Person* are as "capable" of being administered to a body surface as the films of claims 82 and 161. Moreover, application of the films of *Le Person* to the skin (*e.g.*, transdermal delivery) is clearly contemplated in the Abstract and page 257, col. 1, first paragraph.

Le Person discloses each and every step recited in independent claims 82 and 161 of the '080 Patent and several of its dependent claims. Indeed, the methods disclosed in *Le Person* are far beyond anything described or claimed in the '080 Patent. The obviousness of the premix-related steps in the remaining independent claim 1 and remaining claims is addressed in Tables 11 and 12.

As such, *Le Person* raises a reasonable likelihood of prevailing with respect to at least one of the '080 Patent claims as either the sole or primary reference.

7. ***Horstmann*** US Patent No. 5,629,003 (Exhibit F)

Horstmann, entitled "Rapidly Disintegrating Sheet-Like Presentations of Multiple Dosage Units," issued in 1997, which is more than one year before the October 12, 2001 priority date of the '080 Patent. Thus, *Horstmann* qualifies as prior art under 35 U.S.C. § 102(b).[9]

Horstmann teaches the same basic process steps recited in the '080 Patent claims:

a) mixing a water soluble or swellable polymer (*e.g.*, acetylated starch), a solvent (*e.g.*, water), and a drug or other actives (*e.g.,* peppermint oil) to form a flowable polymer matrix (*i.e.*, a uniform blend) (*See* col. 3, lines 20-29, and Example 3);

b) casting the matrix (*See e.g.,* col. 4, lines 34-41; and Example 3, col. 5, lines 51-53);

c) evaporating at least a portion of the solvent to form a visco-elastic film within 10 minutes (*See e.g.,* col. 3, lines 7-13; Example 3, col 5., lines 51-53); and

d) forming a resulting film from the visco-elastic film (to the extent that this step is distinct from step c, *See id.*)

The resulting film of *Horstmann* is then cut into individual dosage units and packaged. *See* Example 3.

Even the desired properties are all anticipated by *Horstmann*. For example, *Horstmann*'s films are viscoelastic in that they can be peeled and packaged as described in Examples 1, 3, and 4. *Horstmann* prepares its films from a coating solution with a homogeneous mixture of

[9] The Examiner, during the prosecution of the '080 Patent, noted that *Horstmann* and other three patents (*i.e.*, US Patent Nos. 4,049,848, 4,872,270, and 5,766,525) were pertinent to Applicant's disclosure in the Office Action mailed on September 29, 2010. Unfortunately, the Examiner did not explain the reason for not citing these patents in substantive rejections.

ingredients, which "result[s] in uniform films." *See* col. 3, lines 19-41 and Examples 1, 3, and 4. Additionally, with respect to independent caim 1, *Horstmann* discloses forming a masterbatch pre-mix of components prior to adding the active. *See* Examples 1, 3, and 4. The premix is homogenized by stirring. *Id.* With respect to independent claim 161, *Horstmann* teaches that its films can be administered to a body surface, *e.g.*, the mouth. *See* col. 1, lines 10-12. So, although not entitled to patentable weight, the recited properties are also anticipated by *Horstmann*.

Since *Horstmann* teaches each and every step of the independent claims 1, 82, and 161, it raises a reasonable likelihood of prevailing with respect to at least one of the '080 Patent claims as either the sole or primary reference.

IV. Explanation of Pertinence and Manner of Applying Cited Prior Art to Every Claim For Which Reexamination is Requested Based Upon Prior Art.

A. Claim Charts Applying *Chen* as Sole or Primary reference

There are three independent claims in the '080 Patent: claims 1, 82 and 161. *Chen* anticipates all three independent claims, and further, anticipates a large number of dependent claims as set forth in detail in Table 1. The remaining dependent claims are merely simple substitutions or combinations of known elements as discussed in detail in Tables 2-4. Accordingly, all 299 claims of the '080 Patent are anticipated by *Chen* or obvious over *Chen* in view of *Staab or Le Person*.

Table 1. Proposed rejection of claims 1, 4, 5, 8-18, 20-32, 34, 36-40, 44-47, 51, 53, 54, 59, 62-71, 82-84, 87-97, 99-111, 113, 115-119, 123-126, 130, 132, 133, 138, 141-150, 161-166, 169-179, 181-193, 195, 197-201, 205-208, 212, 214, 215, 220, 223-232, 243, 244, 246, 247, 249-262, 264, 265, 267-280, 282, 283, and 285-299 under 35 U.S.C. § 102(b) as anticipated by *Chen*

Table 1	
Claims of '080 Patent	*Chen*
1. A process for making a film having a substantially uniform distribution of components, comprising the steps of:	*Chen* discloses a process for making films having a substantially uniform distribution of components. *See e.g.*, p. 17, lines 6-24 and Examples 1-13. The uniformity of the films of *Chen* are demonstrated employing the same criteria established by the '080 Patent itself and meet or exceed the degree of uniformity demonstrated in the '080 Patent. *See* the detailed explanation of step (e) below for extensive discussion of the uniformity of *Chen*.
(a) forming a masterbatch pre-mix comprising a solvent and a polymer selected from the group consisting of water-soluble polymers, water-swellable polymers and combinations thereof;	*Chen* discloses forming a masterbatch pre-mix including a water soluble polymer (*e.g.*, hydrocolloid HPMC), and a solvent (*e.g.*, water), agitated to form a uniform and viscous solution. *See* page 4, lines 24-27; page 17, lines 6-11; and page 20, lines 19-20. HPMC is identified as a water-soluble polymer in the '080 Patent at col. 15, lines 49-51.
(b) adding an active to a pre-determined amount of said masterbatch pre-mix to form a flowable polymer matrix, said matrix having a substantially uniform distribution of said active;	Therapeutic agents are then added to the homogeneous colloid, *i.e.*, the instant pre-mix, until they are uniformly dispersed or dissolved in the polymer matrix. *See*, page 4, lines 26-27, page 17, lines 6-11, and page 20, lines 19-20. The polymer matrix is flowable as it is a uniform and viscous solution. *See* page 17, line 8. The amount of the masterbatch pre-mix is pre-determined as indicated, *e.g.*, by Tables 5 and 7 providing the wet composition.
(c) casting said flowable polymer matrix;	The resulting mixture of *Chen*, *i.e.*, the instant

Table 1	
Claims of '080 Patent	*Chen*
	matrix, is "coated on the non-siliconized side of a polyester film at a wet thickness of 10 mil." *See e.g.,* page 17, lines 13-15, Examples 4-8, and Fig. 2.
(d) evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film within about 10 minutes or fewer to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film; and	*Chen* discloses evaporating the polar solvent from the cast matrix in 9 minutes. *See* page 17, lines 14-15 and Examples 4-8. To the extent that reciting "visco-elastic" further limits this claim (since the '080 Patent repeatedly refers to its matrix and its wet film *prior to drying* as viscoelastic, as discussed in detail in Section III.C.2) *Chen*'s films are viscoelastic because they are flexible, stand alone, self-supporting films (page 17, lines 15-16) made using the HPMC which is disclosed and claimed in the '080 Patent as a suitable film forming polymer. The '080 Patent, col. 15, lines 44-51. The substantially uniform distribution of active is maintained by locking-in or substantially preventing migration of said active within said viscoelastic film. This is evident from the fact that *Chen* prepares its films from a coating solution with a homogeneous mixture of ingredients. *See* page 17, lines 6-11, and 26-28, Examples 5-8, and page 20, lines 17-20. And the substantially uniform distribution has been maintained as discussed in detail directly below for step (e). Moreover, (1) *Chen*'s films are made using the same solvent (*e.g.,* water) and the same polymer (*e.g.*, HPMC), which is disclosed and claimed in the '080 Patent as a suitable film forming polymer (*See* the '080 Patent, col. 15, lines 44-51) and used in the majority of the Examples (See Examples P-AA); (2) they are coated on the non-siliconized side of a polyester film (*See e.g.,* page 17, lines 13-15, Examples 4-8, and Fig. 2); and (3) the resulting films of *Chen* have less than 10% water

Table 1	
Claims of '080 Patent	*Chen*
	(*See e.g.*, Example 6, Table 6 wherein the resulting film has 2.42% water). Indeed, the film of *Chen* is viscoelastic and meets the other desired properties, as it is made using the same materials and dried according to the same method recited in this claim. *See* the '080 Patent, col. 15, lines 44-51. As set forth in MPEP 2112.01 (I): "[w]here the claimed and prior art products are identical or substantially identical in structure or composition, or **are produced by identical or substantially identical processes**, a prima facie case of either anticipation or obviousness has been established." (emphasis added) Thus, *Chen*'s films would be as viscoelastic within a 10 minute time period as the films of the '080 Patent, as they are **produced by identical or substantially identical processes** as the process disclosed in the '080 Patent. As such, *Chen* anticipates this feature.
(e) forming a resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained.	*Chen* discloses that after the step of evaporating the water from the matrix, the matrix includes a water content of from 0.5-10% with a preferred range of 1-5%. *See* page 13, lines 27-28. Examples 1 and 4-8 reported films formed with a water content of less than 3%. *See* Tables 2 and 6 on pages 18 and 22, respectively. Examples 2-3 have a water content of less than 9%. *See* Table 2 on page 18. *Chen* also discloses and demonstrates that its resulting films are formed while maintaining the substantially uniform distribution of active. *Chen* demonstrates the uniformity of its films employing the same criteria set forth in the '080 Patent, and indeed appears to demonstrate a higher degree of uniformity in some instances. The Examiner needs to look no further than Applicant's own specification to immediately understand that the

Table 1	
Claims of '080 Patent	*Chen*
	films of *Chen* are as uniform as those of Applicant, if not more so. *First,* the '080 Patent employs the criteria of unit dosage weight to demonstrate the uniformity of its films in the opening Examples A-I: > Uniformity was also measured by first cutting the film into individual dosage forms. … Then eight of these dosage forms were randomly selected and additively weighed. … The individual dosages were consistently 0.04 gm, which shows that the distribution of the components within the film was consistent and uniform. This is based on the simple principal that each component has a unique density. Therefore, when the components of different densities are combined in a uniform manner in a film, as in the present invention, individual dosages forms from the same film of substantially equal dimensions, will contain the same mass. > The '080 Patent, col.31, line 46 through col. 32, line 34 (emphasis added). As shown in Table 2, all films of Examples A-I were reported to be consistently 0.04 g/unit dosage. The '080 Patent, col. 32, lines 26-28. *Chen* demonstrates the uniformity of its films to at least the same degree as the films of the '080 Patent by consistent unit dosage weight. For example, *Chen* demonstrates the uniformity of its films in Table 4 where the films of Example 1 are

Table 1	
Claims of '080 Patent	*Chen*
	reported to have a consistent weight of 0.028 ± 0.001 grams per unit dosage. Any argument by Applicant that weight is unrelated to the content of the product let alone any uniformity of content of the product is contrary to the teachings of Applicant's own Specification. The '080 Patent employs this very measurement to demonstrate the uniformity of their films. Indeed, the film weights of *Chen* are consistent out to the second decimal place, whereas the films of the '080 Patent are rounded to the second decimal place and could vary as much as 25%. Accordingly, the films of *Chen* are as uniform as those disclosed and claimed in the '080 Patent. Any argument by the Applicant that the uniformity of the films of Example 1-3 would not be present in the films of Examples 5-8 because there is no disclosure of homogeneous mixing of the active must disregard *Chen*'s disclosure that the additional ingredients in Examples 1-8 were added "under agitated mixing until they were uniformly dispersed or dissolved in the hydrocolloid." *See* p. 17, lines 6-11. Even more importantly, any such argument must also disregard the data shown in *Chen*'s Figure 5. Figure 5 shows not only the release rates, but also the total amount of active released by each dosage unit in Examples 5-8. At the last time noted, 10 minutes, all measurements of active appear approximately within ± 10% of 100 percent. There are many factors involved in release rate, some of which may account for the modest variation in percentage release. Although not a direct measurement, Figure 5 evidences that the films of *Chen* have substantial uniformity of content per dosage unit. Second, the '080 Patent specification identifies visual inspection as yet another alternative for

Table 1	
Claims of '080 Patent	*Chen*
	demonstrating uniformity: The uniform distribution of the components within the film was apparent by examination by either the naked eye or under slight magnification. By viewing the films it was apparent that they were substantially free of aggregation, *i.e.* the carrier and the actives remained substantially in place and did not move substantially from one portion of the film to another. Therefore, there was substantially no disparity among the amount of active found in any portion of the film. The '080 Patent, col. 31, lines 37-45 (emphasis added). *Chen* explicitly describes its films as "glossy, substantially transparent", *i.e.*, visually free of aggregation. *See e.g., Chen*, p. 17, line 15. *Chen* applies the same standards to demonstrate uniformity of its films as Applicant did in the '080 Patent specification. Both the '080 Patent and *Chen* employ and meet identical standards. Third, the '080 Patent specification states that uniformity is maintained during drying by avoiding drying conditions that cause surface disruption or mottle: When a controlled or rapid drying process is desired, this may be through a variety of methods. A variety of methods may be used including those that require the application of heat. The liquid

Table 1	
Claims of '080 Patent	*Chen*
	carriers are removed from the film in a manner such that the uniformity, or more specifically, the non-self-aggregating uniform heterogeneity, that is obtained in the wet film is maintained. Desirably, the film is dried from the bottom of the film to the top of the film. Substantially no air flow is present across the top of the film during its initial setting period, during which a solid, visco-elastic structure is formed. This can take place within the first few minutes, *e.g.* about the first 0.5 to about 4.0 minutes of the drying process. Controlling the drying in this manner, prevents the destruction and reformation of the film's top surface, which results from conventional drying methods. This is accomplished by…. The '080 Patent, col. 27, lines 26-42 (emphasis added). *Chen* also maintains its uniformity during drying by avoiding drying conditions that cause surface disruption or mottle. *Chen* discloses films that are glossy and substantially transparent and the drying parameters for doing so. *See e.g.*, *Chen*, p. 17, lines 13-16, Figure 2 (showing controlled drying). Finally, Applicant submits the Declaration of Dr. Edward Cohen ("Cohen Declaration" Exhibit L). Dr. Cohen, an independent expert in the coating and drying field, confirms that a homogeneous coating mixture, such as those in *Chen*, would be expected to yield a film having uniform content of

Table 1	
Claims of '080 Patent	*Chen*
	active per dosage unit. More specifically, as stated in the Cohen Declaration: *Chen* provides coating mixtures containing active that are described as "homogeneous", "completely dissolved", or "completely dispersed". Drying such hydrocolloid coating mixtures would be expected to yield films with substantially uniform content of active per unit of film, where the unit of film is a typical dosage unit or per sheet of uncut film. It is my opinion that *Chen* teaches films with substantially uniform content of active per unit of film, where the unit of film is, for example, a dosage unit or an uncut sheet of film. In general, as a homogeneous or completely dispersed coating mixture is dried, the solvent is removed, the viscosity increases and the active would be more firmly fixed in place. *When working with a homogeneous or completely dissolved coating mixture, for example, it would be difficult for a person of ordinary skill in the thin film art not to obtain a film that has uniform content of active*. Cohen Declaration, p. 2-3, ¶¶ 8-9 (emphasis added).
4. The process of claim 1, wherein said water-soluble polymer comprises	*Chen* discloses where the water-soluble polymer includes one or more polyethylene oxides. *Chen*,

Table 1	
Claims of '080 Patent	*Chen*
polyethylene oxide.	p. 14, line 29.
5. The process of claim 1, wherein said polymer comprises a polymer selected from the group consisting of cellulose, a cellulose derivative, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyvinyl copolymers, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof, alone or in combination with polyethylene oxide.	*Chen* discloses that polymers can be pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, xanthan gum, tragacanth gum, guar gum, acacia gum, or arabic gum. *Chen*, p. 14, lines 12-31.
8. The process of claim 5, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.	*Chen* discloses that polymers can be xanthan gum, tragacanth gum, guar gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, or gellan gum. *Chen*, p. 14, lines 12-21.
9. The process of claim 5, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer,	*Chen* discloses that polymers can be gelatin, xanthan gum, tragacanth gum, guar gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, or gellan gum. *Chen*, p. 14, lines 12-21.

Table 1	
Claims of '080 Patent	*Chen*
poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(d-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.	
10. The process of claim 1, wherein said solvent is selected from the group consisting of water, polar organic solvent, and combinations thereof.	*Chen* teaches the use of water and polar solvents such as ethanol to form its films. *See* page 10, line 19; Table 1 on page 18 (Example 2 employs water and ethanol).
11. The process of claim 10, wherein said solvent is selected from the group consisting of ethanol, isopropanol, acetone, and combinations thereof.	*See* the detailed explanation above for claim 10.
12. The process of claim 1, wherein said active is selected from the group consisting of bioactive active, pharmaceutical actives, drugs, medicaments and combinations thereof.	In *Chen*, the films in Examples 5-8 contain a drug, *i.e.*, nicotine, hydromorphone, oxybutynin or estradiol. *See* Table 5 at page 21. In Example 13, sildenafil citrate is the active ingredient. *See* Table 11, page 28.
13. The process of claim 1, wherein said active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory	*Chen* discloses that nicotine, hydromorphone (*i.e.*, analgesics), oxybutynin, estradiol (*i.e.*, fertility agents), and sildenafil citrate (*i.e.*, erectile dysfunction therapies) can be an active. *Chen*'s actives also include analgesics, α-adrenergic receptor blockers, anti-Alzheimer's disease medication, antianginal, antianxiety, antiarrythmics, antiarthritics, antibiotics,

Table 1	
Claims of '080 Patent	*Chen*
agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics,	anticoagulants/thrombolytics, anticonvulsants/anti-Parkinson medication, anti- depressants, anti-diabetics, anti-dianheal. anti-epileptics, anti-fungal, anti-gout, anti- heartworm medication for dogs, anti-histamines, anti-hypertensives, anti-inflammatories, anti-infectives, antimigranes, anti-nasuants/anti-emetics, anti-neoplastics/anti-tumor active agents, anti-pruitics, anti-psychotics, anti-pyretics, anti-spasmodics, anti-virals, bronchial dilators/anti-asthmatics, calcium antagonists, cardiac agents, cardiotonics, central nervous system actives, contraceptives, coronary vasodilators, cough/cold remedies, dietary supplements, including vitamins and minerals, and other drugs. *See* page 10, line 23 through page 11, line 12.

Table 1	
Claims of '080 Patent	*Chen*
tranquilizers, anti-psychotics, anti-tumor drugs, anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, anti-convulsants, neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, anti-asthmatics, cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.	
14. The process of claim 1, wherein said active is selected from the group consisting of cosmetic actives, antigens, allergens, spores, microorganisms, *See*ds, mouthwash components, flavors, fragrances, enzymes, preservatives, sweetening agents, colorants, spices, vitamins and combinations thereof.	*Chen* discloses that flavoring agents can be incorporated before or after film forming. *See* page 15, line 24. Moreover, the film may further include one or more of an emulsifier, a plasticizer, a taste modifying agent (*e.g.*, flavoring agents, sweetening agents, spices), a preservative, a coloring agent, a permeation enhancer, and a stabilizer. *See* page 4, lines 4-6; and page 10, lines 7-14.
15. The process of claim 1, wherein said active is a bioactive active.	*Chen* discloses that the active agent can be proteins such as insulin, which is a bioactive active, at page 11, line 4.
16. The process of claim 1, wherein said active is a biological response modifier.	The phrase "biological response modifier" appears only once in the '080 Patent at col. 19, line 63. To the extent that Applicant ascribes any special meaning to this term, such has not been made apparent in the '080 Patent specification. As such, all actives are biological response modifiers. *Chen* already discloses a long list of therapeutic agents that can be used in its films. *See* page 10 line 23, through page 11, line 12.
17. The process of claim 1, wherein said active is an opiate or opiate-derivative.	*Chen* discloses that the active agent can be hydromorphone in Table 5 on page 21. Hydromorphone is an opioid, *i.e.*, an opiate-

Table 1	
Claims of '080 Patent	*Chen*
	derivative.
18. The process of claim 1, wherein said active is an anti-emetic.	*Chen* discloses that the active agent can be anti-emetic at page 10, line 29.
20. The process of claim 1, wherein said active is selected from the group consisting of sildenafils, tadalafils, vardenafils, apomorphines, yohimbine hydrochlorides, alprostadils and combinations thereof.	*Chen* discloses that the active agent can be sildenafil at page 4, line 8.
21. The process of claim 1, wherein said active is a protein.	*Chen* discloses that the active agent can be proteins such as insulin at page 11, line 4.
22. The process of claim 1, wherein said active is insulin.	*Chen* discloses that the active agent can be proteins such as insulin at page 11, line 4.
23. The process of claim 1, wherein said active is an anti-diabetic.	*Chen* discloses that the active agent can be an anti-diabetic at page 10, line 27.
24. The process of claim 1, wherein said active is an antihistamine.	*Chen* discloses that the active agent can be an antihistamine at page 10, line 28.
25. The process of claim 1, wherein said active is an anti-tussive.	*Chen* discloses that the active agent can be cough/cold remedies at page 10, line 32 through page 11, line 1. An anti-tussive is an agent that is capable of relieving or depressing coughing.
26. The process of claim 1, wherein said active is a non-steroidal anti-inflammatory.	*Chen* discloses that the active agent can be non-steroidal anti-inflammatory agents at page 11, line 11.
27. The process of claim 1, wherein said active is an anti-asthmatics.	*Chen* discloses that the active agent can be an anti-asthmatics at page 10, line 31.
28. The process of claim 1, wherein said active is an anti-diarrhea.	*Chen* discloses that the active agent can be an anti-diarrhea at page 10, line 27.
29. The process of claim 1, wherein said active is an alkaloid.	*Chen* discloses that the active agent can be nicotine in Table 5 at page 21. Nicotine is an alkaloid.

Table 1	
Claims of '080 Patent	*Chen*
30. The process of claim 1, wherein said active is an anti-psychotic.	*Chen* discloses that the active agent can be anti-psychotics at page 10, line 30.
31. The process of claim 1, wherein said active is an anti-spasmodic.	*Chen* discloses that the active agent can be anti-spasmodics at page 10, line 30.
32. The process of claim 1, wherein said active is a biological response modifier.	Claim 32 is a duplicate of claim 16, *i.e.*, there is no difference in scope. *See* the detailed explanation above for claim 16.
34. The process of claim 1, wherein said active is an H_2-antagonist.	*Chen* discloses that the active agent can be an H_2 receptor antagonist at page 11, line 2.
36. The process of claim 1, wherein said active is a smoking cessation aid.	*Chen* discloses that the active agent can be smoking cessation aids at page 11, line 6.
37. The process of claim 1, wherein said active is an anti-parkinsonian agent.	*Chen* discloses that the active agent can be anti-Parkinson mediation at page 10, line 26.
38. The process of claim 1, wherein said active is an anti-depressant.	*Chen* discloses that the active agent can be an anti-depressant at page 10, lines 26 and 27.
39. The process of claim 1, wherein said active is an anti-migraine.	*Chen* discloses that the active agent can be an anti-migraine at page 10, line 29.
40. The process of claim 1, wherein said active is an anti-Alzheimer's agents.	*Chen* discloses that the active agent can be anti-Alzheimer's disease medication at page 10, line 24.
44. The process of claim 1, wherein said active is an antibiotic.	*Chen* discloses that the active agent can be an antibiotic at page 10, line 25.
45. The process of claim 1, wherein said active is an anesthetic.	*Chen* discloses that the active agent can be an anesthetic at page 11, line 9.
46. The process of claim 1, wherein said active is a contraceptive.	*Chen* discloses that the active agent can be a contraceptive at page 10, line 32.
47. The process of claim 1, wherein said active is an anti-thrombotic drug.	*Chen* discloses that the active agent can be an anticoagulant/thrombolytic at page 10, line 26.
51. The process of claim 1, wherein said	*Chen* discloses that the active agent can be an

Table 1	
Claims of '080 Patent	*Chen*
active is an anti-tumor drug.	anti-tumor active agent at page 10, lines 29 and 30.
53. The process of claim 1, wherein said active is an analgesic.	*Chen* discloses that the active agent can be an analgesic at page 10, line 24.
54. The process of claim 1, wherein said active is a hormone.	*Chen* discloses that the active agent can be a hormone at page 11, line 3.
59. The process of claim 1, wherein said active is selected from the group consisting of an analgesic, an anti-inflammatory, an antihistamine, a decongestant, a cough suppressant and combinations thereof.	*See* the detailed explanation for claim 13.
62. The process of claim 1, wherein said active is a hypnotic.	*Chen* discloses that the active agent can be a hypnotic at page 11, line 5.
63. The process of claim 1, wherein said active is taste-masked.	*Chen* discloses that the active agent can be taste-masked at page 9, line 15.
64. The process of claim 1, wherein said active is taste-masked using a flavor.	*Chen* discloses that taste modifying agents used therein include flavor agents at page 10, line 7.
65. The process of claim 1, wherein said active is coated with a controlled release composition.	*Chen* discloses that its films may release the active agent over a period of time that is determined by a number of different factors. *See* page 6, line 30 through page 7, line 21. More specifically, *Chen* discloses: "Depending on the optimal program for a specific application of the invention, the disintegration time and the dissolution time can be controlled within a prescribed range by adjustment of the formulation and the thickness of the film. In some cases, it is desirable for release of the active agent to occur after dissolution of the film. For these applications, the active agent may be encapsulated in a matenal with dissolution properties that are different from those of the hydrocolloid." *See* page 9, lines 9-14. Slow release films are also discussed, *e.g.*, at page 7, lines 16-21.

Table 1	
Claims of '080 Patent	*Chen*
66. The process of claim 65, wherein said controlled release composition provides an immediate release.	*See* the detailed explanation for claim 65.
67. The process of claim 65, wherein said controlled release composition provides a delayed release.	*See* the detailed explanation for claim 65.
68. The process of claim 65, wherein said controlled release composition provides a sustained release.	*See* the detailed explanation for claim 65.
69. The process of claim 65, wherein said controlled release composition provides a sequential release.	*See* the detailed explanation for claim 65.
70. The process of claim 1, wherein said active is a particulate.	To the extent that the term "particulate" further limits this claim, particularly since it doesn't specify, *e.g.*, when the active is a particulate, *Chen* teaches many actives in that are particulates, *e.g.*, monoclonal antibodies at col. 6, lines 49-54.
71. The process of claim 1, further comprising adding a degassing agent to said masterbatch premix.	The term "degassing agent" is not defined in the specification and appears only in the claims of the '080 Patent. Yet, during the prosecution of US Application No. 11/858,214, a related patent application owned by Applicant, Applicant noted, in the response to the Office Action filed December 20, 2010 (Exhibit O), that peppermint oil is one of foam reducing flavoring agents which "act to both flavor the film and prevent and/or **remove air** from the film-forming compositions." *See* page 3, claim 5; and page 5, last paragraph. (emphasis added) *Chen* teaches using peppermint oil as a component in its films. *See* Table 3 at page 19. As such, claim 71 is anticipated by *Chen*.
82. A process for making a film having a substantially uniform distribution of	*Chen* discloses a process for making films having a substantially uniform distribution of

Table 1	
Claims of '080 Patent	*Chen*
components, comprising the steps of:	components. *See e.g.*, p. 17, lines 6-24 and Examples 1-13. The uniformity of the films of *Chen* are demonstrated employing the same criteria established by the '080 Patent itself and meet or exceed the degree of uniformity demonstrated in the '080 Patent. *See* the detailed explanation of step (e) below for extensive discussion of the uniformity of *Chen*.
(a) forming a flowable polymer matrix comprising a polymer selected from the group consisting of a water-soluble polymer, a water swellable polymer and combinations thereof, a solvent and an active selected from the group consisting of bioactive actives, pharmaceutical actives, drugs, medicaments and combinations thereof, said matrix having a substantially uniform distribution of said active;	In Examples 5-8, *Chen* prepares hydroxypropyl methyl cellulose (HPMC) based, quick-dissolving films containing therapeutic agents. *See* p. 20, lines 17-20 and Tables 5 and 7. In particular, the films in Examples 5-8 contain a water soluble polymer (*i.e.*, HPMC), a solvent (*i.e.,* water), and an active (*i.e.*, nicotine, hydromorphone, oxybutynin, or estradiol). *See* Table 5. In Example 13, sildenafil citrate is the active ingredient. *See* Table 7. In the method of preparation of the films, the HPMC (*i.e.*, hydrocolloid) is dissolved in water under agitated mixing until they are uniformly dispersed or dissolved in the hydrocolloid to form a uniform and viscous solution and additional ingredients are added under agitation until they are uniformly dispersed or dissolved in the hydrocolloid. *See* p. 17, lines 6-29. Notably, even the specific polymers, solvent and actives exemplified in *Chen*, are identical to those exemplified and claimed in the '080 Patent. HPMC is employed in almost every example of the '080 Patent, and claimed in claims 84 and 166. The same solvent, *i.e.,* water, is employed in almost every example and claimed in claims 89 and 171. And, the active, *e.g.*, sildenafil is exemplified in Examples CI and FB and claimed in claims 99 and 181. The polymer matrix is flowable as it is a uniform

Table 1	
Claims of '080 Patent	*Chen*
	and viscous solution. *See* page 17, line 8.
(b) casting said flowable polymer matrix;	The resulting mixture of *Chen*, *i.e.*, the instant matrix, is "coated on the non-siliconized side of a polyester film at a wet thickness of 10 mil." *See e.g.,* page 17, lines 13-15, Examples 4-8, and Fig. 2.
(c) evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film within about 10 minutes or fewer to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film; and	*Chen* discloses evaporating the polar solvent from the cast matrix in 9 minutes. *See* page 17, lines 14-15 and Examples 4-8. To the extent that reciting "visco-elastic" further limits this claim (since the '080 Patent repeatedly refers to its matrix and its wet film *prior to drying* as viscoelastic, as discussed in detail in Section III.C.2) *Chen*'s films are viscoelastic because they are flexible, stand alone, self-supporting films (page 17, lines 15-16) made using the HPMC which is disclosed and claimed in the '080 Patent as a suitable film forming polymer. The '080 Patent, col. 15, lines 44-51. The substantially uniform distribution of active is maintained by locking-in or substantially preventing migration of said active within said viscoelastic film. This is evident from the fact that *Chen* prepares its films from a coating solution with a homogeneous mixture of ingredients. *See* page 17, lines 6-11, and 26-28, Examples 5-8, and page 20, lines 17-20. And the substantially uniform distribution has been maintained as discussed in detail directly below for step (e). Moreover, (1) *Chen*'s films are made using the same solvent (*e.g.,* water) and the same polymer (*e.g.*, HPMC), which is disclosed and claimed in the '080 Patent as a suitable film forming polymer (*See* the '080 Patent, col. 15, lines 44-51) and used in the majority of the Examples (See Examples P-AA); (2) they are coated on the non-siliconized

Table 1	
Claims of '080 Patent	*Chen*
	side of a polyester film (*See e.g.,* page 17, lines 13-15, Examples 4-8, and Fig. 2); and (3) the resulting films of *Chen* have less than 10% water (*See e.g.*, Example 6, Table 6 wherein the resulting film has 2.42% water). Indeed, the film of *Chen* is viscoelastic and meets the other desired properties, as it is made using the same materials and dried according to the same method recited in this claim. *See* the '080 Patent, col. 15, lines 44-51. As set forth in MPEP 2112.01 (I): "[w]here the claimed and prior art products are identical or substantially identical in structure or composition, or **are produced by identical or substantially identical processes**, a prima facie case of either anticipation or obviousness has been established." (emphasis added) Thus, *Chen*'s films would be as viscoelastic within a 10 minute time period as the films of the '080 Patent, as they are **produced by identical or substantially identical processes** as the process calimed in the '080 Patent. As such, *Chen* anticipates this feature.
(d) forming a resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained.	*Chen* discloses that after the step of evaporating the water from the matrix, the matrix includes a water content of from 0.5-10% with a preferred range of 1-5%. *See* page 13, lines 27-28. Examples 1 and 4-8 reported films formed with a water content of less than 3%. *See* Tables 2 and 6 on pages 18 and 22, respectively. Examples 2-3 have a water content of less than 9%. *See* Table 2 on page 18. *Chen* also discloses and demonstrates that its resulting films are formed while maintaining the substantially uniform distribution of active. *Chen* demonstrates the uniformity of its films employing the same criteria set forth in the '080 Patent, and indeed appears to demonstrate a higher degree of

Table 1	
Claims of '080 Patent	*Chen*
	uniformity in some instances. The Examiner needs to look no further than Applicant's own specification to immediately understand that the films of *Chen* are as uniform as those of Applicant, if not more so. *First,* the '080 Patent employs the criteria of unit dosage weight to demonstrate the uniformity of its films in the opening Examples A-I: > Uniformity was also measured by first cutting the film into individual dosage forms. … Then eight of these dosage forms were randomly selected and additively weighed. … The individual dosages were consistently 0.04 gm, which shows that the distribution of the components within the film was consistent and uniform. This is based on the simple principal that each component has a unique density. Therefore, when the components of different densities are combined in a uniform manner in a film, as in the present invention, individual dosages forms from the same film of substantially equal dimensions, will contain the same mass. > The '080 Patent, col.31, line 46 through col. 32, line 34 (emphasis added). As shown in Table 2, all films of Examples A-I were reported to be consistently 0.04 g/unit dosage. The '080 Patent, col. 32, lines 26-28. *Chen* demonstrates the uniformity of its films to at least the same degree as the films of the '080

Table 1	
Claims of '080 Patent	*Chen*
	Patent by consistent unit dosage weight. For example, *Chen* demonstrates the uniformity of its films in Table 4 where the films of Example 1 are reported to have a consistent weight of 0.028 ± 0.001 grams per unit dosage. Any argument by Applicant that weight is unrelated to the content of the product let alone any uniformity of content of the product is contrary to the teachings of Applicant's own Specification. The '080 Patent employs this very measurement to demonstrate the uniformity of their films. Indeed, the film weights of *Chen* are consistent out to the second decimal place, whereas the films of the '080 Patent are rounded to the second decimal place and could vary as much as 25%. Accordingly, the films of *Chen* are as uniform as those disclosed and claimed in the '080 Patent. Any argument by the Applicant that the uniformity of the films of Example 1-3 would not be present in the films of Examples 5-8 because there is no disclosure of homogeneous mixing of the active must disregard *Chen*'s disclosure that the additional ingredients in Examples 1-8 were added "under agitated mixing until they were uniformly dispersed or dissolved in the hydrocolloid." *See* p. 17, lines 6-11. Even more importantly, any such argument must also disregard the data shown in *Chen*'s Figure 5. Figure 5 shows not only the release rates, but also the total amount of active released by each dosage unit in Examples 5-8. At the last time noted, 10 minutes, all measurements of active appear approximately within ± 10% of 100 percent. There are many factors involved in release rate, some of which may account for the modest variation in percentage release. Although not a direct measurement, Figure 5 evidences that the films of *Chen* have substantial uniformity of content per dosage unit.

Table 1	
Claims of '080 Patent	*Chen*
	Second, the '080 Patent specification identifies visual inspection as yet another alternative for demonstrating uniformity: The uniform distribution of the components within the film was apparent by examination by either the naked eye or under slight magnification. By viewing the films it was apparent that they were substantially free of aggregation, *i.e.* the carrier and the actives remained substantially in place and did not move substantially from one portion of the film to another. Therefore, there was substantially no disparity among the amount of active found in any portion of the film. The '080 Patent, col. 31, lines 37-45 (emphasis added). *Chen* explicitly describes its films as "glossy, substantially transparent", *i.e.*, visually free of aggregation. *See e.g., Chen*, p. 17, line 15. *Chen* applies the same standards to demonstrate uniformity of its films as Applicant did in the '080 Patent specification. Both the '080 Patent and *Chen* employ and meet identical standards. Third, the '080 Patent specification states that uniformity is maintained during drying by avoiding drying conditions that cause surface disruption or mottle: When a controlled or rapid drying process is desired, this may be through a variety of methods. A variety of methods may be used

Table 1	
Claims of '080 Patent	*Chen*
	including those that require the application of heat. The liquid carriers are removed from the film in a manner such that the uniformity, or more specifically, the non-self-aggregating uniform heterogeneity, that is obtained in the wet film is maintained. Desirably, the film is dried from the bottom of the film to the top of the film. Substantially no air flow is present across the top of the film during its initial setting period, during which a solid, visco-elastic structure is formed. This can take place within the first few minutes, *e.g.* about the first 0.5 to about 4.0 minutes of the drying process. Controlling the drying in this manner, prevents the destruction and reformation of the film's top surface, which results from conventional drying methods. This is accomplished by…. The '080 Patent, col. 27, lines 26-42 (emphasis added). *Chen* also maintains its uniformity during drying by avoiding drying conditions that cause surface disruption or mottle. *Chen* discloses films that are glossy and substantially transparent and the drying parameters for doing so. *See e.g.*, *Chen*, p. 17, lines 13-16, Figure 2 (showing controlled drying). Finally, Applicant submits the Declaration of Dr. Edward Cohen ("Cohen Declaration" Exhibit L). Dr. Cohen, an independent expert in the coating and drying field, confirms that a homogeneous

Table 1	
Claims of '080 Patent	*Chen*
	coating mixture, such as those in *Chen*, would be expected to yield a film having uniform content of active per dosage unit. More specifically, as stated in the Cohen Declaration: *Chen* provides coating mixtures containing active that are described as "homogeneous", "completely dissolved", or "completely dispersed". Drying such hydrocolloid coating mixtures would be expected to yield films with substantially uniform content of active per unit of film, where the unit of film is a typical dosage unit or per sheet of uncut film. It is my opinion that *Chen* teaches films with substantially uniform content of active per unit of film, where the unit of film is, for example, a dosage unit or an uncut sheet of film. In general, as a homogeneous or completely dispersed coating mixture is dried, the solvent is removed, the viscosity increases and the active would be more firmly fixed in place. *When working with a homogeneous or completely dissolved coating mixture, for example, it would be difficult for a person of ordinary skill in the thin film art not to obtain a film that has uniform content of active*. Cohen Declaration, p. 2-3, ¶¶ 8-9 (emphasis added).

Table 1	
Claims of '080 Patent	*Chen*
83. The process of claim 82, wherein said water-soluble polymer comprises polyethylene oxide.	*See* the detailed explanation above for claim 4.
84. The process of claim 82, wherein said polymer comprises a polymer selected from the group consisting of cellulose, a cellulose derivative, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyvinyl copolymers, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof, alone or in combination with polyethylene oxide.	*See* the detailed explanation above for claim 5.
87. The process of claim 84, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.	*See* the detailed explanation above for claim 8.
88. The process of claim 84, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone, methylmethacrylate	*See* the detailed explanation above for claim 9.

Table 1	
Claims of '080 Patent	*Chen*
copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(α-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.	
89. The process of claim 82, wherein said solvent is selected from the group consisting of water, polar organic solvent, and combinations thereof.	*See* the detailed explanation above for claim 10.
90. The process of claim 89, wherein said solvent is selected from the group consisting of ethanol, isopropanol, acetone, and combinations thereof.	*See* the detailed explanation above for claim 10.
91. The process of claim 82, wherein said active is selected from the group consisting of bioactive active, pharmaceutical actives, drugs, medicaments and combinations thereof.	*See* the detailed explanation above for claim 12.
92. The process of claim 82, wherein the active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents,	*See* the detailed explanation above for claim 13.

Table 1	
Claims of '080 Patent	*Chen*
anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, anti-tumor	

Table 1	
Claims of '080 Patent	*Chen*
drugs, anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, anti-convulsants, neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, anti-asthmatics, cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.	
93. The process of claim 82, wherein said active is selected from the group consisting of cosmetic actives, antigens, allergens, spores, microorganisms, *See*ds, mouthwash components, flavors, fragrances, enzymes, preservatives, sweetening agents, colorants, spices, vitamins and combinations thereof.	*See* the detailed explanation above for claim 14.
94. The process of claim 82, wherein said active is a bioactive active.	*See* the detailed explanation above for claim 15.
95. The process of claim 82, wherein said active is a biological response modifier.	*See* the detailed explanation above for claim 16.
96. The process of claim 82, wherein said active is an opiate or opiate-derivative.	*See* the detailed explanation above for claim 17.
97. The process of claim 82, wherein said active is an anti-emetic.	*See* the detailed explanation above for claim 18.
99. The process of claim 82, wherein said active is selected from the group consisting of sildenafils, tadalafils, vardenafils, apomorphines, yohimbine hydrochlorides, alprostadils and combinations thereof.	*See* the detailed explanation above for claim 20.
100. The process of claim 82, wherein said active is a protein.	*See* the detailed explanation above for claim 21.
101. The process of claim 82, wherein said active is insulin.	*See* the detailed explanation above for claim 22.
102. The process of claim 82, wherein said active is an anti-diabetic.	*See* the detailed explanation above for claim 23.
103. The process of claim 82, wherein said	*See* the detailed explanation above for claim 24.

Table 1	
Claims of '080 Patent	*Chen*
active is an antihistamine.	
104. The process of claim 82, wherein said active is an anti-tussive.	*See* the detailed explanation above for claim 25.
105. The process of claim 82, wherein said active is a non-steroidal anti-inflammatory.	*See* the detailed explanation above for claim 26.
106. The process of claim 82, wherein said active is an anti-asthmatics.	*See* the detailed explanation above for claim 27.
107. The process of claim 82, wherein said active is an anti-diarrhea.	*See* the detailed explanation above for claim 28.
108. The process of claim 82, wherein said active is an alkaloid.	*See* the detailed explanation above for claim 29.
109. The process of claim 82, wherein said active is an anti-psychotic.	*See* the detailed explanation above for claim 30.
110. The process of claim 82, wherein said active is an anti-spasmodic.	*See* the detailed explanation above for claim 31.
111. The process of claim 82, wherein said active is a biological response modifier.	*See* the detailed explanation above for claim 32.
113. The process of claim 82, wherein said active is an H_2-antagonist.	*See* the detailed explanation above for claim 34.
115. The process of claim 82, wherein said active is a smoking cessation aid.	*See* the detailed explanation above for claim 36.
116. The process of claim 82, wherein said active is an anti-parkinsonian agent.	*See* the detailed explanation above for claim 37.
117. The process of claim 82, wherein said active is an anti-depressant.	*See* the detailed explanation above for claim 38.
118. The process of claim 82, wherein said active is an anti-migraine.	*See* the detailed explanation above for claim 39.
119. The process of claim 82, wherein said active is an anti-Alzheimer's agents.	*See* the detailed explanation above for claim 40.
123. The process of claim 82, wherein said active is an antibiotic.	*See* the detailed explanation above for claim 44.
124. The process of claim 82, wherein said active is an anesthetic.	*See* the detailed explanation above for claim 45.
125. The process of claim 82, wherein said active is a contraceptive.	*See* the detailed explanation above for claim 46.
126. The process of claim, 82, wherein said active is an anti-thrombotic drug.	*See* the detailed explanation above for claim 47.
130. The process of claim 82, wherein said	*See* the detailed explanation above for claim 51.

Table 1	
Claims of '080 Patent	*Chen*
active is an anti-tumor drug.	
132. The process of claim 82, wherein said active is an analgesic.	*See* the detailed explanation above for claim 53.
133. The process of claim 82, wherein said active is a hormone.	*See* the detailed explanation above for claim 54.
138. The process of claim 82, wherein said active is selected from the group consisting of an analgesic, an anti-inflammatory, an antihistamine, a decongestant, a cough suppressant and combinations thereof.	*See* the detailed explanation above for claim 59.
141. The process of claim 82, wherein said active is a hypnotic.	*See* the detailed explanation above for claim 62.
142. The process of claim 82, wherein said active is taste-masked.	*See* the detailed explanation above for claim 63.
143. The process of claim 82, wherein said active is taste-masked using a flavor.	*See* the detailed explanation above for claim 64.
144. The process of claim 82, wherein said active is coated with a controlled release composition.	*See* the detailed explanation above for claim 65.
145. The process of claim 144, wherein said controlled release composition provides an immediate release.	*See* the detailed explanation for claim 65.
146. The process of claim 144, wherein said controlled release composition provides a delayed release.	*See* the detailed explanation for claim 65.
147. The process of claim 144, wherein said controlled release composition provides a sustained release.	*See* the detailed explanation for claim 65.
148. The process of claim 144, wherein said controlled release composition provides a sequential release.	*See* the detailed explanation for claim 65.
149. The process of claim 82, wherein said active is a particulate.	*See* the detailed explanation above for claim 70.
150. The process of claim 82, further comprising adding a degassing agent to said flowable polymer matrix.	*See* the detailed explanation above for claim 71.
161. A process for making a film capable of being administered to a body surface	Claim 161 is substantially similar to claim 82, but additionally recites that the film is "capable of

Table 1	
Claims of '080 Patent	*Chen*
having a substantially uniform distribution of components, comprising the steps of: (a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and an active, said matrix having a substantially uniform distribution of said active; (b) casting said flowable polymer matrix; (c) evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film within about 10 minutes or fewer to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film; (d) forming a resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained; and (e) administering said resulting film to a body surface.	being administered to a body surface" (preamble) and the last step "(e) administering said resulting film to a body surface." *See* claim 82 in this Table for the detailed discussion of *Chen*'s disclosure of the recited process. *Chen* teaches that the films are suitable for administration to any mucosal surface, *e.g.*, the buccal cavity. *See* page 8, lines 9-10 and Figure 1. Thus the films are clearly "capable" to being administered to a body surface. With respect to step (e), *Chen* discloses administering the films to a body surface, *i.e.*, the oral mucosa in Examples 12 and 13.
162. The process of claim 161, wherein said body surface is a mucous membrane.	*Chen* discloses that its dosage form may be administered to the subject by placing the film on a mucous surface. *See* page 8, lines 24-26.
163. The process of claim 162, wherein said mucous membrane is oral, anal, vaginal or ophthalmological.	*Chen* discloses that its dosage form may be applied to mucosal surface via oral, rectal, vaginal delivery.
164. The process of claim 161, wherein said body surface is the surface of a wound.	*Chen* discloses that its dosage form may be administered to the subject by placing the film on a mucous surface. *See* page 8, lines 24-26. *Chen* further discloses that mucosal surface includes a wound surface. *See* page 7, lines 31 and 32.

Table 1	
Claims of '080 Patent	*Chen*
165. The process of claim 161, wherein said water-soluble polymer comprises polyethylene oxide.	*See* the detailed explanation above for claim 4.
166. The process of claim 161, wherein said polymer comprises a polymer selected from the group consisting of cellulose, a cellulose derivative, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyvinyl copolymers, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof, alone or in combination with polyethylene oxide.	*See* the detailed explanation above for claim 5.
169. The process of claim 166, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.	*See* the detailed explanation above for claim 8.
170. The process of claim 166, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone, methylmethacrylate	*See* the detailed explanation above for claim 9.

Table 1	
Claims of '080 Patent	*Chen*
copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(α-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.	
171. The process of claim 161, wherein said solvent is selected from the group consisting of water, polar organic solvent, and combinations thereof.	*See* the detailed explanation above for claim 10.
172. The process of claim 161, wherein said solvent is selected from the group consisting of ethanol, isopropanol, acetone, and combinations thereof.	*See* the detailed explanation above for claim 10.
173. The process of claim 161, wherein said active is selected from the group consisting of bioactive active, pharmaceutical actives, drugs, medicaments and combinations thereof.	*See* the detailed explanation above for claim 12.
174. The process of claim 161, wherein said active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents,	*See* the detailed explanation above for claim 13.

Table 1	
Claims of '080 Patent	*Chen*
anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, anti-tumor	

Table 1	
Claims of '080 Patent	*Chen*
drugs, anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, anti-convulsants, neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, anti-asthmatics, cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.	
175. The process of claim 161, wherein said active is selected from the group consisting of cosmetic actives, antigens, allergens, spores, microorganisms, *See*ds, mouthwash components, flavors, fragrances, enzymes, preservatives, sweetening agents, colorants, spices, vitamins and combinations thereof.	*See* the detailed explanation above for claim 14.
176. The process of claim 161, wherein said active is a bioactive active.	*See* the detailed explanation above for claim 15.
177. The process of claim 161, wherein said active is a biological response modifier.	*See* the detailed explanation above for claim 16.
178. The process of claim 161, wherein said active is an opiate or opiate-derivative.	*See* the detailed explanation above for claim 17.
179. The process of claim 161, wherein said active is an anti-emetic.	*See* the detailed explanation above for claim 18.
181. The process of claim 161, wherein said active is selected from the group consisting of sildenafils, tadalafils, vardenafils, apomorphines, yohimbine hydrochlorides, alprostadils and combinations thereof.	*See* the detailed explanation above for claim 20.
182. The process of claim 161, wherein said active is a protein.	*See* the detailed explanation above for claim 21.
183. The process of claim 161, wherein said active is insulin.	*See* the detailed explanation above for claim 22.

Table 1	
Claims of '080 Patent	*Chen*
184. The process of claim 161, wherein said active is an anti-diabetic.	*See* the detailed explanation above for claim 23.
185. The process of claim 161, wherein said active is an antihistamine.	*See* the detailed explanation above for claim 24.
186. The process of claim 161, wherein said active is an anti-tussive.	*See* the detailed explanation above for claim 25.
187. The process of claim 161, wherein said active is a non-steroidal anti-inflammatory.	*See* the detailed explanation above for claim 26.
188. The process of claim 161, wherein said active is an anti-asthmatics.	*See* the detailed explanation above for claim 27.
189. The process of claim 161, wherein said active is an anti-diarrhea.	*See* the detailed explanation above for claim 28.
190. The process of claim 161, wherein said active is an alkaloid.	*See* the detailed explanation above for claim 29.
191. The process of claim 161, wherein said active is an anti-psychotic.	*See* the detailed explanation above for claim 30.
192. The process of claim 161, wherein said active is an anti-spasmodic.	*See* the detailed explanation above for claim 31.
193. The process of claim 161, wherein said active is a biological response modifier.	*See* the detailed explanation above for claim 16.
195. The process of claim 161, wherein said active is an H_2-antagonist.	*See* the detailed explanation above for claim 34.
197. The process of claim 161, wherein said active is a smoking cessation aid.	*See* the detailed explanation above for claim 36.
198. The process of claim 161, wherein said active is an anti-parkinsonian agent.	*See* the detailed explanation above for claim 37.
199. The process of claim 161, wherein said active is an anti-depressant.	*See* the detailed explanation above for claim 38.
200. The process of claim 161, wherein said active is an anti-migraine.	*See* the detailed explanation above for claim 39.
201. The process of claim 161, wherein said active is an anti-Alzheimer's agents.	*See* the detailed explanation above for claim 40.
205. The process of claim 161, wherein said active is an antibiotic.	*See* the detailed explanation above for claim 44.
206. The process of claim 161, wherein said active is an anesthetic.	*See* the detailed explanation above for claim 45.

Table 1	
Claims of '080 Patent	*Chen*
207. The process of claim 161, wherein said active is a contraceptive.	*See* the detailed explanation above for claim 46.
208. The process of claim 161, wherein said active is an anti-thrombotic drug.	*See* the detailed explanation above for claim 47.
212. The process of claim 161, wherein said active is an anti-tumor drug.	*See* the detailed explanation above for claim 51.
214. The process of claim 161, wherein said active is an analgesic.	*See* the detailed explanation above for claim 53.
215. The process of claim 161, wherein said active is a hormone.	*See* the detailed explanation above for claim 54.
220. The process of claim 161, wherein said active is selected from the group consisting of an analgesic, an anti-inflammatory, an antihistamine, a decongestant, a cough suppressant and combinations thereof.	*See* the detailed explanation above for claim 59.
223. The process of claim 161, wherein said active is a hypnotic.	*See* the detailed explanation above for claim 62.
224. The process of claim 161, wherein said active is taste-masked.	*See* the detailed explanation above for claim 63.
225. The process of claim 161, wherein said active is taste-masked using a flavor.	*See* the detailed explanation above for claim 64.
226. The process of claim 161, wherein said active is coated with a controlled release composition.	*See* the detailed explanation above for claim 65.
227. The process of claim 226, wherein said controlled release composition provides an immediate release.	*See* the detailed explanation above for claim 65.
228. The process of 226, wherein said controlled release composition provides a delayed release.	*See* the detailed explanation above for claim 65.
229. The process of claim 226, wherein said controlled release composition provides a sustained release.	*See* the detailed explanation above for claim 65.
230. The process of claim 226, wherein said controlled release composition provides a sequential release.	*See* the detailed explanation above for claim 65.

Table 1	
Claims of '080 Patent	*Chen*
231. The process of claim 161, wherein said active is a particulate.	*See* the detailed explanation above for claim 70.
232. The process of claim 161, further comprising adding a degassing agent to said flowable polymer matrix.	*See* the detailed explanation above for claim 71.
243. The process of claim 1, said active is an anti-nauseant.	*Chen* discloses that the active agent can be anti-nauseant at page 10, line 29.
244. The process of claim 1, said active is an erectile dysfunction.	*Chen* discloses that the active agent can be sildenafil citrate for treating erectile dysfunction at page 5, lines 15-16, and Example 13 at page 28.
246. The process of claim 1, said active is a stimulant.	*Chen* discloses that the active agent can be nicotine in Table 5 at page 21. It is well known that nicotine is a stimulant.
247. The process of claim 1, said active is a migraine treatment.	*Chen* discloses that the active agent can be an anti-migraine at page 10, line 29.
249. The process of claim 1, wherein said resulting film provides administration of said active to an individual through the buccal cavity of said individual.	*Chen* discloses that its films can be applied to buccal surfaces. *See* page 8, line 9.
250. The process of claim 1, wherein said resulting film provides administration of said active through gingival application of said individual.	*Chen* discloses that its films can be applied to gingival surfaces. *See* page 8, line 9.
251. The process of claim 1, wherein said resulting film provides administration of said active through sublingual application of said individual.	*Chen* discloses that its films may be applied on sublingual surfaces. *See* page 8, line 9.
252. The process of claim 1, wherein said resulting film provides administration of said active to an individual through a mucosal membrane of said individual.	*Chen* discloses that its films may be applied on a mucosal surface. *See* page 8, line 4.
253. The process of claim 1, wherein said resulting film provides administration of said active to an individual by administration within the body of the individual during surgery.	*Chen* discloses that its films can be applied to mucosal surface, which refers to any moist surface in the body. As such, *Chen* anticipates that its films can be administered within the body of the

Table 1	
Claims of '080 Patent	*Chen*
	individual during surgery.
254. The process of claim 1, wherein said resulting film has a variation of active content of less than 10% per film unit.	*See* the detailed explanation above for claim 1, steps (d) and (e) regarding the uniformity of *Chen*'s films. For example, Figure 5 indicates that the active content has a variation of less than 10% per unit film. Moreover, as acknowledged by the Examiners in the '588 Patent reexamination, "the films in Examples 5-8 inherently have a variation of active content of less than 10% per film unit, as here claimed." *See* the '588 Reexamination, Action Closing Prosecution, mailed July 20, 2012, page 13, lines 18-19. (Exhibit N). Finally, the recited desired result is a mere obvious matter of choice dependent on the desired final product *and of little patentable consequence to the claimed process since it is not a manipulative feature or step of the claimed process*. The claimed product limitations are well-known in the ingestible or insertable film art as admitted by Applicant in its own Background at col. 2, lines 40-47 of the '080 Patent. ("Currently, as required by various world regulatory authorities, dosage forms may not vary more than 10% in the amount of active present").
255. The process of claim 1, further comprising the step of forming a plurality of individual dosage units of substantially the same size, wherein the active content of individual dosage units has a variance of no more than 10%.	*See* the detailed explanation above for claim 254. Forming a plurality of individual dosage units of substantially the same size is depicted in Figure 3 and described, *e.g.*, at p. 16, lines 2-8.
256. The method of claim 1, wherein said resulting film contains less than about 6% by weight solvent.	*Chen* discloses that after the step of removing the water from the matrix, the matrix includes a water content of from 0.5-10% with a preferred range of 1-5%. *See* page 13, lines 27-28. Examples 1 and 4-8 reported films formed with a water content of

Table 1	
Claims of '080 Patent	*Chen*
	less than 3%. *See* Tables 2 and 6 on page 18 and 22, respectively.
257. The method of claim 1, wherein said at least one edible polymer, said active, and said at least one polar solvent are each ingestible materials.	*Chen* teaches using water as a polar solvent in the preparation of its films. *See* page 23, Table 7. Water is ingestible. *Chen* also teaches using HPMC as a water soluble polymer. *See* page 14, line 27. It is well known that HPMC can be food grade. In other words, it is an ingestible material.
258. The method of claim 1, wherein said resulting film is orally administrable.	*Chen* discloses that its films can be administered orally. *See* page 8, line 9.
259. The method of claim 1, wherein said active is in the form of a particle.	To the extent that the term "particle" further limits this claim, particularly since it doesn't specify, *e.g.*, when the active is a particle, *Chen* teaches actives in the form of particles. *See* page 10 line 22 through page 11, line 1.
260. The method of claim 1, wherein said matrix comprises a dispersion.	*Chen* teaches that "additional ingredients were then added sequentially to the viscous solution . . . under agitated mixing until they were uniformly dispersed or dissolved in the hydrocolloid." *See* page 17, lines 7-11.
261. The process of claim 82, said active is an anti-nauseant.	*See* the detailed explanation above for claim 243.
262. The process of claim 82, said active is an erectile dysfunction.	*See* the detailed explanation above for claim 244.
264. The process of claim 82, said active is a stimulant.	*See* the detailed explanation above for claim 246.
265. The process of claim 82, said active is a migraine treatment.	*See* the detailed explanation above for claim 247.
267. The process of claim 82, wherein said resulting film provides administration of said active to an individual through the buccal cavity of said individual.	*See* the detailed explanation above for claim 249.
268. The process of claim 82, wherein said resulting film provides administration of said active through gingival application of	*See* the detailed explanation above for claim 250.

Table 1	
Claims of '080 Patent	*Chen*
said individual.	
269. The process of claim 82, wherein said resulting film provides administration of said active through sublingual application of said individual.	*See* the detailed explanation above for claim 251.
270. The process of claim 82, wherein said resulting film provides administration of said active to an individual through a mucosal membrane of said individual.	*See* the detailed explanation above for claim 252.
271. The process of claim 82, wherein said resulting film provides administration of said active to an individual by administration within the body of the individual during surgery.	*See* the detailed explanation above for claim 253.
272. The process of claim 82, wherein said resulting film has a variation of active content of less than 10% per film unit.	*See* the detailed explanation above for claim 254.
273. The process of claim 82, further comprising the step of forming a plurality of individual dosage units of substantially the same size, wherein the active content of individual dosage units has a variance of no more than 10%.	*See* the detailed explanation above for claim 255.
274. The method of claim 82, wherein said resulting film contains less than about 6% by weight solvent.	*See* the detailed explanation above for claim 256.
275. The method of claim 82, wherein said at least one edible polymer, said active, and said at least one polar solvent are each ingestible materials.	*See* the detailed explanation above for claim 257.
276. The method of claim 82, wherein said resulting film is orally administrable.	*See* the detailed explanation above for claim 258.
277. The method of claim 82, wherein said active is in the form of a particle.	*See* the detailed explanation above for claim 259.
278. The method of claim 82, wherein said matrix comprises a dispersion.	*See* the detailed explanation above for claim 260.
279. The process of claim 161, said active is an anti-nauseant.	*See* the detailed explanation above for claim 243.

Table 1	
Claims of '080 Patent	*Chen*
280. The process of claim 161, said active is an erectile dysfunction.	*See* the detailed explanation above for claim 244.
282. The process of claim 161, said active is a stimulant.	*See* the detailed explanation above for claim 246.
283. The process of claim 161, said active is a migraine treatment.	*See* the detailed explanation above for claim 247.
285. The process of claim 161, wherein said resulting film provides administration of said active to an individual through the buccal cavity of said individual.	*See* the detailed explanation above for claim 249.
286. The process of claim 161, wherein said resulting film provides administration of said active through gingival application of said individual.	*See* the detailed explanation above for claim 250.
287. The process of claim 161, wherein said resulting film provides administration of said active through sublingual application of said individual.	*See* the detailed explanation above for claim 251.
288. The process of claim 161, wherein said resulting film provides administration of said active to an individual through a mucosal membrane of said individual.	*See* the detailed explanation above for claim 252.
289. The process of claim 161, wherein said resulting film provides administration of said active to an individual by administration within the body of the individual during surgery.	*See* the detailed explanation above for claim 253.
290. The process of claim 161, wherein said resulting film has a variation of active content of less than 10% per film unit.	*See* the detailed explanation above for claim 254.
291. The process of claim 161, further comprising the step of forming a plurality of individual dosage units of substantially the same size, wherein the active content of individual dosage units has a variance of no more than 10%.	*See* the detailed explanation above for claim 255.
292. The method of claim 161, wherein said resulting film contains less than about	*See* the detailed explanation above for claim 256.

Table 1	
Claims of '080 Patent	*Chen*
6% by weight solvent.	
293. The method of claim 161, wherein said at least one edible polymer, said active, and said at least one polar solvent are each ingestible materials.	*See* the detailed explanation above for claim 257.
294. The method of claim 161, wherein said resulting film is orally administrable.	*See* the detailed explanation above for claim 258.
295. The method of claim 161, wherein said active is in the form of a particle.	*See* the detailed explanation above for claim 259.
296. The method of claim 161, wherein said matrix comprises a dispersion.	*See* the detailed explanation above for claim 260.
297. The method of claim 1, wherein said matrix comprises an emulsion, a colloid or a suspension.	*Chen* discloses use of a hydrocolloid in the premix. *See* page 15, lines 19-21. *Chen* also teaches that "additional ingredients were then added sequentially to the viscous solution . . . under agitated mixing until they were uniformly dispersed or dissolved in the hydrocolloid." *See* page 17, lines 7-11.
298. The method of claim 82, wherein said matrix comprises an emulsion, a colloid or a suspension.	*See* the detailed explanation above for claim 297.
299. The method of claim 161, wherein said matrix comprises an emulsion, a colloid or a suspension.	*See* the detailed explanation above for claim 297.

Table 2. Proposed rejection of claims 2, 3, 6, 7, 19, 33, 35, 41-43, 48-50, 52, 55-58, 60, 61, 65-69, 71, 85, 86, 98, 112, 114, 120-122, 127-129, 131, 134-137, 139, 140, 144-148, 150, 167, 168, 180, 194, 196, 202-204, 209-211, 213, 216-219, 221, 222, 226-230, 232, 245, 248, 253, 263, 266, 271, 281, 284, and 289 under 35 U.S.C. § 103 as obvious over *Chen*

Table 2	
Claims of '080 Patent	*Chen*
2. The process of claim 1, wherein said pre-determined amount of master batch pre-	*Chen* does not explicitly describe the use of a

Table 2	
Claims of '080 Patent	*Chen*
mix is controllably fed via a first metering pump and a control valve to a first mixer and a second mixer.	premix, together with its attendant metering pumps, multiple mixing vessels, and control valves. However, merely reciting routine methods of commercial manufacture does not render this claim patentable. As noted by the Examiner during reexamination of related US Patent No. 7,824,588, the use of a premix is a well-known and effective method of mixing components. *See* the Action Closing Prosecution in Reexamination of US Patent 7,824,588 mailed July 20, 2012 at page 82, last two paragraphs (Exhibit N). Metering pumps, multiple mixing vessels, and control valves are standard equipment. Reciting them in a claim does not make the claim patentable. As set for the in MPEP § 2143 D., if a particular known technique was recognized as part of the ordinary capabilities of one skilled in the art, one of ordinary skill in the art would have been capable of applying this known technique to a known device (method, or product) that was ready for improvement and the results would have been predictable to one of ordinary skill in the art. As such, it would have been obvious for one of ordinary skill in the art, at the time of the invention was made, to employ those standard equipments (*e.g.*, metering pumps, multiple mixing vessels, and control valves) in the claimed method.
3. The process of claim 2, wherein said first mixer and said second mixer are arranged in parallel, series or a combination thereof.	*Chen* does not explicitly describe the use of two mixers. However, merely reciting routine methods of commercial manufacture does not render this claim patentable. As noted by the Examiner during reexamination of related US Patent No. 7,824,588, the use of a premix is a well-known and effective method of mixing components. *See* the Action Closing

Table 2	
Claims of '080 Patent	*Chen*
	Prosecution in Reexamination of US Patent 7,824,588 mailed July 20, 2012 at page 82, last two paragraphs (Exhibit N). Of course, multiple mixers are standard equipments and are inherently part of the process of *Chen*. Reciting them in a claim does not make the claim patentable. As set for the in MPEP § 2143 (D), if a particular known technique was recognized as part of the ordinary capabilities of one skilled in the art, one of ordinary skill in the art would have been capable of applying this known technique to a known device (method, or product) that was ready for improvement and the results would have been predictable to one of ordinary skill in the art. As such, it would have been obvious for one of ordinary skill in the art, at the time of the invention, to employ standard equipment (*e.g.*, multiple mixing vessels) in different ways (parallel or series) in the claimed method.
6. The process of claim 5, wherein said polymer further comprises a water insoluble polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone and combinations thereof.	*Chen* does not explicitly describe the recited water insoluble polymers. However, merely reciting commonly used polymers does not render this claim patentable. As set forth in MPEP § 2143(B), a claim would have been obvious in that the substitution of one known element for another yields predictable results to one of ordinary skill in the art. In this case, these polymers can readily be employed to speed up or slow down the dissolution of the films without undue experimentation. It would have been obvious for one skilled in the art to use different polymers to change the disintegration or dissolution time of controlled release as described in *Chen* on page 9, lines 9-14.

Table 2	
Claims of '080 Patent	*Chen*
7. The process of claim 5, wherein said polymer further comprises a polymer selected from the group consisting of methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(α-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof.	*See* the detailed explanation above for claim 6.
19. The process of claim 1, wherein said active is an amino acid preparation.	*Chen* does not explicitly describe the active can be an amino acid preparation. However, merely reciting an active does not render this claim patentable. Indeed, *Chen* already discloses a long list of therapeutic agents that can be used in its films including proteins. *See* page 10, line 23; through page 11, line 12. As set forth in MPEP § 2143(B), a claim would have been obvious in that the substitution of one known element for another yields predictable results to one of ordinary skill in the art. In this case, it would have been obvious for one skilled in the art to try to use different actives in the films.
33. The process of claim 1, wherein said active is an anti-obesity drug.	*See* the detailed explanation above for claim 16.
35. The process of claim 34, wherein said H_2-antagonist is selected from the group consisting of cimetidine, ranitidine hydrochloride, famotidine, nizatidine, ebrotidine, mifentidine, roxatidine,	*Chen* discloses that the active agent can be an H_2 receptor antagonist at page 11, line 2. As set forth in MPEP § 2143(B), a claim would have been obvious in that the substitution of one

Table 2	
Claims of '080 Patent	*Chen*
pisatidine, aceroxatidine and combinations thereof.	known element for another yields predictable results to one of ordinary skill in the art. Accordingly, it would have been obvious for one skilled in the art to try to use different H_2-antagonists recited in claim 35.
41. The process of claim 1, wherein said active is a dopamine receptor agonist.	*Chen* discloses that the active agent can be anti-Parkinson medication at page 10, line 26. It is well known that a dopamine receptor agonist can be used to treat Parkinson's disease. As set forth in MPEP § 2143(B), a claim would have been obvious in that the substitution of one known element for another yields predictable results to one of ordinary skill in the art. Accordingly, it would have been obvious for one skilled in the art to try to use different dopamine receptor agonist as an active.
42. The process of claim 1, wherein said active is a cerebral dilator.	*Chen* does not explicitly describe the active can be a cerebral dilator. However, merely reciting an active does not render this claim patentable. Indeed, *Chen* already discloses a long list of therapeutic agents that can be used in its films. *See* page 10 line 23, through page 11, line 12. As set forth in MPEP § 2143(B), a claim would have been obvious in that the substitution of one known element for another yields predictable results to one of ordinary skill in the art. It would have been obvious for one skilled in the art to try to use different actives in the films.
43. The process of claim 1, wherein said active is a psychotherapeutic agent.	*Chen* does not explicitly describe the active can be a psychotherapeutic agent. However, merely reciting an active does not render this claim patentable. Indeed, *Chen* already discloses a long list of therapeutic agents that can be used in its films.

Table 2	
Claims of '080 Patent	*Chen*
	See page 10 line 23, through page 11, line 12. As set forth in MPEP § 2143(B), a claim would have been obvious in that the substitution of one known element for another yields predictable results to one of ordinary skill in the art. It would have been obvious for one skilled in the art to try to use different actives in the films.
48. The process of claim 1, wherein said active is diphenhydramine.	*Chen* discloses that the active agent can be an anti-histamine at page 10, line 28. It is well known that diphenhydramine is an anti-histamine. As set forth in MPEP § 2143(B), a claim would have been obvious in that the substitution of one known element for another yields predictable results to one of ordinary skill in the art. Accordingly, it would have been obvious for one skilled in the art to try to use diphenhydramine recited in claim 48.
49. The process of claim 1, wherein said active is nabilone.	*Chen* discloses that the active agent can be an anti-nasuants/anti-emetic at page 10, line 29. It is well known that nabilone is being used to treat nausea and vomiting caused by cancer chemotherapy. As set forth in MPEP § 2143(B), a claim would have been obvious in that the substitution of one known element for another yields predictable results to one of ordinary skill in the art. Accordingly, it would have been obvious for one skilled in the art to try to use nabilone as an active.
50. The process of claim 1, wherein said active is albuterol sulfate.	*Chen* discloses that the active agent can be a bronchial dilator at page 10, line 31. It is well known that albuterol sulfate is a bronchial dilator. As set forth in MPEP § 2143(B), a claim would have been obvious in that the substitution of one known element for another yields predictable results to one of ordinary skill in the art.

Table 2	
Claims of '080 Patent	*Chen*
	Accordingly, it would have been obvious for one skilled in the art to try to use albuterol sulfate as an active.
52. The process of claim 1, wherein said active is a glycoprotein.	*Chen* discloses that the active agent can be proteins such as insulin, calcitonin, LHRH and the like at page 11, lines 4 and 5. It is well known that glycoprotein is a protein. As set forth in MPEP § 2143(B), a claim would have been obvious in that the substitution of one known element for another yields predictable results to one of ordinary skill in the art. Accordingly, it would have been obvious for one skilled in the art to try to use different glycoprotein as an active.
55. The process of claim 1, wherein said active is a decongestant.	*Chen* does not explicitly describe the active can be a decongestant. However, merely reciting an active does not render this claim patentable. Indeed, *Chen* already discloses a long list of therapeutic agents that can be used in its films. *See* page 10 line 23, through page 11, line 12. As set forth in MPEP § 2143(B), a claim would have been obvious in that the substitution of one known element for another yields predictable results to one of ordinary skill in the art. Accordingly, it would have been obvious for one skilled in the art to try to use different actives in the films.
56. The process of claim 1, wherein said active is a loratadine.	*Chen* discloses that the active agent can be an anti-histamine at page 10, line 28. It is well known that loratadine is an anti-histamine. As set forth in MPEP § 2143(B), a claim would have been obvious in that the substitution of one known element for another yields predictable results to one of ordinary skill in the art.

Table 2	
Claims of '080 Patent	*Chen*
	Accordingly, it would have been obvious for one skilled in the art to try to use loratadine as an active.
57. The process of claim 1, wherein said active is dextromethorphan.	*Chen* discloses that the active agent can be cough/cold remedies at page 10, line 32 through page 11, line 1. It is well known that dextromethorphan is a common anti-tussive. As set forth in MPEP § 2143(B), a claim would have been obvious in that the substitution of one known element for another yields predictable results to one of ordinary skill in the art. Accordingly, it would have been obvious for one skilled in the art to try to use dextromethorphan as an active.
58. The process of claim 1, wherein said active is chlorpheniramine maleate.	*Chen* discloses that the active agent can be an anti-histamine at page 10, line 28. It is well known that chlorpheniramine maleate is an anti-histamine. As set forth in MPEP § 2143(B), a claim would have been obvious in that the substitution of one known element for another yields predictable results to one of ordinary skill in the art. Accordingly, it would have been obvious for one skilled in the art to try to use chlorpheniramine maleate as an active.
60. The process of claim 1, wherein said active is an appetite stimulant.	*Chen* discloses that the active agent can be a nutritional supplement at page 10, line 23. It is well known that an appetite stimulant is a nutritional supplement. As set forth in MPEP § 2143(B), a claim would have been obvious in that the substitution of one known element for another yields predictable results to one of ordinary skill in the art. Accordingly, it would have been obvious for one skilled in the art to try to use an appetite stimulant

Table 2	
Claims of '080 Patent	*Chen*
	as an active.
61. The process of claim 1, wherein said active is a gastrointstinal agent.	*Chen* does not explicitly describe the active can be a gastrointestinal agent. However, merely reciting an active does not render this claim patentable. Indeed, *Chen* already discloses a long list of therapeutic agents that can be used in its films. *See* page 10 line 23, through page 11, line 12. As set forth in MPEP § 2143(B), a claim would have been obvious in that the substitution of one known element for another yields predictable results to one of ordinary skill in the art. Accordingly, it would have been obvious for one skilled in the art to try to use a gastrointstinal agent as an active.
65. The process of claim 1, wherein said active is coated with a controlled release composition.	*See* the detailed explanation for claim 65 in Table 1. To the extent that *Chen* is not deemed to explicitly disclose an active coated with a controlled release composition, such would be obvious in view of the disclosure of encapsulation and many polymers that can be employed to produce controlled release compostions with different release rates. As set forth in MPEP § 2143(E), if a person of ordinary skill has good reason to pursue the known options within his or her technical grasp, and if this leads to the anticipated success, it is likely that product was not of innovation but of ordinary skill and common sense. In this case, it would have been obvious for one skilled in the art at the time of the invention to modify different factors to yield films with different release profile.
66. The process of claim 65, wherein said controlled release composition provides an immediate release.	*See* the detailed explanation for claim 65.

Table 2	
Claims of '080 Patent	*Chen*
67. The process of claim 65, wherein said controlled release composition provides a delayed release.	*See* the detailed explanation for claim 65.
68. The process of claim 65, wherein said controlled release composition provides a sustained release.	*See* the detailed explanation for claim 65.
69. The process of claim 65, wherein said controlled release composition provides a sequential release.	*See* the detailed explanation for claim 65.
71. The process of claim 1, further comprising adding a degassing agent to said masterbatch premix.	*See* the detailed explanation for claim 65 in Table 1. To the extent that *Chen* does not explicitly disclose adding peppermint oil to its masterbatch premix, this is an obvious choice since a person of ordinary skill would be motivated to avoid gas from the outset by adding the oil to a premix. As set forth in MPEP § 2143(E), if a person of ordinary skill has good reason to pursue the known options within his or her technical grasp, and if this leads to the anticipated success, it is likely that product was not of innovation but of ordinary skill and common sense.
85. The process of claim 84, wherein said polymer further comprises a water insoluble polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone and combinations thereof.	*See* the detailed explanation above for claim 6.
86. The process of claim 84, wherein said polymer further comprises a polymer selected from the group consisting of	*See* the detailed explanation above for claim 6.

Table 2	
Claims of '080 Patent	*Chen*
methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(α-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof.	
98. The process of claim 82, wherein said active is an amino acid preparation.	*See* the detailed explanation above for claim 19.
112. The process of claim 82, wherein said active is an anti-obesity drug.	*See* the detailed explanation above for claim 33.
114. The process of claim 82, wherein said H_2-antagonist is selected from the group consisting of cimetidine, ranitidine hydrochloride, famotidine, nizatidine, ebrotidine, mifentidine, roxatidine, pisatidine, aceroxatidine and combinations thereof.	*See* the detailed explanation above for claim 35.
120. The process of claim 82, wherein said active is a dopamine receptor agonist.	*See* the detailed explanation above for claim 41.
121. The process of claim 82, wherein said active is a cerebral dilator.	*See* the detailed explanation above for claim 42.
122. The process of claim 82, wherein said active is a psychotherapeutic agent.	*See* the detailed explanation above for claim 43.
127. The process of claim 82, wherein said active is diphenhydramine.	*See* the detailed explanation above for claim 48.
128. The process of claim 82, wherein said active is nabilone.	*See* the detailed explanation above for claim 49.
129. The process of claim 82, wherein said active is albuterol sulfate.	*See* the detailed explanation above for claim 50.
131. The process of claim 82, wherein said active is a glycoprotein.	*See* the detailed explanation above for claim 52.

Table 2	
Claims of '080 Patent	*Chen*
134. The process of claim 82, wherein said active is a decongestant.	*See* the detailed explanation above for claim 55.
135. The process of claim 82, wherein said active is a loratadine.	*See* the detailed explanation above for claim 56.
136. The process of claim 82, wherein said active is dextromethorphan.	*See* the detailed explanation above for claim 57.
137. The process of claim 82, wherein said active is chlorpheniramine maleate.	*See* the detailed explanation above for claim 58.
139. The process of claim 82, wherein said active is an appetite stimulant.	*See* the detailed explanation above for claim 60.
140. The process of claim 82, wherein said active is a gastrointestinal agent.	*See* the detailed explanation above for claim 61.
144. The process of claim 82, wherein said active is coated with a controlled release composition.	*See* the detailed explanation above for claim 65.
145. The process of claim 144, wherein said controlled release composition provides an immediate release.	*See* the detailed explanation above for claim 65.
146. The process of claim 144, wherein said controlled release composition provides a delayed release.	*See* the detailed explanation above for claim 65.
147. The process of claim 144, wherein said controlled release composition provides a sustained release.	*See* the detailed explanation above for claim 65.
148. The process of claim 144, wherein said controlled release composition provides a sequential release.	*See* the detailed explanation above for claim 65.
150. The process of claim 82, further comprising adding a degassing agent to said flowable polymer matrix.	*See* the detailed explanation above for claim 71.
167. The process of claim 166, wherein said polymer further comprises a water insoluble polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic	*See* the detailed explanation above for claim 6.

Table 2	
Claims of '080 Patent	*Chen*
acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone and combinations thereof.	
168. The process of claim 166, wherein said polymer further comprises a polymer selected from the group consisting of methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(α-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof.	*See* the detailed explanation above for claim 6.
180. The process of claim 161 wherein said active is an amino acid preparation.	*See* the detailed explanation above for claim 19.
194. The process of claim 161, wherein said active is an anti-obesity drug.	*See* the detailed explanation above for claim 33.
196. The process of claim 195, wherein said H_2-antagonist is selected from the group consisting of cimetidine, ranitidine hydrochloride, famotidine, nizatidine, ebrotidine, mifentidine, roxatidine, pisatidine, aceroxatidine and combinations thereof.	*See* the detailed explanation above for claim 35.
202. The process of claim 161, wherein said active is a dopamine receptor agonist.	*See* the detailed explanation above for claim 41.
203. The process of claim 161, wherein said active is a cerebral dilator.	*See* the detailed explanation above for claim 42.
204. The process of claim 161, wherein said active is a psychotherapeutic agent.	*See* the detailed explanation above for claim 43.
209. The process of claim 161, wherein said active is diphenhydramine.	*See* the detailed explanation above for claim 48.

Table 2	
Claims of '080 Patent	*Chen*
210. The process of claim 161, wherein said active is nabilone.	*See* the detailed explanation above for claim 49.
211. The process of claim 161, wherein said active is albuterol sulfate.	*See* the detailed explanation above for claim 50.
213. The process of claim 161, wherein said active is a glycoprotein.	*See* the detailed explanation above for claim 52.
216. The process of claim 161, wherein said active is a decongestant.	*See* the detailed explanation above for claim 55.
217. The process of claim 161, wherein said active is a loratadine.	*See* the detailed explanation above for claim 56.
218. The process of claim 161, wherein said active is dextromethorphan.	*See* the detailed explanation above for claim 57.
219. The process of claim 161, wherein said active is chlorpheniramine maleate.	*See* the detailed explanation above for claim 58.
221. The process of claim 161, wherein said active is an appetite stimulant.	*See* the detailed explanation above for claim 60.
222. The process of claim 161, wherein said active is a gastrointestinal agent.	*See* the detailed explanation above for claim 61.
226. The process of claim 161, wherein said active is coated with a controlled release composition.	*See* the detailed explanation above for claim 65.
227. The process of claim 226, wherein said controlled release composition provides an immediate release.	*See* the detailed explanation above for claim 65.
228. The process of 226, wherein said controlled release composition provides a delayed release.	*See* the detailed explanation above for claim 65.
229. The process of claim 226, wherein said controlled release composition provides a sustained release.	*See* the detailed explanation above for claim 65.
230. The process of claim 226, wherein said controlled release composition provides a sequential release.	*See* the detailed explanation above for claim 65.
232. The process of claim 161, further comprising adding a degassing agent to said flowable polymer matrix.	*See* the detailed explanation above for claim 71.
245. The process of claim 1, said active is a vasoconstrictor.	As set forth in MPEP § 2143(B), a claim would

Table 2	
Claims of '080 Patent	*Chen*
	have been obvious if the substitution of one known element for another yields predictable results to one of ordinary skill in the art. In this case, *Chen* discloses that the active agent can be an α-adrenergic receptor blocker at page 10, line 24. It is well known that α-adrenergic receptor blockers can cause vasoconstriction. it would have been obvious for one skilled in the art at the time of the invention to try to use vasoconstrictor as an active in the films.
248. The process of claim 1, said active is granisetron hydrochloride.	As set forth in MPEP § 2143(B), a claim would have been obvious in that the substitution of one known element for another yields predictable results to one of ordinary skill in the art. In this case, *Chen* discloses that the active agent can be an anti-nauseant/anti-emetic at page 10, line 29. It is well known that granisetron hydrochloride is used to prevent nausea and vomiting caused by cancer chemotherapy. it would have been obvious for one skilled in the art at the time of the invention was made to try to use different anti-nauseant/anti-emetic (*e.g.*, granisetron hydrochloride) in the films.
253. The process of claim 1, wherein said resulting film provides administration of said active to an individual by administration within the body of the individual during surgery.	As set forth in MPEP § 2143(B), a claim would have been obvious in that the substitution of one known element for another yields predictable results to one of ordinary skill in the art. Since *Chen* discloses that its films can be applied to mucosal surface, it would have been obvious for one skilled in the art to apply *Chen*'s films within the body of the individual during surgery which would yield a predictable result.
263. The process of claim 82, said active is a vasoconstrictor.	*See* the detailed explanation above for claim 245.
266. The process of claim 82, said active is	*See* the detailed explanation above for claim 248.

Table 2	
Claims of '080 Patent	*Chen*
granisetron hydrochloride.	
271. The process of claim 82, wherein said resulting film provides administration of said active to an individual by administration within the body of the individual during surgery.	*See* the detailed explanation above for claim 253.
281. The process of claim 161, said active is a vasoconstrictor.	*See* the detailed explanation above for claim 245.
284. The process of claim 161, said active is granisetron hydrochloride.	*See* the detailed explanation above for claim 248.
289. The process of claim 161, wherein said resulting film provides administration of said active to an individual by administration within the body of the individual during surgery.	*See* the detailed explanation above for claim 253.

Table 3. Proposed rejection of claims 1-3, 16, 32, 55, 65-69, 72-75, 78-82, 95, 111, 134, 144-148, 151-154, 157-161, 177, 193, 216, 226-230, 233-236, 239-242, 254, 255, 257-259, 272, 273, 275-277, 290, 291, and 293-295 under 35 U.S.C. § 103 as obvious over *Chen* in view of *Staab*

Both *Chen* and *Staab* teach methods to prepare thin films for drug delivery, including teaching each and every step of at least independent claims 1, 82, and 161 of the '080 Patent. A person of ordinary skill in the art would have been motivated to combine the teachings of these two references, *e.g.*, applying the laminating and premixing teachings of *Staab* to methods of *Chen*, or produce multiple layer films as taught in *Staab* to customerize the films for a specific application. It is obvious in that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art. MPEP § 2143 (A).

Table 3	
Claims of '080 Patent	*Chen* and *Staab*
1. A process for making a film having a substantially uniform distribution of components, comprising the steps of: (a) forming a masterbatch pre-mix comprising a solvent and a polymer selected from the group consisting of water-soluble polymers, water-swellable polymers and combinations thereof; (b) adding an active to a pre-determined amount of said masterbatch pre-mix to form a flowable polymer matrix, said matrix having a substantially uniform distribution of said active; (c) casting said flowable polymer matrix; (d) evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film within about 10 minutes or fewer to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film; and (e) forming a resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained.	*See* the detailed explanation of the anticipation of claim 1 and claim 82 by *Chen* in Table 1. The only difference between claim 1 and claim 82 relate to forming a masterbatch pre-mix and adding an active to a pre-determined amount of the masterbatch premix in steps (a) and (b). 82.1. A process for making a film having a substantially uniform distribution of components, comprising the steps of: (a) forming a flowable polymer matrix masterbatch pre mix comprising a solvent and a polymer selected from the group consisting of a water soluble polymers, water swellable polymers and combinations thereof a solvent and; (b) adding an active selected from the group consisting to a pre-determined amount of bioactive actives, pharmaceutical actives, drugs, medicaments and combinations thereof said masterbatch pre mix to form a flowable polymer matrix, said matrix having a substantially uniform distribution of said active; (b)(c) casting said flowable polymer matrix; (c)(d) evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco elastic film within about 10 minutes or fewer to maintain said substantially uniform distribution of said active by locking in or substantially preventing migration of said active within said visco elastic film; and (d) (e) forming a resulting film from said

Table 3	
Claims of '080 Patent	*Chen* and *Staab*
	visco elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking in or substantially preventing migration of said active is maintained. With respect to steps (a) and (b), *Staab* teaches forming a pre-mix including a water soluble polymer and water at a first temperature (*e.g.*, 104°-140°F) and then transferring to another vessel of a cooler temperature (*e.g.*, 68°-104°F), and then other heat sensitive ingredients introduced with stirring. *Staab*, col. 7, lines 37-48. Pharmaceuticals and other agents may be heat sensitive. *Staab*, col. 7, lines 48-51. *Staab* teaches using dissolvable polymer materials. *See* col. 2, lines 38-42. The polymers are the same polymers recited in dependent claims 4 and 5, *e.g.*, polyvinyl alcohol, polyethylene oxide, HPMC, and carboxymethyl cellulose. *See* the Abstract. *Staab* also teaches that the pre-mix was formed a uniform blend. *See* col. 7, lines 40-41. With respect to the "substantially uniform distribution of active", *Staab* discloses that that the active is evenly distributed throughout the film. *See* col. 5, line 68 through col. 6, line 1. Additionally, the film prepared in Example 1 each contains 19 mg benzalkonium chloride and about 190 mg in weight. *See* col. 11, lines 49-51. Thus, *Staab* discloses and demonstrates that its resulting films are formed while maintaining the substantially uniform distribution of active. It would have been obvious for one skilled in the art to combine the teachings of *Chen* and *Staab* to employ a premix and arrive at a film with a

Table 3	
Claims of '080 Patent	*Chen* and *Staab*
	desired property, *e.g.*, substantial uniformity of active.
2. The process of claim 1, wherein said pre-determined amount of master batch pre-mix is controllably fed via a first metering pump and a control valve to a first mixer and a second mixer.	*Staab* teaches forming a pre-mix including a water soluble polymer and water in proper concentrations at a first temperature and then transferring to another vessel of a cooler temperature, and then stirring in heat sensitive ingredients. *See* col. 7, lines 37-48. Figure 5 depicts three mixing vessels that can readily be employed for practicing the claimed method. Accordingly, the first mixer and a second mixer are disclosed and shown in Fig. 5. Any transfer from one vessel to another would inherently involve a metering pump. This claim is obvious in that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art. MPEP § 2143 (A).
3. The process of claim 2, wherein said first mixer and said second mixer are arranged in parallel, series or a combination thereof.	The arrangement of the first and second mixer – whether parallel or in series – is obvious and provides no patentable distinction over the combination of references. Figure 5 of *Staab* depicts three mixing vessels that can readily be employed for practicing the claimed method. Accordingly, the first mixer and a second mixer, disclosed and shown in Fig. 5, are arranged in parallel. Arrangement in parallel would accommodate a choice of heat sensitive actives, such as those disclosed in *Staab*. *See* col. 7, lines 37-48. This claim is obvious in that all the claimed

Table 3	
Claims of '080 Patent	*Chen* and *Staab*
	elements were known in the prior art (*i.e.*, *Chen* and *Staab*) and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art. MPEP § 2143 (A).
16. The process of claim 1, wherein said active is a biological response modifier.	*See* the detailed explanation of the anticipation of claim 16 by *Chen* in Table 1. The phrase "biological response modifier" appears only once in the '080 Patent at col. 19, line 63. To the extent that *Chen* does not teach using a biological response modifier as an active, *Staab* identifies several, including monoclonal antibodies and biologically prepared actives. *Staab*, col. 6, lines 49-51; and col. 7, line 1. This claim is obvious in that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art. MPEP § 2143 (A).
32. The process of claim 1, wherein said active is a biological response modifier.	*See* above for claim 16.
55. The process of claim 1, wherein said active is a decongestant.	*Staab* teaches films where the active is a decongestant. Col. 7, line 1. This claim is obvious in that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the

Table 3	
Claims of '080 Patent	*Chen* and *Staab*
	combination yielded nothing more than predictable results to one of ordinary skill in the art. MPEP § 2143 (A).
65. The process of claim 1, wherein said active is coated with a controlled release composition.	*Staab* teaches films including different layers as a way of readily controlling the dissolution rate of the laminate. Thus, a composite of desired release properties and agent materials is obtained. *See* col. 9, lines 28-43. Accordingly, the active is coated with the controlled release matrix. As set forth in MPEP § 2143 (D), a claim would have been obvious if a particular known technique was recognized as part of the ordinary capabilities of one skilled in the art. One of ordinary skill in the art would have been capable of applying this known technique to a known device (method, or product) that was ready for improvement and the results would have been predictable to one of ordinary skill in the art. To the extent it is believed that *Chen* does not teach its active can be coated with a controlled release composition. However, one of ordinary skill in the art would have been capable of applying this known technique taught in *Staab* to *Chen*'s films that was ready for improvement and the results would have been predictable to one of ordinary skill in the art.
66. The process of claim 65, wherein said controlled release composition provides an immediate release.	*Staab* teaches that "in the case of medications to be administered via the oral cavity, it is advantageous that dissolution take place fairly rapidly." *See* col. 4, lines 59-61. An embodiment of immediate release composition is discussed at col. 9, lines 29-31. An example is discussed at col 13, lines 13-41. One of ordinary skill in the art would have been capable of applying this known technique taught

Table 3	
Claims of '080 Patent	*Chen* and *Staab*
	in *Staab* to *Chen*'s films that was ready for improvement and the results would have been predictable to one of ordinary skill in the art. MPEP § 2143 (D)
67. The process of claim 65, wherein said controlled release composition provides a delayed release.	*Staab* teaches films where a laminate of multiple film layers, each layer is made of different polymer materials having different dissolving rates. A delayed release embodiment is discussed at col. 9, lines 28-37. One of ordinary skill in the art would have been capable of applying this known technique taught in *Staab* to *Chen*'s films that was ready for improvement and the results would have been predictable to one of ordinary skill in the art. MPEP § 2143 (D)
68. The process of claim 65, wherein said controlled release composition provides a sustained release.	*Staab* teaches films which provide a sustained release. *Staab*, col. 9, lines 35-37. An example is discussed at col 13, lines 13-41. One of ordinary skill in the art would have been capable of applying this known technique taught in *Staab* to *Chen*'s films that was ready for improvement and the results would have been predictable to one of ordinary skill in the art. MPEP § 2143 (D)
69. The process of claim 65, wherein said controlled release composition provides a sequential release.	*Staab* teaches films where a laminate of multiple film layers, each layer is made of different polymer materials having different dissolving rates. As such, it provides a sequential release. *See* col. 9, lines 28-37. One of ordinary skill in the art would have been capable of applying this known technique taught in *Staab* to *Chen*'s films that was ready for improvement and the results would have been predictable to one of ordinary skill in the art.

Table 3	
Claims of '080 Patent	*Chen* and *Staab*
	MPEP § 2143 (D)
72. The process of claim 1, further comprising a step of providing a second film layer.	*Staab* teaches that the film may be a laminate of two or more layers. *See e.g.*, col. 5, lines 30-31; col. 9, lines 28-43; and Figure 2. One of ordinary skill in the art would have been capable of applying this known technique taught in *Staab* to *Chen*'s films that was ready for improvement and the results would have been predictable to one of ordinary skill in the art. MPEP § 2143 (D)
73. The process of claim 72, wherein said second film layer is coated onto said resulting film.	The second film layer of *Staab* can be formed in a conventional manner by coating the second layer onto the film. *See e.g.*, col. 5, lines 51-58. One of ordinary skill in the art would have been capable of applying this known technique taught in *Staab* to *Chen*'s films that was ready for improvement and the results would have been predictable to one of ordinary skill in the art. MPEP § 2143 (D)
74. The process of claim 72, wherein said second film layer is spread onto said resulting film.	The second film layer of *Staab* can be poured or cast on the first film. *See e.g.*, col. 5, lines 51-58. One of ordinary skill in the art would have been capable of applying this known technique taught in *Staab* to *Chen*'s films that was ready for improvement and the results would have been predictable to one of ordinary skill in the art. MPEP § 2143 (D)
75. The process of claim 72, wherein said second film layer is cast onto said resulting film.	The second film layer of *Staab* can be cast on the first film. *See e.g.*, col. 5, lines 51-58 and Figure 5, which is described as having five casting lines at col. 10, lines 29-30. One of ordinary skill in the art would have been capable of applying this known technique taught

Table 3	
Claims of '080 Patent	*Chen* and *Staab*
	in *Staab* to *Chen*'s films that was ready for improvement and the results would have been predictable to one of ordinary skill in the art. MPEP § 2143 (D)
78. The process of claim 72, wherein said second film layer is laminated onto said resulting film.	*Staab* teaches that "[f]ully formed films can also be laminated to each other." Col. 5, lines 59-60. One of ordinary skill in the art would have been capable of applying this known technique taught in *Staab* to *Chen*'s films that was ready for improvement and the results would have been predictable to one of ordinary skill in the art. MPEP § 2143 (D)
79. The process of claim 72, further comprising laminating said resulting film to another film.	*Staab* teaches that "[f]ully formed films can also be laminated to each other." Col. 5, lines 59-60. The laminate can be made with the first and/or a third layer. *See e.g.*, col. 9, lines 28-43 and Figure 2. One of ordinary skill in the art would have been capable of applying this known technique taught in *Staab* to *Chen*'s films that was ready for improvement and the results would have been predictable to one of ordinary skill in the art. MPEP § 2143 (D)
80. The process of claim 72, wherein said second film comprises an active.	*Staab* teaches that two films can be used which dissolve at different rates, so that *e.g.*, a first film can deliver an active immediately and a second deliver the active over an extended period of time. Col. 5, lines 41-46. *See also* Example 2, col. 13, lines 13-42, wherein both the first and second film include contraceptive. One of ordinary skill in the art would have been capable of applying this known technique taught in *Staab* to *Chen*'s films that was ready for improvement and the results would have been predictable to one of ordinary skill in the art.

Table 3	
Claims of '080 Patent	*Chen* and *Staab*
	MPEP § 2143 (D)
81. The process of claim 72, wherein said active in said second film is different than said active in said resulting film.	*Staab* teaches films where the active in the second film is different from the active in the first film. For example, referring to Figure 2 of *Staab*: "A first film layer 13 is made of, for example, a faster dissolving polymer material for release of a drug material 14a. A second film layer 15 is made of slower dissolving polymer material for release of more drug or another drug material 14b in combination, for example, a spermicide and an anti-infective or anti-inflammatory medication. …" Col. 9, lines 28-43 and Figure 2. One of ordinary skill in the art would have been capable of applying this known technique taught in *Staab* to *Chen*'s films that was ready for improvement and the results would have been predictable to one of ordinary skill in the art. MPEP § 2143 (D)
82. A process for making a film having a substantially uniform distribution of components, comprising the steps of: (a) forming a flowable polymer matrix comprising a polymer selected from the group consisting of a water-soluble polymer, a water swellable polymer and combinations thereof, a solvent and an active selected from the group consisting of bioactive actives, pharmaceutical actives, drugs, medicaments and combinations thereof, said matrix having a substantially uniform distribution of said active; (b) casting said flowable polymer matrix; (c) evaporating at least a portion of said solvent from said flowable polymer matrix	*See* the detailed explanation of the anticipation of claim 82 by *Chen* in Table 1. *Staab* also teaches films made of dissolvable polymer material (*e.g.*, PEO and/or HPMC, both of which are identified as water soluble polymers in the '080 Patent at col. 15, lines 49-51), wherein the films also contain an active such as a drug or medication (*See* the Abstract). *Staab* teaches that "[t]he agent material is evenly distributed throughout the film, so as the film slowly dissolves, it releases the agent material in the proper dosage…" *See* col. 5, line 68 to col. 6, line 3. *Staab* discloses that "the polymer solids, water, or other solvent, contraceptive [*i.e.*, an active]… are

Table 3	
Claims of '080 Patent	*Chen* and *Staab*
to form a visco-elastic film within about 10 minutes or fewer to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film; and (d) forming a resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained.	admixed in the proper concentrations and the mixture heated to the appropriated temperature for dissolution and formation of a uniform blend to take place." *See* col. 7, lines 38-42. As such, *Staab* teaches formation a flowable polymer matrix. *Staab* also discloses that "[t]he device of the invention thus is composed of a biologically compatible material that has been blended homogeneously" with the drug. *See* col. 6, lines 6-10. The disclosure of a film with active material "evenly distributed throughout" meets the instantly claimed limitation of substantially uniform distribution of components. *Staab* discloses that that the active is evenly distributed throughout the film. *See* col. 5, line 68 through col. 6, line 1. Additionally, the film prepared in Example 1 each contains 19 mg benzalkonium chloride and about 190 mg in weight. *See* col. 11, lines 49-51. Thus, *Staab* discloses and demonstrates that its resulting films are formed while maintaining the substantially uniform distribution of active. It would have been obvious for one skilled in the art to combine the teachings of *Chen* and *Staab* to arrive at a film with a desired property, *e.g.*, substantial uniformity of active.
95. The process of claim 82, wherein said active is a biological response modifier.	*See* the detailed explanation for claim 16 in this Table.
111. The process of claim 82, wherein said active is a biological response modifier.	*See* the detailed explanation for claim 32 in this Table.
134. The process of claim 82, wherein said active is a decongestant.	*See* the detailed explanation for claim 55 in this Table.
144. The process of claim 82, wherein said	*See* the detailed explanation for claim 65 in this

Table 3	
Claims of '080 Patent	*Chen* and *Staab*
active is coated with a controlled release composition.	Table.
145. The process of claim 144, wherein said controlled release composition provides an immediate release.	*See* the detailed explanation for claim 66 in this Table.
146. The process of claim 144, wherein said controlled release composition provides a delayed release.	*See* the detailed explanation for claim 67 in this Table.
147. The process of claim 144, wherein said controlled release composition provides a sustained release.	*See* the detailed explanation for claim 68 in this Table.
148. The process of claim 144, wherein said controlled release composition provides a sequential release.	*See* the detailed explanation for claim 69 in this Table.
151. The process of claim 82, further comprising a step of providing a second film layer.	*See* the detailed explanation for claim 72 in this Table.
152. The process of claim 151, wherein said second film layer is coated onto said resulting film.	*See* the detailed explanation for claim 73 in this Table.
153. The process of claim 151, wherein said second film layer is spread onto said resulting film.	*See* the detailed explanation for claim 74 in this Table.
154. The process of claim 151, wherein said second film layer is cast onto said resulting film.	*See* the detailed explanation for claim 75 in this Table.
157. The process of claim 151, wherein said second film layer is laminated onto said resulting film.	*See* the detailed explanation for claim 78 in this Table.
158. The process of claim 151, further	*See* the detailed explanation for claim 79 in this

Table 3	
Claims of '080 Patent	*Chen* and *Staab*
comprising laminating said resulting film to another film.	Table.
159. The process of claim 151, wherein said second film comprises an active.	*See* the detailed explanation for claim 80 in this Table.
160. The process of claim 151, wherein said active in said second film is different than said active in said resulting film.	*See* the detailed explanation for claim 81 in this Table.
161. A process for making a film capable of being administered to a body surface having a substantially uniform distribution of components, comprising the steps of: (a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and an active, said matrix having a substantially uniform distribution of said active; (b) casting said flowable polymer matrix; (c) evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film within about 10 minutes or fewer to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film; (d) forming a resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained; and (e) administering said resulting film to a body surface.	Claim 161 is substantially similar to claim 82, but additionally recites that the film is "capable of being administered to a body surface" (preamble) and the last step "(e) administering said resulting film to a body surface." *See* claim 82 in this Table. With respect to the preamble recitation of a film "capable" of being administered to a body surface, *Staab* additionally discloses films "capable" of being administered to a body surface and administering such films to a body surface, *e.g.*, at col. 7, lines 3-8. *Chen* teaches that the films are suitable for administration to any mucosal surface, *e.g.*, the buccal cavity. *See* p. 8, lines 9-10 and Figure 1. Thus the films are clearly "capable" to being administered to a body surface. With respect to step (e), *Chen* discloses administering the films to a body surface, *i.e.*, the oral mucosa in Examples 12 and 13. To the extent that step (a) differs between the claims, step (a) is broader in claim 161 than claim 82 and is anticipated for the same reasons disclosed above. The reason that this claim is obvious over *Chen* in view of *Staab* is the same as the on discussed in

Table 3	
Claims of '080 Patent	*Chen* and *Staab*
	claim 82.
177. The process of claim 161, wherein said active is a biological response modifier.	*See* the detailed explanation for claim 16 in this Table.
193. The process of claim 161, wherein said active is a biological response modifier.	*See* the detailed explanation for claim 32 in this Table.
216. The process of claim 161, wherein said active is a decongestant.	*See* the detailed explanation for claim 55 in this Table.
226. The process of claim 161, wherein said active is coated with a controlled release composition.	*See* the detailed explanation for claim 65 in this Table.
227. The process of claim 226, wherein said controlled release composition provides an immediate release.	*See* the detailed explanation for claim 66 in this Table.
228. The process of 226, wherein said controlled release composition provides a delayed release.	*See* the detailed explanation for claim 67 in this Table.
229. The process of claim 226, wherein said controlled release composition provides a sustained release.	*See* the detailed explanation for claim 68 in this Table.
230. The process of claim 226, wherein said controlled release composition provides a sequential release.	*See* the detailed explanation for claim 69 in this Table.
233. The process of claim 161, further comprising a step of providing a second film layer.	*See* the detailed explanation for claim 72 in this Table.
234. The process of claim 233, wherein said second film layer is coated onto said	*See* the detailed explanation for claim 73 in this Table.

Table 3	
Claims of '080 Patent	*Chen* and *Staab*
resulting film.	
235. The process of claim 233, wherein said second film layer is spread onto said resulting film.	*See* the detailed explanation for claim 74 in this Table.
236. The process of claim 233, wherein said second film layer is cast onto said resulting film.	*See* the detailed explanation for claim 75 in this Table.
239. The process of claim 233, wherein said second film layer is laminated onto said resulting film.	*See* the detailed explanation for claim 78 in this Table.
240. The process of claim 233, further comprising laminating said resulting film to another film.	*See* the detailed explanation for claim 79 in this Table.
241. The process of claim 233, wherein said second film comprises an active.	*See* the detailed explanation for claim 80 in this Table.
242. The process of claim 233, wherein said active in said second film is different than said active in said resulting film.	*See* the detailed explanation for claim 81 in this Table.
254. The process of claim 1, wherein said resulting film has a variation of active content of less than 10% per film unit.	To the extent that *Chen* does not teach its film has a variation of active content of less than 10% per film unit, *Staab* teaches this feature. More specifically, the disclosure of a film with active material "evenly distributed throughout" meets the instantly claimed limitation of a variation of less than 10% of the active composition. *Staab*, col. 5, line 68 through col. 6, line 3. It would have been obvious for one skilled in the art to combine the teachings of *Chen* and *Staab* to arrive at a film with a desired property, *e.g.*, variation of active content of less than 10% per film unit.

Table 3	
Claims of '080 Patent	*Chen* and *Staab*
255. The process of claim 1, further comprising the step of forming a plurality of individual dosage units of substantially the same size, wherein the active content of individual dosage units has a variance of no more than 10%.	*See* claim 254 directly above regarding *Staab*'s teacing of a film having a variation of active of less than 10% per unit film. *Staab* additionally teaches forming a plurality of individual dosing units of substantially the same size. *Staab*, col. 9, lines 8-14, Figures 1-4, and col. 11, lines 11-18.
257. The method of claim 1, wherein said at least one edible polymer, said active, and said at least one polar solvent are each ingestible materials.	*Staab* teaches the use of HPMC and water, both of which are food grade, ingestible materials. Col. 5, lines 15-28.
258. The method of claim 1, wherein said resulting film is orally administrable.	*See* the detailed explanation for claim 249 in this Table.
259. The method of claim 1, wherein said active is in the form of a particle.	To the extent that the term "particle" further limits this claim, particularly since it doesn't specify, *e.g.*, when the active is a particle, *Staab* teaches actives in the form of particles, *e.g.*, monoclonal antibodies at col. 6, lines 49-54.
272. The process of claim 82, wherein said resulting film has a variation of active content of less than 10% per film unit.	*See* the detailed explanation for claim 254 in this Table.
273. The process of claim 82, further comprising the step of forming a plurality of individual dosage units of substantially the same size, wherein the active content of individual dosage units has a variance of no more than 10%.	*See* the detailed explanation for claim 255 in this Table.
275. The method of claim 82, wherein said at least one edible polymer, said active, and said at least one polar solvent are each ingestible materials.	*See* the detailed explanation for claim 257 in this Table.
276. The method of claim 82, wherein said	*See* the detailed explanation for claim 258 in this

Table 3	
Claims of '080 Patent	*Chen* and *Staab*
resulting film is orally administrable.	Table.
277. The method of claim 82, wherein said active is in the form of a particle.	*See* the detailed explanation for claim 259 in this Table.
290. The process of claim 161, wherein said resulting film has a variation of active content of less than 10% per film unit.	*See* the detailed explanation for claim 254 in this Table.
291. The process of claim 161, further comprising the step of forming a plurality of individual dosage units of substantially the same size, wherein the active content of individual dosage units has a variance of no more than 10%.	*See* the detailed explanation for claim 255 in this Table.
293. The method of claim 161, wherein said at least one edible polymer, said active, and said at least one polar solvent are each ingestible materials.	*See* the detailed explanation for claim 257 in this Table.
294. The method of claim 161, wherein said resulting film is orally administrable.	*See* the detailed explanation for claim 258 in this Table.
295. The method of claim 161, wherein said active is in the form of a particle.	*See* the detailed explanation for claim 259 in this Table.

Table 4. Proposed rejection of claims 82 and 161 under 35 U.S.C. § 103 as obvious over *Chen in view of Le Person*

Table 4	
Claims of '080 Patent	*Chen* and *Le Person*
82. A process for making a film having a substantially uniform distribution of components, comprising the steps of: (a)	*See* the detailed explanation of the anticipation of claim 82 by *Chen* in Table 1. *Le Person* provides and compares several

Table 4	
Claims of '080 Patent	*Chen* and *Le Person*
forming a flowable polymer matrix comprising a polymer selected from the group consisting of a water-soluble polymer, a water swellable polymer and combinations thereof, a solvent and an active selected from the group consisting of bioactive actives, pharmaceutical actives, drugs, medicaments and combinations thereof, said matrix having a substantially uniform distribution of said active; (b) casting said flowable polymer matrix; (c) evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film within about 10 minutes or fewer to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film; and (d) forming a resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained.	processes for the drying of pharmaceutical wet films including drying by convection, conduction, and infra-red drying. *See* page 258, first sentences of § 2.2. The resulting films have a substantially uniform distribution of components. *See* pp.262-263 and detailed discussion directly below for this claim. Using a short infra-red drying process, *Le Person* teaches that in 10 minutes, 99% of the initial water from a 100 μm thick coating is evaporated. *See* page 260, col. 2, line 12-14 and Figure 5. To the extent that *Chen* does not teach "said uniform distribution of said active component by locking-in or substantially preventing migration of said active component within said visco-elastic film," *Le Person* teaches this feature. *Le Person* teaches that the active is homogeneously distributed throughout the wet film initially (*See* page 260, col. 1, line 4.), and then studies the migration and eventual homogenization of the active vertically (*i.e.,* throughout the thickness) of the film throughout the drying process. *See* page 262, col. 1, line 11 to col. 2, line 3. *Le Person* discloses that after 5 min of the drying, "the polymeric network is not turgescent and the meshes are densely packed. The polymer skeleton acts as a filter for the active substance [*i.e.*, a drug] when the system reequilibrates." (Page 262, col. 2, third full paragraph.) *Le Person* also explicitly discloses that "[b]etween the 5^{th} and 10^{th} min of drying the heavy solvent migrates. . . active substance, slowed down in its migration, stays at the bottom of the layer." *See* the last four lines at page 262, col. 2. Of note, the heavy solvent only accounts for 2% of the wet composition of the

Table 4	
Claims of '080 Patent	*Chen* and *Le Person*
	coating. *See* page 258, Table 1. As such, within 5-10 minutes, the solvent has been sufficiently evaporated such that the substantial uniform distribution of the active is locked-in and migration is substantially prevented with the film. As *Le Person* teaches the same steps recited in this claim and both the matrix formed in step (a) and the final film in step (d) are uniform, *Le Person* anticipates this feature. As discussed above, 99% of the water has been evaporated in 10 minutes. *See* § 3.1 at pp. 260-261, in particular Figure 5. Thus, the resulting film of *Le Person* has a water content of 10% or less, and moreover, *Le Person* discloses that the active substance homogenises in its final films. *See* page 263, lines 8-13. One would have been motivated by *Le Person,* which identified short infrared radiation plus convection as the drying method as the drying method they would implement in their pilot plant. *See* page 263, last sentence of § 5, § 2.2, and Figure 1. A person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely that product was not of innovation but of ordinary skill and common sense. MPEP § 2143(E). Moreover, an implicit motivation to combine exists when the 'improvement' results in a process faster, or more efficient. MPEP § 2144.
161. A process for making a film capable of being administered to a body surface having a substantially uniform distribution of components, comprising the steps of: (a) forming a flowable polymer matrix comprising a water-soluble polymer, a	Claim 161 is substantially similar to claim 82, but additionally recites that the film is "capable of being administered to a body surface" (preamble) and the last step "(e) administering said resulting film to a body surface." *See* claim 82 in this

Table 4	
Claims of '080 Patent	*Chen* and *Le Person*
solvent and an active, said matrix having a substantially uniform distribution of said active; (b) casting said flowable polymer matrix; (c) evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film within about 10 minutes or fewer to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film; (d) forming a resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained; and (e) administering said resulting film to a body surface.	Table. With respect to the preamble recitation of a film "capable" of being administered to a body surface, *Le Person* discloses films made from the same materials and made by the same methods claimed in the '080 Patent. As such the films of *Le Person* are as "capable" of being administered to a body surface as the films of claim 161. Moreover, application of the films of *Le Person* to the skin is clearly contemplated in the Abstract and on page 257, col. 1, first paragraph. To the extent that step (a) differs between the claims, step (a) is broader in claim 161 than claim 82 and is anticipated for the same reasons disclosed above. Step (e) does not even require drug delivery, only administering the film to a body surface. As such, this claim is anticipated by *Le Person*'s disclosure of the use of the films for, *e.g.*, transdermal delivery, where the films would not only be administered to the body, but would also deliver the drug to the body. *See* Abstract, last sentence.

B. Claim Charts Applying *Staab* as Sole or Primary reference

Staab anticipates independent claims 1, 82 and 161, and further, anticipates a large number of dependent claims as set forth in detail in Table 5. The remaining dependent claims are merely simple substitutions or combinations of known elements as discussed in detail in Tables 6 and 7.

Table 5. Proposed rejection of claims 1-5, 10, 12-15, 21, 24, 25, 44-46, 54, 55, 59, 63-70, 72-75, 78-84, 89, 91-94, 100, 103, 104, 123-125, 133, 134, 138, 142-149, 151-154, 157-166, 171, 173-176, 182, 185, 186, 205-207, 215, 216, 220, 224-231, 233-236, 239-242, 249-252, 254, 255, 257-260, 267-270, 272, 273, 275-278, 285-288, 290, 291, and 293-299 under 35 U.S.C. § 102(b) as anticipated by *Staab*

Table 5	
Claims of '080 Patent	*Staab*
1. A process for making a film having a substantially uniform distribution of components, comprising the steps of: (a) forming a masterbatch pre-mix comprising a solvent and a polymer selected from the group consisting of water-soluble polymers, water-swellable polymers and combinations thereof; (b) adding an active to a pre-determined amount of said masterbatch pre-mix to form a flowable polymer matrix, said matrix having a substantially uniform distribution of said active; (c) casting said flowable polymer matrix; (d) evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film within about 10 minutes or fewer to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film; and (e) forming a resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained.	*See* the detailed explanation of the anticipation of claim 82 in this table. The only difference between claim 1 and claim 82 relates to forming a masterbatch pre-mix and adding an active to a pre-determined amount of the masterbatch premix in steps (a) and (b). ~~82.~~1. A process for making a film having a substantially uniform distribution of components, comprising the steps of: (a) forming a ~~flowable polymer matrix~~ masterbatch pre mix comprising a solvent and a polymer selected from the group consisting of a water soluble polymers, water swellable polymers and combinations thereof ~~a solvent and~~; (b) adding an active ~~selected from the group consisting~~ to a pre-determined amount of ~~bioactive actives, pharmaceutical actives, drugs, medicaments and combinations thereof~~ said masterbatch pre-mix to form a flowable polymer matrix, said matrix having a substantially uniform distribution of said active; ~~(b)~~(c) casting said flowable polymer matrix; ~~(c)~~(d) evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco elastic film within

Table 5	
Claims of '080 Patent	*Staab*
	about 10 minutes or fewer to maintain said substantially uniform distribution of said active by locking in or substantially preventing migration of said active within said visco elastic film; and ~~(d)~~ (e) forming a resulting film from said visco elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking in or substantially preventing migration of said active is maintained. With respect to steps (a) and (b), *Staab* teaches forming a pre-mix including a water soluble polymer and water at a first temperature (*e.g.*, 104°-140°F) and then transferring to another vessel of a cooler temperature (*e.g.*, 68°-104°F), and then other heat sensitive ingredients introduced with stirring. *Staab*, col. 7, lines 37-48. Pharmaceuticals and other agents may be heat sensitive. *Staab*, col. 7, lines 48-51. *Staab* teaches using dissolvable polymer materials. *See* col. 2, lines 38-42. The polymers are the same polymers recited in dependent claims 4 and 5, *e.g.*, polyvinyl alcohol, polyethylene oxide, HPMC, and carboxymethyl cellulose. *See* the Abstract. *Staab* also teaches that the pre-mix was formed a uniform blend. *See* col. 7, lines 40-41.
2. The process of claim 1, wherein said pre-determined amount of master batch pre-mix is controllably fed via a first metering pump and a control valve to a first mixer and a second mixer.	*Staab* teaches forming a pre-mix including a water soluble polymer and water in proper concentrations at a first temperature and then transferring to another vessel of a cooler temperature, and then stirring in heat sensitive ingredients. *See* col. 7, lines 37-48. Figure 5 depicts three mixing vessels that can readily be

Table 5	
Claims of '080 Patent	*Staab*
	employed for practicing the claimed method. Accordingly, the first mixer and a second mixer are disclosed and shown in Fig. 5. Any transfer from one vessel to another would inherently involve a metering pump.
3. The process of claim 2, wherein said first mixer and said second mixer are arranged in parallel, series or a combination thereof.	Figure 5 depicts three mixing vessels that can readily be employed for practicing the claimed method. Accordingly, the first mixer and a second mixer, disclosed and shown in Fig. 5, are arranged in parallel. Arrangement in parallel would accommodate a choice of heat sensitive actives, such as those disclosed in *Staab*. *See* col. 7, lines 37-48.
4. The process of claim 1, wherein said water-soluble polymer comprises polyethylene oxide.	*Staab* teaches that "[p]olyethylene oxide (PEO) is another good material for the film because it has very good moisture, particularly humidity, stability and further is a good contact grade material." *Staab,* col. 4, lines 62-65. It is very compatible with many medications. *Staab,* col. 4, lines 65-66.
5. The process of claim 1, wherein said polymer comprises a polymer selected from the group consisting of cellulose, a cellulose derivative, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyvinyl copolymers, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof, alone or in	*Staab* teaches that films including polyvinyl alcohol (PVA), polyethylene oxide (PEO) and/or complex carbohydrate material are preferred. *Staab*, col. 4, lines 22-27. PVA is preferred because it is non-toxic and medically safe to be used internally. *Id. See* also the Abstract.

Table 5	
Claims of '080 Patent	*Staab*
combination with polyethylene oxide.	
10. The process of claim 1, wherein said solvent is selected from the group consisting of water, polar organic solvent, and combinations thereof.	*Staab* teaches the use of polar solvents such as water to form a homogeneous matrix. *Staab*, col. 7, lines 37-41.
12. The process of claim 1, wherein said active is selected from the group consisting of bioactive active, pharmaceutical actives, drugs, medicaments and combinations thereof.	The actives of *Staab* include different drugs and medicaments (to the extent that these categories are even different) including contraceptives. *See e.g.*, col. 7, lines 37-41 and col. 6, lines 33-49.
13. The process of claim 1, wherein said active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents,	Among many other actives, *Staab* discloses where the active is a contraceptive. Col. 7, lines 37-41. *Staab* provides a long list of drugs that can be included. *See* col. 6, line 35 to col 7, line 3.

Table 5	
Claims of '080 Patent	*Staab*
homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, anti-tumor drugs, anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, anti-convulsants, neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, anti-asthmatics, cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.	
14. The process of claim 1, wherein said active is selected from the group consisting of cosmetic actives, antigens, allergens, spores, microorganisms, *See*ds, mouthwash components, flavors, fragrances, enzymes, preservatives, sweetening agents, colorants,	*Staab* teaches the use of flavors, fragrances and coloring agents at, *e.g.*, col. 7, lines 28-29.

Table 5	
Claims of '080 Patent	*Staab*
spices, vitamins and combinations thereof.	
15. The process of claim 1, wherein said active is a bioactive active.	*Staab* discloses that the actives can be monoclonal antibodies and biologically prepared actives. *Staab*, col. 6, lines 49-51; and col. 7, line 1.
21. The process of claim 1, wherein said active is a protein.	*Staab* teaches films where the actives can be a monoclonal antibody. Col. 6, lines 49-51. A monoclonal antibody is a protein.
24. The process of claim 1, wherein said active is an antihistamine.	*Staab* teaches films where the active is an antihistamine. Col. 6, line 46.
25. The process of claim 1, wherein said active is an anti-tussive.	*Staab* teaches films where the active is an anti-tussive. Col. 6, line 45.
44. The process of claim 1, wherein said active is an antibiotic.	*Staab* teaches films where the active is an antibiotic. Col. 6, line 35.
45. The process of claim 1, wherein said active is an anesthetic.	*Staab* teaches films where the active is an anesthetic. Col. 6, line 48.
46. The process of claim 1, wherein said active is a contraceptive.	*See* above for claim 13.
54. The process of claim 1, wherein said active is a hormone.	*Staab* teaches films where the active is a hormone. Col. 6, line 68.
55. The process of claim 1, wherein said active is a decongestant.	*Staab* teaches films where the active is a decongestant. Col. 7, line 1.
59. The process of claim 1, wherein said active is selected from the group consisting of an analgesic, an anti-inflammatory, an antihistamine, a decongestant, a cough suppressant and combinations thereof.	*Staab* teaches films where the active is, *e.g.*, an anti-inflammatory, an antihistamine, and a decongestant. col. 6, lines 38 and 46; and col. 7, line 1.
63. The process of claim 1, wherein said active is taste-masked.	*Staab* teaches films where the active is taste masked. *Staab*, col. 7, lines 28-29.

Table 5	
Claims of '080 Patent	*Staab*
64. The process of claim 1, wherein said active is taste-masked using a flavor.	*Staab* teaches films where the active is taste masked using a flavor. *Staab*, col. 7, lines 28-29.
65. The process of claim 1, wherein said active is coated with a controlled release composition.	*Staab* teaches films including different layers as a way of readily controlling the dissolution rate of the laminate. Thus, a composite of desired release properties and agent materials is obtained. *See* col. 9, lines 28-43. Accordingly, the active is coated with the controlled release matrix.
66. The process of claim 65, wherein said controlled release composition provides an immediate release.	*Staab* teaches that "in the case of medications to be administered via the oral cavity, it is advantageous that dissolution take place fairly rapidly." *See* col. 4, lines 59-61. An embodiment of immediate release composition is discussed at col. 9, lines 29-31. An example is discussed at col 13, lines 13-41.
67. The process of claim 65, wherein said controlled release composition provides a delayed release.	*Staab* teaches films where a laminate of multiple film layers, each layer is made of different polymer materials having different dissolving rates. A delayed release embodiment is discussed at col. 9, lines 28-37.
68. The process of claim 65, wherein said controlled release composition provides a sustained release.	*Staab* teaches films which provide a sustained release. *Staab*, col. 9, lines 35-37. An example is discussed at col 13, lines 13-41.
69. The process of claim 65, wherein said controlled release composition provides a sequential release.	*Staab* teaches films where a laminate of multiple film layers, each layer is made of different polymer materials having different dissolving rates. As such, it provides a sequential release. *See* col. 9, lines 28-37.

Table 5	
Claims of '080 Patent	*Staab*
70. The process of claim 1, wherein said active is a particulate.	To the extent that the term "particulate" further limits this claim, particularly since it doesn't specify, *e.g.*, when the active is a particulate, *Staab* teaches many actives in that are particulates, *e.g.*, monoclonal antibodies at col. 6, lines 49-54.
72. The process of claim 1, further comprising a step of providing a second film layer.	*Staab* teaches that the film may be a laminate of two or more layers. *See e.g.*, col. 5, lines 30-31; col. 9, lines 28-43; and Figure 2.
73. The process of claim 72, wherein said second film layer is coated onto said resulting film.	The second film layer of *Staab* can be formed in a conventional manner by coating the second layer onto the film. *See e.g.*, col. 5, lines 51-58.
74. The process of claim 72, wherein said second film layer is spread onto said resulting film.	The second film layer of *Staab* can be poured or cast on the first film. *See e.g.*, col. 5, lines 51-58.
75. The process of claim 72, wherein said second film layer is cast onto said resulting film.	The second film layer of *Staab* can be cast on the first film. *See e.g.*, col. 5, lines 51-58 and Figure 5, which is described as having five casting lines at col. 10, lines 29-30.
78. The process of claim 72, wherein said second film layer is laminated onto said resulting film.	*Staab* teaches that "[f]ully formed films can also be laminated to each other." Col. 5, lines 59-60.
79. The process of claim 72, further comprising laminating said resulting film to another film.	*Staab* teaches that "[f]ully formed films can also be laminated to each other." Col. 5, lines 59-60. The laminate can be made with the first and/or a third layer. *See e.g.*, col. 9, lines 28-43 and Figure 2.
80. The process of claim 72, wherein said second film comprises an active.	*Staab* teaches that two films can be used which dissolve at different rates, so that *e.g.*, a first film can deliver an active immediately and a second deliver the active over an extended period of time. Col. 5, lines 41-46. *See also* Example 2,

Table 5	
Claims of '080 Patent	*Staab*
	col. 13, lines 13-42, wherein both the first and second film include contraceptive.
81. The process of claim 72, wherein said active in said second film is different than said active in said resulting film.	*Staab* teaches films where the active in the second film is different from the active in the first film. For example, referring to Figure 2 of *Staab*: "A first film layer 13 is made of, for example, a faster dissolving polymer material for release of a drug material 14a. A second film layer 15 is made of slower dissolving polymer material for release of more drug or another drug material 14b in combination, for example, a spermicide and an anti-infective or anti-inflammatory medication. …" Col. 9, lines 28-43 and Figure 2.
82. A process for making a film having a substantially uniform distribution of components, comprising the steps of:	*Staab* discloses a process for making films having a substantially uniform distribution of components. *See* detailed discussion of step (d) below.
(a) forming a flowable polymer matrix comprising a polymer selected from the group consisting of a water-soluble polymer, a water swellable polymer and combinations thereof, a solvent and an active selected from the group consisting of bioactive actives, pharmaceutical actives, drugs, medicaments and combinations thereof, said matrix having a substantially uniform distribution of said active;	With respect to step (a), *Staab* teaches films made of dissolvable polymer material (*e.g.*, PEO and/or HPMC, both of which are identified as water soluble polymers in the '080 Patent at col. 15, lines 49-51), wherein the films also contain an active such as a drug or medication (*See* the Abstract). *Staab* teaches that "[t]he agent material is evenly distributed throughout the film, so as the film slowly dissolves, it releases the agent material in the proper dosage…" *See* col. 5, line 68 to col. 6, line 3. *Staab* discloses that "the polymer solids, water, or other solvent, contraceptive [*i.e.*, an active]… are admixed in the proper concentrations and the mixture heated to the appropriated temperature for dissolution and formation of a uniform blend

Table 5	
Claims of '080 Patent	*Staab*
	to take place." *See* col. 7, lines 38-42. As such, *Staab* teaches formation a flowable polymer matrix. *Staab* also discloses that "[t]he device of the invention thus is composed of a biologically compatible material that has been blended homogeneously" with the drug. *See* col. 6, lines 6-10. The disclosure of a film with active material "evenly distributed throughout" meets the instantly claimed limitation of substantially uniform distribution of components. *Staab* prepares its films from a blend mixture of evenly distributed ingredients. *See* col. 7, lines 40-41.
(b) casting said flowable polymer matrix;	With respect to step (b), *Staab* further discloses that "the mixture in liquid form will be poured or cast on to a plate or into a mold. . ." *See* col. 5, lines 52-54. *See* also the casting lines depicted in Figure 5.
(c) evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film within about 10 minutes or fewer to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film; and	With respect to step (c), *Staab* discloses drying the film for approximately 20 minutes. *See* col. 11, line 45. Accordingly, within 10 minutes or fewer (the half time of the drying), at least a portion of the solvent has been evaporated to form a film. Also, (1) *Staab*'s films are made using the same solvent (*e.g.*, water) and the same polymer (*e.g.*, HPMC), which is disclosed and claimed in the '080 Patent as a suitable film forming polymer (*See* the '080 Patent, col. 15, lines 44-51) and used in the majority of the Examples (See Examples P-AA); (2) *Staab*'s films are also formed from a blend mixture of evenly distributed ingredients (*See* col. 7, lines 37-41); and (3) *Staab*'s films (*e.g.*, in Example 1), have only 5% water in HPMC prior to drying, which is far less water than in the films of the '080 Patent

Table 5	
Claims of '080 Patent	*Staab*
	prior to drying. Indeed, the film of *Staab* is viscoelastic and meets the other desired properties, as it is made using the same materials and dried according to the same method recited in this claim. *See* the '080 Patent, col. 15, lines 44-51. As set forth in MPEP 2112.01 (I): "[w]here the claimed and prior art products are identical or substantially identical in structure or composition, or **are produced by identical or substantially identical processes**, a prima facie case of either anticipation or obviousness has been established." (emphasis added) Thus, *Staab*'s films would be as viscoelastic within a 10 minute time period as the films of the '080 Patent, as they are **produced by identical or substantially identical processes** as the process claimed in the '080 Patent. As such, *Staab* anticipates this feature. If Applicant meant to recite one or more method steps that differentiates the claimed invention from the methods of *Staab*, it has not.
(d) forming a resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained.	With respect step (d), *Staab* discloses that in Example 1, 10% wt. of the premix is benzalkonium chloride solution (50% aqueous). *See* col. 11, lines 27-35. In other words, the premix contains 5% wt. water as a solvent. As such, the final product of *Staab* has a water content of 10% or less. *Staab* also discloses that that the active is evenly distributed throughout the film. *See* col. 5, line 68 through col. 6, line 1. Additionally, the film prepared in Example 1 each contains 19 mg benzalkonium chloride and about 190 mg in weight. *See* col. 11, lines 49-51. Thus, *Staab* discloses and demonstrates that its resulting films are formed while maintaining the substantially

Table 5	
Claims of '080 Patent	*Staab*
	uniform distribution of active.
83. The process of claim 82, wherein said water-soluble polymer comprises polyethylene oxide.	*See* the detailed explanation for claim 4 in this Table.
84. The process of claim 82, wherein said polymer comprises a polymer selected from the group consisting of cellulose, a cellulose derivative, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyvinyl copolymers, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof, alone or in combination with polyethylene oxide.	*See* the detailed explanation for claim 5 in this Table.
89. The process of claim 82, wherein said solvent is selected from the group consisting of water, polar organic solvent, and combinations thereof.	*See* the detailed explanation for claim 10 in this Table.
91. The process of claim 82, wherein said active is selected from the group consisting of bioactive active, pharmaceutical actives, drugs, medicaments and combinations thereof.	*See* the detailed explanation for claim 12 in this Table.
92. The process of claim 82, wherein the active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-	*See* the detailed explanation for claim 13 in this Table.

Table 5	
Claims of '080 Patent	*Staab*
diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-	

Table 5	
Claims of '080 Patent	*Staab*
tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, anti-tumor drugs, anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, anti-convulsants, neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, anti-asthmatics, cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.	
93. The process of claim 82, wherein said active is selected from the group consisting of cosmetic actives, antigens, allergens, spores, microorganisms, *See*ds, mouthwash components, flavors, fragrances, enzymes, preservatives, sweetening agents, colorants, spices, vitamins and combinations thereof.	*See* the detailed explanation for claim 14 in this Table.
94. The process of claim 82, wherein said active is a bioactive active.	*See* the detailed explanation for claim 15 in this Table.
100. The process of claim 82, wherein said active is a protein.	*See* the detailed explanation for claim 21 in this Table.
103. The process of claim 82, wherein said active is an antihistamine.	*See* the detailed explanation for claim 24 in this Table.
104. The process of claim 82, wherein said active is an anti-tussive.	*See* the detailed explanation for claim 25 in this Table.
123. The process of claim 82, wherein said active is an antibiotic.	*See* the detailed explanation for claim 44 in this Table.
124. The process of claim 82, wherein said	*See* the detailed explanation for claim 45 in this

Table 5	
Claims of '080 Patent	*Staab*
active is an anesthetic.	Table.
125. The process of claim 82, wherein said active is a contraceptive.	*See* the detailed explanation for claim 46 in this Table.
133. The process of claim 82, wherein said active is a hormone.	*See* the detailed explanation for claim 54 in this Table.
134. The process of claim 82, wherein said active is a decongestant.	*See* the detailed explanation for claim 55 in this Table.
138. The process of claim 82, wherein said active is selected from the group consisting of an analgesic, an anti-inflammatory, an antihistamine, a decongestant, a cough suppressant and combinations thereof.	*See* the detailed explanation for claim 59 in this Table.
142. The process of claim 82, wherein said active is taste-masked.	*See* the detailed explanation for claim 63 in this Table.
143. The process of claim 82, wherein said active is taste-masked using a flavor.	*See* the detailed explanation for claim 64 in this Table.
144. The process of claim 82, wherein said active is coated with a controlled release composition.	*See* the detailed explanation for claim 65 in this Table.
145. The process of claim 144, wherein said controlled release composition provides an immediate release.	*See* the detailed explanation for claim 66 in this Table.
146. The process of claim 144, wherein said controlled release composition provides a delayed release.	*See* the detailed explanation for claim 67 in this Table.
147. The process of claim 144, wherein said controlled release composition provides a sustained release.	*See* the detailed explanation for claim 68 in this Table.

Table 5	
Claims of '080 Patent	*Staab*
148. The process of claim 144, wherein said controlled release composition provides a sequential release.	*See* the detailed explanation for claim 69 in this Table.
149. The process of claim 82, wherein said active is a particulate.	*See* the detailed explanation for claim 70 in this Table.
151. The process of claim 82, further comprising a step of providing a second film layer.	*See* the detailed explanation for claim 72 in this Table.
152. The process of claim 151, wherein said second film layer is coated onto said resulting film.	*See* the detailed explanation for claim 73 in this Table.
153. The process of claim 151, wherein said second film layer is spread onto said resulting film.	*See* the detailed explanation for claim 74 in this Table.
154. The process of claim 151, wherein said second film layer is cast onto said resulting film.	*See* the detailed explanation for claim 75 in this Table.
157. The process of claim 151, wherein said second film layer is laminated onto said resulting film.	*See* the detailed explanation for claim 78 in this Table.
158. The process of claim 151, further comprising laminating said resulting film to another film.	*See* the detailed explanation for claim 79 in this Table.
159. The process of claim 151, wherein said second film comprises an active.	*See* the detailed explanation for claim 80 in this Table.
160. The process of claim 151, wherein said active in said second film is different than said active in said resulting film.	*See* the detailed explanation for claim 81 in this Table.
161. A process for making a film capable of being administered to a body surface having	Claim 161 is substantially similar to claim 82, but additionally recites that the film is "capable of

Table 5	
Claims of '080 Patent	*Staab*
a substantially uniform distribution of components, comprising the steps of: (a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and an active, said matrix having a substantially uniform distribution of said active; (b) casting said flowable polymer matrix; (c) evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film within about 10 minutes or fewer to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film; (d) forming a resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained; and (e) administering said resulting film to a body surface.	being administered to a body surface" (preamble) and the last step "(e) administering said resulting film to a body surface." *See* claim 82 in this Table for the detailed discussion of *Staab's* disclosure of the recited process. *Staab* additionally discloses films "capable" of being administered to a body surface and administering such films to a body surface, *e.g.*, at col. 7, lines 3-8. To the extent that step (a) differs between the claims, step (a) is broader in claim 161 than claim 82 and is anticipated for the same reasons disclosed above.
162. The process of claim 161, wherein said body surface is a mucous membrane.	*Staab* teaches application of its films to the mucous membrane of the mouth or vagina. *See e.g.*, Col. 7, lines 3-9.
163. The process of claim 162, wherein said mucous membrane is oral, anal, vaginal or ophthalmological.	*See* the detailed explanation for claim 162 in this Table.
164. The process of claim 161, wherein said body surface is the surface of a wound.	*Staab* teaches treatment of burn wounds with its films. *See* col. 7, lines 7-9.
165. The process of claim 161, wherein said water-soluble polymer comprises polyethylene oxide.	*See* the detailed explanation for claim 4 in this Table.

Table 5	
Claims of '080 Patent	*Staab*
166. The process of claim 161, wherein said polymer comprises a polymer selected from the group consisting of cellulose, a cellulose derivative, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyvinyl copolymers, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof, alone or in combination with polyethylene oxide.	*See* the detailed explanation for claim 5 in this Table.
171. The process of claim 161, wherein said solvent is selected from the group consisting of water, polar organic solvent, and combinations thereof.	*See* the detailed explanation for claim 10 in this Table.
173. The process of claim 161, wherein said active is selected from the group consisting of bioactive active, pharmaceutical actives, drugs, medicaments and combinations thereof.	*See* the detailed explanation for claim 12 in this Table.
174. The process of claim 161, wherein said active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations,	*See* the detailed explanation for claim 13 in this Table.

Table 5	
Claims of '080 Patent	*Staab*
anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, anti-tumor drugs, anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, anti-convulsants, neuromuscular drugs, hyper- and hypo-	

Table 5	
Claims of '080 Patent	*Staab*
glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, anti-asthmatics, cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.	
175. The process of claim 161, wherein said active is selected from the group consisting of cosmetic actives, antigens, allergens, spores, microorganisms, *See*ds, mouthwash components, flavors, fragrances, enzymes, preservatives, sweetening agents, colorants, spices, vitamins and combinations thereof.	*See* the detailed explanation for claim 14 in this Table.
176. The process of claim 161, wherein said active is a bioactive active.	*See* the detailed explanation for claim 15 in this Table.
182. The process of claim 161, wherein said active is a protein.	*See* the detailed explanation for claim 21 in this Table.
185. The process of claim 161, wherein said active is an antihistamine.	*See* the detailed explanation for claim 24 in this Table.
186. The process of claim 161, wherein said active is an anti-tussive.	*See* the detailed explanation for claim 25 in this Table.
205. The process of claim 161, wherein said active is an antibiotic.	*See* the detailed explanation for claim 44 in this Table.
206. The process of claim 161, wherein said active is an anesthetic.	*See* the detailed explanation for claim 45 in this Table.
207. The process of claim 161, wherein said active is a contraceptive.	*See* the detailed explanation for claim 46 in this Table.
215. The process of claim 161, wherein said active is a hormone.	*See* the detailed explanation for claim 54 in this Table.

Table 5	
Claims of '080 Patent	*Staab*
216. The process of claim 161, wherein said active is a decongestant.	*See* the detailed explanation for claim 55 in this Table.
220. The process of claim 161, wherein said active is selected from the group consisting of an analgesic, an anti-inflammatory, an antihistamine, a decongestant, a cough suppressant and combinations thereof.	*See* the detailed explanation for claim 59 in this Table.
224. The process of claim 161, wherein said active is taste-masked.	*See* the detailed explanation for claim 63 in this Table.
225. The process of claim 161, wherein said active is taste-masked using a flavor.	*See* the detailed explanation for claim 64 in this Table.
226. The process of claim 161, wherein said active is coated with a controlled release composition.	*See* the detailed explanation for claim 65 in this Table.
227. The process of claim 226, wherein said controlled release composition provides an immediate release.	*See* the detailed explanation for claim 66 in this Table.
228. The process of 226, wherein said controlled release composition provides a delayed release.	*See* the detailed explanation for claim 67 in this Table.
229. The process of claim 226, wherein said controlled release composition provides a sustained release.	*See* the detailed explanation for claim 68 in this Table.
230. The process of claim 226, wherein said controlled release composition provides a sequential release.	*See* the detailed explanation for claim 69 in this Table.
231. The process of claim 161, wherein said active is a particulate.	*See* the detailed explanation for claim 70 in this Table.
233. The process of claim 161, further	*See* the detailed explanation for claim 72 in this

Table 5	
Claims of '080 Patent	*Staab*
comprising a step of providing a second film layer.	Table.
234. The process of claim 233, wherein said second film layer is coated onto said resulting film.	*See* the detailed explanation for claim 73 in this Table.
235. The process of claim 233, wherein said second film layer is spread onto said resulting film.	*See* the detailed explanation for claim 74 in this Table.
236. The process of claim 233, wherein said second film layer is cast onto said resulting film.	*See* the detailed explanation for claim 75 in this Table.
239. The process of claim 233, wherein said second film layer is laminated onto said resulting film.	*See* the detailed explanation for claim 78 in this Table.
240. The process of claim 233, further comprising laminating said resulting film to another film.	*See* the detailed explanation for claim 79 in this Table.
241. The process of claim 233, wherein said second film comprises an active.	*See* the detailed explanation for claim 80 in this Table.
242. The process of claim 233, wherein said active in said second film is different than said active in said resulting film.	*See* the detailed explanation for claim 81 in this Table.
249. The process of claim 1, wherein said resulting film provides administration of said active to an individual through the buccal cavity of said individual.	*Staab* teaches that if the drug can be applied on or in a moist area of the body, such as the mouth, then the film can be used to deliver the drug effectively. Col. 7, lines 3-8.
250. The process of claim 1, wherein said resulting film provides administration of said active through gingival application of	*See* the detailed explanation for claim 249 in this Table.

Table 5	
Claims of '080 Patent	*Staab*
said individual.	
251. The process of claim 1, wherein said resulting film provides administration of said active through sublingual application of said individual.	*See* the detailed explanation for claim 249 in this Table.
252. The process of claim 1, wherein said resulting film provides administration of said active to an individual through a mucosal membrane of said individual.	*See* the detailed explanation for claim 249 in this Table.
254. The process of claim 1, wherein said resulting film has a variation of active content of less than 10% per film unit.	The disclosure of a film with active material "evenly distributed throughout" meets the instantly claimed limitation of a variation of less than 10% of the active composition. *Staab*, col. 5, line 68 through col. 6, line 3. Also, an example shows each film prepared contains 19 mg benzalkonium chloride and about 190 mg in weight. *Staab,* col. 11, lines 49-51.
255. The process of claim 1, further comprising the step of forming a plurality of individual dosage units of substantially the same size, wherein the active content of individual dosage units has a variance of no more than 10%.	*See* claim 254 directly above regarding *Staab*'s teaching of a film having a variation of active of less than 10% per unit film. *Staab* additionally teaches forming a plurality of individual dosing units of substantially the same size. *Staab*, col. 9, lines 8-14; Figures 1-4; col. 11, lines 11-18 and 49-51. Moreover, as correctly noted by the Examiner of the '588 Patent in his February 4, 2010 Office Action at p. 5 (Exhibit K), the limitation of less than 10% variation (recited in claim 76) "is a mere obvious matter of choice dependent on the desired final product *and of little patentable consequence to the claimed process since it is not a manipulative feature or step of the claimed process*. The claimed product limitations are well-known

Table 5	
Claims of '080 Patent	*Staab*
	in the ingestible or insertable film art as admitted by Applicant in its own Background at col. 2, lines 40-47 of the '080 Patent. ("Currently, as required by various world regulatory authorities, dosage forms may not vary more than 10% in the amount of active present").
257. The method of claim 1, wherein said at least one edible polymer, said active, and said at least one polar solvent are each ingestible materials.	*Staab* teaches the use of HPMC and water, both of which are food grade, ingestible materials. *See* col. 5, lines 15-28.
258. The method of claim 1, wherein said resulting film is orally administrable.	*See* the detailed explanation for claim 249 in this Table.
259. The method of claim 1, wherein said active is in the form of a particle.	To the extent that the term "particle" further limits this claim, particularly since it doesn't specify, *e.g.*, when the active is a particle, *Staab* teaches actives in the form of particles, *e.g.*, monoclonal antibodies at col. 6, lines 49-54.
260. The method of claim 1, wherein said matrix comprises a dispersion.	*Staab* teaches admixing polymer solids, water or other solvent and an active (*e.g.*, monoclonal antibodies at col. 6, lines 49-54) to form a uniform blend. *Staab*, col. 7, lines 37-41. Accordingly, *e.g.*, the monoclonal antibodies would be dispersed in the matrix.
267. The process of claim 82, wherein said resulting film provides administration of said active to an individual through the buccal cavity of said individual.	*See* the detailed explanation for claim 249 in this Table.
268. The process of claim 82, wherein said resulting film provides administration of said active through gingival application of said individual.	*See* the detailed explanation for claim 249 in this Table.
269. The process of claim 82, wherein said resulting film provides administration of	*See* the detailed explanation for claim 249 in this

Table 5	
Claims of '080 Patent	*Staab*
said active through sublingual application of said individual.	Table.
270. The process of claim 82, wherein said resulting film provides administration of said active to an individual through a mucosal membrane of said individual.	*See* the detailed explanation for claim 249 in this Table.
272. The process of claim 82, wherein said resulting film has a variation of active content of less than 10% per film unit.	*See* the detailed explanation for claim 254 in this Table.
273. The process of claim 82, further comprising the step of forming a plurality of individual dosage units of substantially the same size, wherein the active content of individual dosage units has a variance of no more than 10%.	*See* the detailed explanation for claim 255 in this Table.
275. The method of claim 82, wherein said at least one edible polymer, said active, and said at least one polar solvent are each ingestible materials.	*See* the detailed explanation for claim 257 in this Table.
276. The method of claim 82, wherein said resulting film is orally administrable.	*See* the detailed explanation for claim 258 in this Table.
277. The method of claim 82, wherein said active is in the form of a particle.	*See* the detailed explanation for claim 259 in this Table.
278. The method of claim 82, wherein said matrix comprises a dispersion.	*See* the detailed explanation for claim 260 in this Table.
285. The process of claim 161, wherein said resulting film provides administration of said active to an individual through the buccal cavity of said individual.	*See* the detailed explanation for claim 249 in this Table.
286. The process of claim 161, wherein said resulting film provides administration of	*See* the detailed explanation for claim 249 in this

Table 5	
Claims of '080 Patent	*Staab*
said active through gingival application of said individual.	Table.
287. The process of claim 161, wherein said resulting film provides administration of said active through sublingual application of said individual.	*See* the detailed explanation for claim 249 in this Table.
288. The process of claim 161, wherein said resulting film provides administration of said active to an individual through a mucosal membrane of said individual.	*See* the detailed explanation for claim 249 in this Table.
290. The process of claim 161, wherein said resulting film has a variation of active content of less than 10% per film unit.	*See* the detailed explanation for claim 254 in this Table.
291. The process of claim 161, further comprising the step of forming a plurality of individual dosage units of substantially the same size, wherein the active content of individual dosage units has a variance of no more than 10%.	*See* the detailed explanation for claim 255 in this Table.
293. The method of claim 161, wherein said at least one edible polymer, said active, and said at least one polar solvent are each ingestible materials.	*See* the detailed explanation for claim 257 in this Table.
294. The method of claim 161, wherein said resulting film is orally administrable.	*See* the detailed explanation for claim 258 in this Table.
295. The method of claim 161, wherein said active is in the form of a particle.	*See* the detailed explanation for claim 259 in this Table.
296. The method of claim 161, wherein said matrix comprises a dispersion.	*See* the detailed explanation for claim 260 in this Table.
297. The method of claim 1, wherein said	*Staab* teaches that the matrix can include, *e.g.*, a

Table 5	
Claims of '080 Patent	*Staab*
matrix comprises an emulsion, a colloid or a suspension.	colloid, which is obtained with mixing HPMC with water. Col. 5, lines 15-29 and col. 7, lines 37-45.
298. The method of claim 82, wherein said matrix comprises an emulsion, a colloid or a suspension.	*See* the detailed explanation for claim 297 in this Table.
299. The method of claim 161, wherein said matrix comprises an emulsion, a colloid or a suspension.	*See* the detailed explanation for claim 297 in this Table.

Table 6. Proposed rejection of claims 6-9, 16, 32, 76, 77, 85-88, 95, 111, 155, 156, 167-170, 177, 193, 237, and 238, under 35 U.S.C. § 103 as obvious over *Staab*

Table 6	
Claims of '080 Patent	*Staab*
6. The process of claim 5, wherein said polymer further comprises a water insoluble polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone and combinations thereof.	*Staab* does not explicitly describe the recited water insoluble polymers. However, merely reciting commonly used polymers does not render this claim patentable. These polymers can readily be employed to speed up or slow down the dissolution of the films without undue experimentation. It would have been obvious for one skilled in the art to use different polymers in the claimed process. This would be obvious, *e.g.*, to change the dissolution rate of the layers as described in col. 9, lines 28-35. ("A first film layer 13 is made of, for example, a faster dissolving polymer material for release of a drug material 14a. A second film layer 15 is made of slower dissolving polymer material for release of more drug…").

Table 6	
Claims of '080 Patent	*Staab*
7. The process of claim 5, wherein said polymer further comprises a polymer selected from the group consisting of methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(α-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof.	*See* the detailed explanation above for claim 6.
8. The process of claim 5, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.	*See* the detailed explanation above for claim 6.
9. The process of claim 5, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic	*See* the detailed explanation above for claim 6.

Table 6	
Claims of '080 Patent	*Staab*
acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(d-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.	
16. The process of claim 1, wherein said active is a biological response modifier.	The phrase "biological response modifier" appears only once in the '080 Patent at col. 19, line 63. To the extent that Applicant ascribes any special meaning to this term, such has not been made apparent in the '080 Patent specification. As such, all actives are biological response modifiers. *Staab* identifies several, including monoclonal antibodies and biologically prepared actives. *Staab*, col. 6, lines 49-51; and col. 7, line 1. Alternatively, to the extent that *Staab* does not explicitly describe the active can be a biological response modifier, in view of the extensive list of agents throughout the *Staab*'s specification, to the extent that this term describes a different type of agent, such would be obvious to substitute to the active of *Staab*. As set forth in MPEP § 2143(E), if a person of ordinary skill has good reason to pursue the known options within his or her technical grasp, and if this leads to the anticipated success, it is likely that product was not of innovation but of ordinary skill and common sense. In this case, it would have been obvious for one skilled in the art at the time of the invention to try to use different

Table 6	
Claims of '080 Patent	*Staab*
	actives (*e.g.*, a biological response modifier) in the films.
32. The process of claim 1, wherein said active is a biological response modifier.	Claim 32 is a duplicate of claim 16, *i.e.*, there is no difference in scope. *See* the detailed explanation above for claim 16.
76. The process of claim 72, wherein said second film layer is extruded onto said resulting film.	Although not explicitly disclosed in *Staab*, this is an obvious variant of the coating and casting techniques taught in *Staab* as alternative methods to form a laminate. *Staab*, col. 5, lines 30-65. As such, it does not represent a patentable distinction over the teachings of the references. As set for the in MPEP § 2143 (D), if a particular known technique was recognized as part of the ordinary capabilities of one skilled in the art, one of ordinary skill in the art would have been capable of applying this known technique to a known device (method, or product) that was ready for improvement and the results would have been predictable to one of ordinary skill in the art. As such, it would have been obvious for one of ordinary skill in the art, at the time of the invention, to employ extrusion technique in the claimed method.
77. The process of claim 72, wherein said second film layer is sprayed onto said resulting film.	Although not explicitly disclosed in *Staab*, this is an obvious variant of the coating and casting techniques taught in *Staab* as alternative methods to form a laminate. *Staab*, col. 5, lines 30-65. As such, it does not represent a patentable distinction over the teachings of the references. As set for the in MPEP § 2143 (D), if a particular known technique was recognized as part of the ordinary capabilities of one skilled in the art, one of ordinary skill in the art would have been

Table 6	
Claims of '080 Patent	*Staab*
	capable of applying this known technique to a known device (method, or product) that was ready for improvement and the results would have been predictable to one of ordinary skill in the art. As such, it would have been obvious for one of ordinary skill in the art, at the time of the invention, to employ spraying technique in the claimed method.
85. The process of claim 84, wherein said polymer further comprises a water insoluble polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone and combinations thereof.	*See* the detailed explanation above for claim 6.
86. The process of claim 84, wherein said polymer further comprises a polymer selected from the group consisting of methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(α-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof.	*See* the detailed explanation above for claim 6.
87. The process of claim 84, wherein said polymer further comprises a polymer	*See* the detailed explanation above for claim 8.

Table 6	
Claims of '080 Patent	*Staab*
selected from the group consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.	
88. The process of claim 84, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(α-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.	*See* the detailed explanation above for claim 9.
95. The process of claim 82, wherein said active is a biological response modifier.	*See* the detailed explanation for claim 16 in this Table.
111. The process of claim 82, wherein said active is a biological response modifier.	*See* the detailed explanation for claim 16 in this Table.
155. The process of claim 151, wherein said	*See* the detailed explanation for claim 76 in this

Table 6	
Claims of '080 Patent	*Staab*
second film layer is extruded onto said resulting film.	Table.
156. The process of claim 151, wherein said second film layer is sprayed onto said resulting film.	*See* the detailed explanation for claim 77 in this Table.
167. The process of claim 166, wherein said polymer further comprises a water insoluble polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone and combinations thereof.	*See* the detailed explanation above for claim 6.
168. The process of claim 166, wherein said polymer further comprises a polymer selected from the group consisting of methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(α-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof.	*See* the detailed explanation above for claim 6.
169. The process of claim 166, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum,	*See* the detailed explanation above for claim 8.

Table 6	
Claims of '080 Patent	*Staab*
dextran, gellan gum and combinations thereof.	
170. The process of claim 166, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(α-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.	*See* the detailed explanation above for claim 9.
177. The process of claim 161, wherein said active is a biological response modifier.	*See* the detailed explanation for claim 16 in this Table.
193. The process of claim 161, wherein said active is a biological response modifier	*See* the detailed explanation for claim 16 in this Table.
237. The process of claim 233, wherein said second film layer is extruded onto said resulting film.	*See* the detailed explanation for claim 76 in this Table.
238. The process of claim 233, wherein said	*See* the detailed explanation for claim 77 in this

Table 6	
Claims of '080 Patent	*Staab*
second film layer is sprayed onto said resulting film.	Table.

Table 7. Proposed rejection of claims 1, 8, 9, 17, 71, 82, 87, 88, 96, 150, 161, 169, 170, 178, 232, 260, 278, and 296-299, under 35 U.S.C. § 103 as obvious over *Staab* in view of *Chen*

Table 7	
Claims of '080 Patent	*Staab* and *Chen*
1. A process for making a film having a substantially uniform distribution of components, comprising the steps of: (a) forming a masterbatch pre-mix comprising a solvent and a polymer selected from the group consisting of water-soluble polymers, water-swellable polymers and combinations thereof; (b) adding an active to a pre-determined amount of said masterbatch pre-mix to form a flowable polymer matrix, said matrix having a substantially uniform distribution of said active; (c) casting said flowable polymer matrix; (d) evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film within about 10 minutes or fewer to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film; and (e) forming a resulting film from said	*See* the detailed explanation of the anticipation of claims 1 and 82 by *Staab* in Table 5. Also *See* the detailed explanation below for claim 82 in this table. The only difference between claim 1 and claim 82 relate to forming a masterbatch pre-mix and adding an active to a pre-determined amount of the masterbatch premix in steps (a) and (b). ~~82.~~1. A process for making a film having a substantially uniform distribution of components, comprising the steps of: (a) forming a ~~flowable polymer matrix~~ masterbatch pre mix comprising a solvent and a polymer selected from the group consisting of a water soluble polymers, water swellable polymers and combinations thereof ~~a solvent and~~; (b) adding an active ~~selected from the group consisting~~ to a pre-determined amount of ~~bioactive actives, pharmaceutical actives, drugs,~~

Table 7	
Claims of '080 Patent	*Staab* and *Chen*
visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained.	~~medicaments and combinations thereof~~ said masterbatch pre mix to form a flowable polymer matrix, said matrix having a substantially uniform distribution of said active; ~~(b)~~(c) casting said flowable polymer matrix; ~~(c)~~(d) evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco elastic film within about 10 minutes or fewer to maintain said substantially uniform distribution of said active by locking in or substantially preventing migration of said active within said visco elastic film; and ~~(d)~~ (e) forming a resulting film from said visco elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking in or substantially preventing migration of said active is maintained. To the extent that *Staab* does not teach forming a masterbatch pre-mix, *Chen* discloses forming a masterbatch pre-mix including a water soluble polymer, *e.g.*, hydrocolloid HPMC, and a solvent, *i.e.*, water, agitated to form a uniform and viscous solution. *See* page 4, lines 24-26; page 17, lines 7-11; and page 20, lines 19-20. It would have been obvious to one of ordinary skill in the art at the time of the invention to have prepared *Staab*'s films by first forming a premix of the polymer and water, and then adding an active to a pre-determined amount of the premix prior to casting. The predetermined amount can

Table 7	
Claims of '080 Patent	*Staab* and *Chen*
	be all or a portion of the premix. One would be motivated to use a premix to protect the drug, which is usually the most expensive component. *Chen* also discloses and demonstrates that its resulting films are formed while maintaining the substantially uniform distribution of active. *See* the detailed explanation for claim 1 in Table 1.
8. The process of claim 5, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.	To the extent that *Staab* does not disclose the polymer recited in claim 8, *Chen* discloses that polymers can be xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, or gellan gum. *Chen*, p. 14, lines 12-21. This claim is obvious in that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art. MPEP § 2143 (A).
9. The process of claim 5, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates,	To the extent that *Staab* does not disclose the polymer recited in claim 9, *Chen* discloses that polymers can be gelatin, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, or gellan gum. *Chen*, p. 14, lines 12-21. This claim is obvious in that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art. MPEP § 2143 (A).

Table 7	
Claims of '080 Patent	*Staab* and *Chen*
poly(d-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.	
17. The process of claim 1, wherein said active is an opiate or opiate-derivative.	To the extent that *Staab* does not disclose an opiate or opiate-derivative recited in claim 17, *Chen* discloses that the active agent can be hydromorphone in Table 5 on page 21. Hydromorphone is an opioid, *i.e.*, an opiate-derivative. This claim is obvious in that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art. MPEP § 2143 (A).
71. The process of claim 1, further comprising adding a degassing agent to said masterbatch premix.	The term "degassing agent" is not defined in the specification and appears only in the claims of the '080 Patent. Yet, during the prosecution of US Application No. 11/858,214, a related patent application owned by Applicant, Applicant noted, in the response to the Office Action filed December 20, 2010 (Exhibit O), that peppermint oil is one of foam reducing flavoring agents which "act to both flavor the film and prevent and/or **remove air** from the film-forming compositions." *See* page 3, claim 5; and page 5, last paragraph. (emphasis added) *Chen* teaches using peppermint oil as a

Table 7	
Claims of '080 Patent	*Staab* and *Chen*
	component in its films. *See* Table 3 at page 19. As such, claim 71 is anticipated by *Chen*. To the extent that *Chen* does not explicitly disclose adding peppermint oil to its masterbatch premix, this is an obvious choice since a person of ordinary skill would be motivated to avoid gas from the outset by adding the oil to a premix. As set forth in MPEP § 2143(E), if a person of ordinary skill has good reason to pursue the known options within his or her technical grasp, and if this leads to the anticipated success, it is likely that product was not of innovation but of ordinary skill and common sense.
82. A process for making a film having a substantially uniform distribution of components, comprising the steps of: (a) forming a flowable polymer matrix comprising a polymer selected from the group consisting of a water-soluble polymer, a water swellable polymer and combinations thereof, a solvent and an active selected from the group consisting of bioactive actives, pharmaceutical actives, drugs, medicaments and combinations thereof, said matrix having a substantially uniform distribution of said active; (b) casting said flowable polymer matrix; (c) evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film within about 10 minutes or fewer to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film; and (d) forming a resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or	*See* the detailed explanation of the anticipation of claim 82 by *Staab* in Table 5. To the extent that *Staab* does not explicitly disclose step (c), *Chen* discloses removing (evaporating) the polar solvent from the cast matrix in 9 minutes. *See* p. 17, lines 14-15 and Examples 4-8. *Chen*'s films are viscoelastic because they are flexible, stand alone, self-supporting films (p. 17, lines 15-16) made using the HPMC which is disclosed and claimed in the *'080 Patent* as a suitable film forming polymer. The '080 Patent, col. 15, lines 44-51. *Chen* prepares its films from a coating solution with a homogeneous mixture of ingredients. *See* p. 17, lines 6-11, and 26-28, Examples 5-8, and p. 20, lines 17-20. The substantially uniform distribution of active is maintained by locking-in or substantially preventing migration of said active within said viscoelastic film. This is evident from the fact that *Chen* performs the same process steps as here claimed, and demonstrates the same degree of

Table 7	
Claims of '080 Patent	*Staab* and *Chen*
less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained.	uniformity. For example, as seen in *Chen*'s Table 4 on p. 20, Example 1 has a uniform weight of 0.028 ± 0.001 g/dosage film, a thickness of 2.1 ± 0.12 mil, and density of 1.0485 ±0.009 g/cm^2, and a water content of 1.7 ± 0.24% It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of *Chen* and *Staab* so as to prepare a film with a desired property, *e.g.*, substantially uniform distribution of active.
87. The process of claim 84, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.	*See* the detailed explanation above for claim 8.
88. The process of claim 84, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(α-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes,	*See* the detailed explanation above for claim 9.

Table 7	
Claims of '080 Patent	*Staab* and *Chen*
polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.	
96. The process of claim 82, wherein said active is an opiate or opiate-derivative.	*See* the detailed explanation above for claim 17.
150. The process of claim 82, further comprising adding a degassing agent to said flowable polymer matrix.	*See* the detailed explanation above for claim 71.
161. A process for making a film capable of being administered to a body surface having a substantially uniform distribution of components, comprising the steps of: (a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and an active, said matrix having a substantially uniform distribution of said active; (b) casting said flowable polymer matrix; (c) evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film within about 10 minutes or fewer to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film; (d) forming a resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained; and (e) administering said resulting film to a body surface.	Claim 161 is substantially similar to claim 82, but additionally recites that the film is "capable of being administered to a body surface" (preamble) and the last step "(e) administering said resulting film to a body surface." *See* claim 82 in this Table for the detailed discussion of *Chen's* and *Staab's* disclosure of the recited process. With respect to the preamble recitation of a film "capable" of being administered to a body surface, *Staab* additionally discloses films "capable" of being administered to a body surface and administering such films to a body surface, *e.g.*, at col. 7, lines 3-8. *Chen* teaches that the films are suitable for administration to any mucosal surface, *e.g.*, the buccal cavity. *See* p. 8, lines 9-10 and Figure 1. Thus the films are clearly "capable" to being administered to a body surface. With respect to step (e), *Chen* discloses administering the films to a body surface, *i.e.*, the oral mucosa in Examples 12 and 13. To the extent that step (a) differs between the claims, step (a) is broader in claim 161 than claim 82 and is anticipated for the same reasons disclosed above.

Table 7	
Claims of '080 Patent	*Staab* and *Chen*
169. The process of claim 166, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.	*See* the detailed explanation above for claim 8.
170. The process of claim 166, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(α-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.	*See* the detailed explanation above for claim 9.
178. The process of claim 161, wherein said active is an opiate or opiate-derivative.	*See* the detailed explanation above for claim 17.
232. The process of claim 161, further comprising adding a degassing agent to said flowable polymer matrix.	*See* the detailed explanation above for claim 71.

Table 7	
Claims of '080 Patent	*Staab* and *Chen*
260. The method of claim 1, wherein said matrix comprises a dispersion.	To the extent that *Staab* does not teach that the matrix comprises a dispersion, *Chen* discloses that "an effective does of sildenafil citrate is formed into a solid dispersion with xylitol." *See* page 5, lines 15 and 16. The reason to combine the teachings of *Chen* and *Staab* is discussed in claims 1 and 82 in this Table.
278. The method of claim 82, wherein said matrix comprises a dispersion.	*See* the detailed explanation above for claim 260.
296. The method of claim 161, wherein said matrix comprises a dispersion.	*See* the detailed explanation above for claim 260.
297. The method of claim 1, wherein said matrix comprises an emulsion, a colloid or a suspension.	*Chen* discloses use of a hydrocolloid in the premix. *See* page 15, lines 19-21. The reason to combine the teachings of *Chen* and *Staab* is discussed in claims 1 and 82 in this Table.
298. The method of claim 82, wherein said matrix comprises an emulsion, a colloid or a suspension.	*See* the detailed explanation above for claim 297.
299. The method of claim 161, wherein said matrix comprises an emulsion, a colloid or a suspension.	*See* the detailed explanation above for claim 297.

C. Claim Charts Applying *Le Person* as Sole or Primary reference

Le Person is a detailed experimental analysis of internal mass transport during the drying of pharmaceutical wet films, focusing on uniformity of active throughout the thickness of the film, *i.e.,* in the z-axis. *See* Title. *Le Person* discloses the methods of independent claims 82 and 161 of the '080 Patent and several of its dependent claims. Indeed the methods of the '080 Patent are described and improved upon in *Le Person*, far beyond anything described or claimed in the '080 Patent. The obviousness of the premix-related steps in the remaining independent claim 1 is addressed in Tables 10 and 11.

Table 8. Proposed rejection of claims 82, 89-91, 161, 171-173, 272-274, and 290-292 under 35 U.S.C. § 102(b) as anticipated by *Le Person*

Table 8	
Claims of '080 Patent	*Le Person*
82. A process for making a film having a substantially uniform distribution of components, comprising the steps of:	*Le Person* provides and compares several processes for the drying of pharmaceutical wet films including drying by convection, conduction, and infra-red drying. *See* page 258, first sentences of § 2.2. The resulting films have a substantially uniform distribution of components. *See* pp.262-263 and detailed discussion directly below for this claim.
(a) forming a flowable polymer matrix comprising a polymer selected from the group consisting of a water-soluble polymer, a water swellable polymer and combinations thereof, a solvent and an active selected from the group consisting of bioactive actives, pharmaceutical actives, drugs, medicaments and combinations thereof, said matrix having a substantially uniform distribution of said active;	The films of *Le Person* include an acrylic adhesive polymer, its solvents (which include water) and an active substance. *See* page 258, first sentence of § 2.1. *See* Table 1. Since the major solvent of the polymer is identified as water, the polymer is water solvent. *Id. Le Person* teaches that the constituents of the active phase, including the pharmaceutical active, in the matrix are homogeneously distributed. *See* page 262, col. 2, lines 4-6.
(b) casting said flowable polymer matrix;	*Le Person* teaches that "[a]fter preparation, the coating mixture is spread on a web…." *See* page 257, col. 1, lines 10-11.
(c) evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film within about 10 minutes or fewer to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film; and	"…and submitted to drying in a tunnel or an oven. Frequently, impinging jets and Infra-red Radiation accomplish the work in a short drying time (100 s as an order of magnitude." *See* page 257, col. 1, lines 11-14. Using a short infra-red drying process, *Le Person* teaches that in 10 minutes, 99% of the initial water from a 100 μm thick coating is evaporated. *See* page 260, col. 2, line 12-14 and Figure 5. With respect to the limitation of "form[ing] a visco-elastic film within about 10 minutes or

Table 8	
Claims of '080 Patent	*Le Person*
	fewer to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, Requester notes that it is only a desirable property. Applicant needs to identify an active step as to how to achieve such a property. Otherwise, it is not entitled to a patentable weight. Nonetheless, Requester respectfully submits that *Le Person* anticipates this feature. Requester elaborates below. *Le Person* teaches that the active is homogeneously distributed throughout the wet film initially (*See* page 262, col. 2, lines 4-6), and then studies the migration and eventual homogenization of the active vertically (*i.e.,* throughout the thickness) of the film throughout the drying process. *See* page 262, col. 1, line 11 to col. 2, line 3. *Le Person* discloses that after 5 min of the drying, "the polymeric network is not turgescent and the meshes are densely packed. The polymer skeleton acts as a filter for the active substance [*i.e.*, a drug] when the system reequilibrates." (Page 262, col. 2, third full paragraph.) *Le Person* also explicitly discloses that "[b]etween the 5^{th} and 10^{th} min of drying the heavy solvent migrates. . . active substance, slowed down in its migration, stays at the bottom of the layer." *See* the last four lines at page 262, col. 2. Of note, the heavy solvent only accounts for 2% of the wet composition of the coating. *See* page 258, Table 1. As such, within 5-10 minutes, the solvent has been sufficiently evaporated such that the substantial uniform distribution of the active is locked-in and migration is substantially prevented with the film.

Table 8	
Claims of '080 Patent	*Le Person*
	As set forth in MPEP 2112.01 (I): "[w]here the claimed and prior art products are identical or substantially identical in structure or composition, or **are produced by identical or substantially identical processes**, a prima facie case of either anticipation or obviousness has been established." (emphasis added) As *Le Person* teaches using the same materials and the same steps recited in this claim and both the matrix formed in step (a) and the final film in step (d) are uniform, *Le Person*'s films would be as viscoelastic within a 10 minute time period as the films of the '080 Patent, as they are **produced by identical or substantially identical processes** as the process claimed in the '080 Patent. As such, *Le Person* anticipates this feature. Even if it is not completely uniform within 10 minutes or less, it is substantially uniform, given that the whole heavy solvent only accounts for 2% in the matrix (*See* Table 1 and the discussion immediately above).
(d) forming a resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained.	As discussed above, 99% of the water has been evaporated in 10 minutes. *See* § 3.1 at pp. 260-261, in particular Figure 5. Thus, the resulting film of *Le Person* has a water content of 10% or less, and moreover, *Le Person* discloses that the active substance homogenizes in its final films. *See* page 263, lines 8-13.
89. The process of claim 82, wherein said solvent is selected from the group consisting of water, polar organic solvent, and combinations thereof.	The major solvent of *Le Person* is water. *See* page 258, Table 1.
90. The process of claim 89, wherein said solvent is selected from the group consisting of ethanol, isopropanol, acetone, and combinations thereof.	*Le Person* discloses its coating mixture contains three light solvents (Sl_i). *See* page 258, Section 2.1. Table 1 indicates that solvent Sl_2 has molecular weight of 46, which is the molecular

Table 8	
Claims of '080 Patent	*Le Person*
	weight of EtOH. Of note, dimethyl ether also has molecular weight of 46. However, it cannot be used as a solvent due to low boiling point (-24°C). Accordingly, claim 90 is anticipated by *Le Person*.
91. The process of claim 82, wherein said active is selected from the group consisting of bioactive active, pharmaceutical actives, drugs, medicaments and combinations thereof.	*Le Person* is directed to pharmaceutical thin films (*See* Title), including, *e.g.*, pharmaceutical actives and drugs (*See* page 258, col. 1, line 5; and page 262, col. 2, line 6.), to the extent that these terms are different.
161. A process for making a film capable of being administered to a body surface having a substantially uniform distribution of components, comprising the steps of: (a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and an active, said matrix having a substantially uniform distribution of said active; (b) casting said flowable polymer matrix; (c) evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film within about 10 minutes or fewer to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film; (d) forming a resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained; and (e) administering said resulting film to a	For the examiner's convenience, the following redline comparison of claims 82 and 161 is provided: ~~82.~~161. A process for making a film capable of being administered to a body surface having a substantially uniform distribution of components, comprising the steps of: (a) forming a flowable polymer matrix comprising ~~a polymer selected from the group consisting of~~ a water soluble polymer, ~~a water swellable polymer and combinations thereof,~~ a solvent and an active ~~selected from the group consisting of bioactive actives, pharmaceutical actives, drugs, medicaments and combinations thereof~~, said matrix having a substantially uniform distribution of said active; (b) casting said flowable polymer matrix; (c) evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco elastic film within about 10 minutes or fewer to maintain said substantially uniform distribution of said active by locking in or substantially

Table 8	
Claims of '080 Patent	*Le Person*
body surface.	preventing migration of said active within said visco elastic film; ~~and~~ (d) forming a resulting film from said visco elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking in or substantially preventing migration of said active is maintained; and (e) administering said resulting film to a body surface. *See* claim 82 in this Table for a detailed explanation of the anticipation of this claim by *Le Person*. With respect to the preamble recitation of a film "capable" of being administered to a body surface, *Le Person* discloses films made from the same materials and made by the same methods claimed in the '080 Patent. As such the films of *Le Person* are as "capable" of being administered to a body surface as the films of claims 82 and 161. Moreover, application of the films of *Le Person* to the skin is clearly contemplated in the Abstract. To the extent that step (a) differs between the claims, step (a) is broader in claim 161 than claim 82 and is anticipated for the same reasons disclosed above. Step (e) does not even require drug delivery, only administering the film to a body surface. As such, this claim is anticipated by *Le Person*'s disclosure of the use of the films for, *e.g.*, transdermal delivery, where the films would not only be administered to the body, but would also deliver the drug to the body. *See* Abstract, last sentence.

Table 8	
Claims of '080 Patent	*Le Person*
171. The process of claim 161, wherein said solvent is selected from the group consisting of water, polar organic solvent, and combinations thereof.	*See* the explanation above for claim 89.
172. The process of claim 161, wherein said solvent is selected from the group consisting of ethanol, isopropanol, acetone, and combinations thereof.	*See* the explanation above for claim 90.
173. The process of claim 161, wherein said active is selected from the group consisting of bioactive active, pharmaceutical actives, drugs, medicaments and combinations thereof.	*See* the explanation above for claim 91.
272. The process of claim 82, wherein said resulting film has a variation of active content of less than 10% per film unit.	This limitation is met by the homogenous films of *Le Person*, which were made by the same basic methods recited in this claim. Moreover, as correctly noted by the Examiner of the '588 Patent in his February 4, 2010 Office Action at p. 5 (Exhibit K), the limitation of less than 10% variation (recited in claim 76) "is a mere obvious matter of choice dependent on the desired final product *and of little patentable consequence to the claimed process since it is not a manipulative feature or step of the claimed process*. The claimed product limitations are well-known in the ingestible or insertable film art as admitted by Applicant in its own Background at col. 2, lines 40-47 of the '080 Patent. ("Currently, as required by various world regulatory authorities, dosage forms may not vary more than 10% in the amount of active present").
273. The process of claim 82, further comprising the step of forming a plurality of individual dosage units of substantially the same size, wherein the active content of	*See* the explanation above for claim 272.

Table 8	
Claims of '080 Patent	*Le Person*
individual dosage units has a variance of no more than 10%.	
274. The method of claim 82, wherein said resulting film contains less than about 6% by weight solvent.	The solvent content of the films of *Le Person* are far under 6% by weight. *See e.g.*, Figures 2 and 5. Using a short infra-red drying process *Le Person* teaches that in 10 minutes, 99% of the initial water from a 100 μm thick coating is evaporated. *See* § 3.1 at pp. 260-261, in particular Figure 5 and the second paragraph of right column at page 260. In view of the water and heavy solvent content shown in Figure 5, the total solvent content by weight would be well under 6%.
290. The process of claim 161, wherein said resulting film has a variation of active content of less than 10% per film unit.	*See* the explanation above for claim 272.
291. The process of claim 161, further comprising the step of forming a plurality of individual dosage units of substantially the same size, wherein the active content of individual dosage units has a variance of no more than 10%.	*See* the detailed explanation in this table for claim 273.
292. The method of claim 161, wherein said resulting film contains less than about 6% by weight solvent.	*See* the explanation above for claim 274.

Table 9. Proposed rejection of claims 90, 92, 172, 174, 273, and 291 under 35 U.S.C. § 103 as obvious over *Le Person*

Table 9	
Claims of '080 Patent	*Le Person*
90. The process of claim 89, wherein said solvent is selected from the group consisting	*See* the detailed explanation for claim 90 in Table

Table 9	
Claims of '080 Patent	*Le Person*
of ethanol, isopropanol, acetone, and combinations thereof.	8. To the extent it is deemed that that *Le Person* does not disclose the solvent recited in claim 90, the solvents recited therein are commonly employed in preparing pharmaceutical compositions. It would have been obvious for one skilled in the art to use these solvents in the process. As set forth in MPEP § 2143(B), a claim would have been obvious in that the substitution of one known element for another yields predictable results to one of ordinary skill in the art. In this case, it would have been obvious for one skilled in the art to try to use different solvents in the preparation of the films.
92. The process of claim 82, wherein the active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary	The thin polymer films disclosed in *Le Person* are used for pharmaceutical purposes. *See* page 257, abstract. *Le Person* also discloses that its product contains a drug. *See* page 258, § 2.1, product composition. Although *Le Person* does not specify which drug is used, merely reciting commonly used categories of drugs by their functions does not render claim 92 patentable. As set forth in MPEP § 2143(B), a claim would have been obvious in that the substitution of one known element for another yields predictable results to one of ordinary skill in the art. In this case, it would have been obvious for one skilled in the art to try to use different actives in the films.

Table 9	
Claims of '080 Patent	*Le Person*
supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, anti-tumor drugs, anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, anti-convulsants, neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, anti-asthmatics, cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.	
172. The process of claim 161, wherein said solvent is selected from the group consisting	*See* the detailed explanation in this table for claim 90.

Table 9	
Claims of '080 Patent	*Le Person*
of ethanol, isopropanol, acetone, and combinations thereof.	
174. The process of claim 161, wherein said active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents,	*See* the detailed explanation in this table for claim 92.

Table 9	
Claims of '080 Patent	*Le Person*
respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, anti-tumor drugs, anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, anti-convulsants, neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, anti-asthmatics, cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.	
273. The process of claim 82, further comprising the step of forming a plurality of individual dosage units of substantially the same size, wherein the active content of individual dosage units has a variance of no more than 10%.	To the extent it is deemed that *Le Person* does not anticipate this claim, claim 273 is rendered obvious in view of *Le Person*, which discloses pharmaceutical thin films which necessarily must be formed into individual dosage units of substantially the same size to comply with the admitted prior art, *i.e.,* the FDA guidelines referenced in Applicant's own Background. *See e.g.*, p. 258, § 2.1, first sentence and Table 1. Moreover, as correctly noted by the Examiner of the '588 Patent in his February 4, 2010 Office Action at p. 5 (Exhibit K), the limitation of less than 10% variation (recited in claim 76) "is a mere obvious matter of choice dependent on the desired final product ***and of little patentable***

Table 9	
Claims of '080 Patent	*Le Person*
	consequence to the claimed process since it is not a manipulative feature or step of the claimed process." The claimed product limitations are well-known in the ingestible or insertable film art as admitted by Applicant in its own Background at col. 2, lines 40-47 of the '080 Patent. ("Currently, as required by various world regulatory authorities, dosage forms may not vary more than 10% in the amount of active present").
291. The process of claim 161, further comprising the step of forming a plurality of individual dosage units of substantially the same size, wherein the active content of individual dosage units has a variance of no more than 10%.	*See* the detailed explanation in this table for claim 273.

Table 10. Proposed rejection of claims 1-5, 10, 12-16, 21, 24, 25, 32, 44-46, 54, 55, 59, 63-70, 72-75, 78-84, 89, 91-95, 100, 103, 104, 111, 123-125, 133, 134, 138, 142-149, 151-154, 157-166, 171, 173-177, 182, 185, 186, 193, 205-207, 215, 216, 220, 224-231, 233-236, 239-242, 249-252, 254, 255, 257-260, 267-270, 272, 273, 275-278, 285-288, 290, 291, and 293-299 under 35 U.S.C. § 103 as obvious over *Le Person* in view of *Staab*.

Table 10	
Claims of '080 Patent	*Le Person* and *Staab*
1. A process for making a film having a substantially uniform distribution of components, comprising the steps of: (a) forming a masterbatch pre-mix comprising a solvent and a polymer selected from the group consisting of water-soluble polymers, water-swellable polymers and combinations thereof; (b) adding an active to a pre-determined	*See* the detailed explanation of the anticipation of claim 82 by *Le Person* in Table 8. The only difference between claim 1 and claim 82 relate to forming a masterbatch pre-mix and adding an active to a pre-determined amount of the masterbatch premix in steps (a) and (b). ~~82.~~1. A process for making a film having a substantially uniform distribution of

Table 10	
Claims of '080 Patent	*Le Person* and *Staab*
amount of said masterbatch pre-mix to form a flowable polymer matrix, said matrix having a substantially uniform distribution of said active; (c) casting said flowable polymer matrix; (d) evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film within about 10 minutes or fewer to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film; and (e) forming a resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained.	components, comprising the steps of: (a) forming a ~~flowable polymer matrix~~ masterbatch pre mix comprising a solvent and a polymer selected from the group consisting of a water soluble polymers, water swellable polymers and combinations thereof ~~a solvent and~~; (b) adding an active ~~selected from the group consisting~~ to a pre determined amount of ~~bioactive actives, pharmaceutical actives, drugs, medicaments and combinations thereof~~ said masterbatch pre mix to form a flowable polymer matrix, said matrix having a substantially uniform distribution of said active; ~~(b)~~(c) casting said flowable polymer matrix; ~~(c)~~(d) evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco elastic film within about 10 minutes or fewer to maintain said substantially uniform distribution of said active by locking in or substantially preventing migration of said active within said visco elastic film; and ~~(d)~~ (e) forming a resulting film from said visco elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking in or substantially preventing migration of said active is maintained. With respect to steps (a) and (b), *Staab* teaches forming a pre-mix including a water soluble

Table 10	
Claims of '080 Patent	*Le Person* and *Staab*
	polymer and water at a first temperature (*e.g.*, 104°-140°F) and then transferring to another vessel of a cooler temperature (*e.g.*, 68°-104°F), and hen other heat sensitive ingredients introduced with stirring. *Staab*, col. 7, lines 37-48. Pharmaceuticals and other agents may be heat sensitive. *Staab*, col. 7, lines 48-51. *Staab* teaches using dissolvable polymer materials. *See* col. 2, lines 38-42. The polymers are the same polymers recited in dependent claims 4 and 5, *e.g.*, polyvinyl alcohol, polyethylene oxide, HPMC, and carboxymethyl cellulose. *See* the Abstract. *Staab* also teaches that the pre-mix formed a uniform blend. *See* col. 7, lines 40-41. It would have been obvious to one of ordinary skill in the art at the time of the invention was made as a matter of commercial scale-up to have prepared *Le Person*'s films by first forming a premix of the polymer and water, and then adding an active to a pre-determined amount of the premix prior to casting. The predetermined amount can be all or a portion of the premix. One also would be motivated to use a premix to protect the drug, which is usually the most expensive component. *Staab* also teaches that the pre-mix was formed a uniform blend. *See* col. 7, lines 40-41. With respect to step (c), *Staab* further discloses that "the mixture in liquid form will be poured or cast on to a plate or into a mold. . ." *See* col. 5, lines 52-54. *See* also the casting lines depicted in Figure 5. With respect to step (d), *Staab* discloses drying the film for approximately 20 minutes. *See* col. 11, line 45. Accordingly, within 10 minutes or

Table 10	
Claims of '080 Patent	*Le Person* and *Staab*
	fewer (the half time of the drying), at least a portion of the solvent has been evaporated to form a film. Also, (1) *Staab*'s films are made using the same solvent (*e.g.,* water) and the same polymer (*e.g.*, HPMC), which is disclosed and claimed in the '080 Patent as a suitable film forming polymer (*See* the '080Patent, col. 15, lines 44-51) and used in the majority of the Examples (See Examples P-AA); (2) *Staab*'s films are also formed from a blend mixture of evenly distributed ingredients (*See* col. 7, lines 37-41); and (3) *Staab*'s films (*e.g.*, in Example 1), have only 5% water in HPMC prior to drying, which is far less water than in the films of the '080 Patent prior to drying. Indeed, the film of *Staab* is viscoelastic and meets the other desired properties, as it is made using the same materials and dried according to the same method recited in this claim. *See* the '080 Patent, col. 15, lines 44-51. As set forth in MPEP 2112.01 (I): "[w]here the claimed and prior art products are identical or substantially identical in structure or composition, or **are produced by identical or substantially identical processes**, a prima facie case of either anticipation or obviousness has been established." (emphasis added) Thus, *Staab*'s films would be as viscoelastic within a 10 minute time period as the films of the '080 Patent, as they are **produced by identical or substantially identical processes** as the process claimed in the '080 Patent. As such, *Staab* anticipates this feature. With respect step (e), *Staab* discloses that in Example 1, 10% wt. of the premix is benzalkonium chloride solution (50% aqueous). *See* col. 11, lines 27-35. In other words, the

Table 10	
Claims of '080 Patent	*Le Person* and *Staab*
	premix contains 5% wt. water as a solvent. As such, the final product of *Staab* has a water content of 10% or less. *Staab* also discloses that that the active is evenly distributed throughout the film. *See* col. 5, line 68 through col. 6, line 1. Additionally, the film prepared in Example 1 each contains 19 mg benzalkonium chloride and about 190 mg in weight. *See* col. 11, lines 49-51. Thus, *Staab* discloses and demonstrates that its resulting films are formed while maintaining the substantially uniform distribution of active. With respect step (e), *Staab* discloses that in Example 1, 10% wt. of the premix is benzalkonium chloride solution (50% aqueous). *See* col. 11, lines 27-35. In other words, the premix contains 5% wt. water as a solvent. As such, the final product of *Staab* has a water content of 10% or less. *Staab* also discloses that that the active is evenly distributed throughout the film. *See* col. 5, line 68 through col. 6, line 1. Additionally, the film dosage unit prepared in Example 1 each contains 19 mg benzalkonium chloride and about 190 mg in weight. *See* col. 11, lines 49-51. Thus, *Staab* discloses and demonstrates that its resulting films are formed while maintaining the substantially uniform distribution of active. It would have been obvious for one skilled in the art to combine the teachings of *Le Person* and *Staab* as a matter of commercial scale up to prepare a film with a desired property, *e.g.*, substantial uniformity of active and to meet FDA requirements.
2. The process of claim 1, wherein said pre-determined amount of master batch pre-	*Staab* teaches forming a pre-mix including polymer and water in proper concentrations at a

Table 10	
Claims of '080 Patent	*Le Person* and *Staab*
mix is controllably fed via a first metering pump and a control valve to a first mixer and a second mixer.	first temperature and then transferring to another vessel of a cooler temperature, and then stirring in heat sensitive ingredients. *Staab*, col. 7, lines 37-48. Accordingly, the first mixer is explicitly disclosed and a second is obvious. Any transfer from one vessel to another would inherently involve a metering pump. This claim is obvious in that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art. MPEP § 2143 (A).
3. The process of claim 2, wherein said first mixer and said second mixer are arranged in parallel, series or a combination thereof.	The arrangement of the first and second mixer – whether parallel or in series – is obvious and provides no patentable distinction over the combination of references. Figure 5 depicts three mixing vessels that can readily be employed for practicing the claimed method. Accordingly, the first mixer and a second mixer, disclosed and shown in Fig. 5, are arranged in parallel. For example, arrangement in parallel would accommodate a choice of heat sensitive actives, such as those disclosed in *Staab*. *See* col. 7, line 37 to col. 8, line 23. This claim is obvious in that all the claimed elements were known in the prior art (*i.e.*, *Chen* and *Staab*) and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art. MPEP § 2143 (A).

Table 10	
Claims of '080 Patent	*Le Person* and *Staab*
4. The process of claim 1, wherein said water-soluble polymer comprises polyethylene oxide.	*Staab* teaches that "[p]olyethylene oxide (PEO) is another good material for the film because it has very good moisture, particularly humidity, stability and further is a good contact grade material." *Staab,* col. 4, lines 62-65. It is very compatible with many medications. *Staab,* col. 4, lines 65-66. This claim is obvious in that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art. MPEP § 2143 (A).
5. The process of claim 1, wherein said polymer comprises a polymer selected from the group consisting of cellulose, a cellulose derivative, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyvinyl copolymers, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof, alone or in combination with polyethylene oxide.	*Staab* teaches that films including polyvinyl alcohol (PVA), polyethylene oxide (PEO) and/or complex carbohydrate material are particularly preferred. *Staab*, col. 4, lines 22-27. PVA is particularly preferred because it is non-toxic and medically safe to be used internally. *Id. See* also the Abstract. This claim is obvious in that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art. MPEP § 2143 (A).
10. The process of claim 1, wherein said solvent is selected from the group consisting of water, polar organic solvent, and combinations thereof.	Both *Le Person* and *Staab* teach the use of polar solvents such as water to form a homogeneous matrix. *Le Person*, p. 258, Table 1. *Staab*, col. 7, lines 37-41. This claim is obvious in that all the claimed

Table 10	
Claims of '080 Patent	*Le Person* and *Staab*
	elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art. MPEP § 2143 (A).
12. The process of claim 1, wherein said active is selected from the group consisting of bioactive active, pharmaceutical actives, drugs, medicaments and combinations thereof.	The actives of *Staab* include different drugs and medicaments (to the extent that these categories are even different) including contraceptives. *See e.g.*, col. 7, lines 37-41 and col. 6, lines 33-49. This claim is obvious in that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art. MPEP § 2143 (A).
13. The process of claim 1, wherein said active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-	Among many other actives, *Staab* discloses where the active is a contraceptive. Col. 7, lines 37-41. *Staab* provides a long list of drugs that can be included. *See* col. 6, line 35 to col 7, line 3. This claim is obvious in that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art. MPEP § 2143 (A)

Table 10	
Claims of '080 Patent	*Le Person* and *Staab*
rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, anti-tumor drugs, anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, anti-convulsants, neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, anti-asthmatics, cough	

Table 10	
Claims of '080 Patent	*Le Person* and *Staab*
suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.	
14. The process of claim 1, wherein said active is selected from the group consisting of cosmetic actives, antigens, allergens, spores, microorganisms, *See*ds, mouthwash components, flavors, fragrances, enzymes, preservatives, sweetening agents, colorants, spices, vitamins and combinations thereof.	*Staab* teaches the use of flavors, fragrances and coloring agents at, *e.g.*, col. 7, lines 28-29. This claim is obvious in that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art. MPEP § 2143 (A).
15. The process of claim 1, wherein said active is a bioactive active.	All drugs, medicaments, etc. are bioactive actives. *Staab* discloses that the actives can be monoclonal antibodies and biologically prepared actives. *Staab*, col. 6, lines 49-51; and col. 7, line 1. This claim is obvious in that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art. MPEP § 2143 (A)
16. The process of claim 1, wherein said active is a biological response modifier.	The phrase "biological response modifier" appears only once in the '080 Patent at col. 19, line 63. To the extent that Applicant ascribes any special meaning to this term, such has not been made apparent in the '080 Patent specification. As such, all actives are biological response modifiers. *Staab* identifies several, including monoclonal antibodies and biologically prepared actives. *Staab*, col. 6, lines 49-51; and col. 7, line 1.

Table 10	
Claims of '080 Patent	*Le Person* and *Staab*
	Alternatively, to the extent that *Staab* does not explicitly describe the active can be a biological response modifier, in view of the extensive list of agents throughout the *Staab*'s specification, to the extent that this term describes a different type of agent, such would be obvious to substitute to the active of *Staab*. As set forth in MPEP § 2143(E), if a person of ordinary skill has good reason to pursue the known options within his or her technical grasp, and if this leads to the anticipated success, it is likely that product was not of innovation but of ordinary skill and common sense. In this case, it would have been obvious for one skilled in the art at the time of the invention to try to use different actives (*e.g.*, a biological response modifier) in the films.
21. The process of claim 1, wherein said active is a protein.	*Staab* teaches films where the actives can be a monoclonal antibody. Col. 6, lines 49-51. A monoclonal antibody is a protein. This claim is obvious in that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art. MPEP § 2143 (A).
24. The process of claim 1, wherein said active is an antihistamine.	*Staab* teaches films where the active is an antihistamine. Col. 6, line 46. This claim is obvious in that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the

Table 10	
Claims of '080 Patent	*Le Person* and *Staab*
	combination yielded nothing more than predictable results to one of ordinary skill in the art. MPEP § 2143 (A).
25. The process of claim 1, wherein said active is an anti-tussive.	*Staab* teaches films where the active is an anti-tussive. Col. 6, line 45. This claim is obvious in that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art. MPEP § 2143 (A).
32. The process of claim 1, wherein said active is a biological response modifier.	Claim 32 is a duplicate of claim 16, *i.e.*, there is no difference in scope. *See* the detailed explanation above for claim 16.
44. The process of claim 1, wherein said active is an antibiotic.	*Staab* teaches films where the active is an antibiotic. Col. 6, line 35. This claim is obvious in that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art. MPEP § 2143 (A).
45. The process of claim 1, wherein said active is an anesthetic.	*Staab* teaches films where the active is an anesthetic. Col. 6, line 48. This claim is obvious in that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than

Table 10	
Claims of '080 Patent	*Le Person* and *Staab*
	predictable results to one of ordinary skill in the art. MPEP § 2143 (A).
46. The process of claim 1, wherein said active is a contraceptive.	*See* above for claim 13.
54. The process of claim 1, wherein said active is a hormone.	*Staab* teaches films where the active is a hormone. Col. 6, line 68. This claim is obvious in that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art. MPEP § 2143 (A).
55. The process of claim 1, wherein said active is a decongestant.	*Staab* teaches films where the active is a decongestant. Col. 7, line 1. This claim is obvious in that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art. MPEP § 2143 (A).
59. The process of claim 1, wherein said active is selected from the group consisting of an analgesic, an anti-inflammatory, an antihistamine, a decongestant, a cough suppressant and combinations thereof.	*Staab* teaches films where the active is, *e.g.*, an anti-inflammatory, an antihistamine, and a decongestant. col. 6, lines 38 and 46; col. 7, line 1. This claim is obvious in that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than

Table 10	
Claims of '080 Patent	*Le Person* and *Staab*
	predictable results to one of ordinary skill in the art. MPEP § 2143 (A).
63. The process of claim 1, wherein said active is taste-masked.	*Staab* teaches films where the active is taste masked. *Staab*, col. 7, lines 28-29. This claim is obvious in that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art. MPEP § 2143 (A).
64. The process of claim 1, wherein said active is taste-masked using a flavor.	*Staab* teaches films where the active is taste masked using a flavor. *Staab*, col. 7, lines 28-29. This claim is obvious in that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art. MPEP § 2143 (A).
65. The process of claim 1, wherein said active is coated with a controlled release composition.	*Staab* teaches films including different layers as a way of readily controlling the dissolution rate of the laminate. Thus, a composite of desired release properties and agent materials is obtained. *See* col. 9, lines 28-43. Accordingly, the active is coated with the controlled release matrix. As set forth in MPEP § 2143 (D), a claim would have been obvious if a particular known technique was recognized as part of the ordinary capabilities of one skilled in the art. One of ordinary skill in the art would have been capable of applying this known technique to a known device (method, or product) that was ready for

Table 10	
Claims of '080 Patent	*Le Person* and *Staab*
	improvement and the results would have been predictable to one of ordinary skill in the art. In this case, *Le Person* does not teach its active can be coated with a controlled release composition. However, one of ordinary skill in the art would have been capable of applying this known technique taught in *Staab* to *Le Person*'s films that was ready for improvement and the results would have been predictable to one of ordinary skill in the art.
66. The process of claim 65, wherein said controlled release composition provides an immediate release.	*Staab* teaches that "in the case of medications to be administered via the oral cavity, it is advantageous that dissolution take place fairly rapidly." *See* col. 4, lines 59-61. An embodiment of immediate release composition is discussed at col. 9, lines 29-31. An example is discussed at col 13, lines 13-41. One of ordinary skill in the art would have been capable of applying this known technique taught in *Staab* to *Le Person*'s films that was ready for improvement and the results would have been predictable to one of ordinary skill in the art. MPEP § 2143 (D).
67. The process of claim 65, wherein said controlled release composition provides a delayed release.	*Staab* teaches films where a laminate of multiple film layers, each layer is made of different polymer materials having different dissolving rates. A delayed release embodiment is discussed at col. 9, lines 28-37. One of ordinary skill in the art would have been capable of applying this known technique taught in *Staab* to *Le Person*'s films that was ready for improvement and the results would have been predictable to one of ordinary skill in the art. MPEP § 2143 (D).
68. The process of claim 65, wherein said	*Staab* teaches films which provide a sustained

Table 10	
Claims of '080 Patent	*Le Person* and *Staab*
controlled release composition provides a sustained release.	release. *Staab*, col. 9, lines 35-37. An example is discussed at col 13, lines 13-41. One of ordinary skill in the art would have been capable of applying this known technique taught in *Staab* to *Le Person*'s films that was ready for improvement and the results would have been predictable to one of ordinary skill in the art. MPEP § 2143 (D).
69. The process of claim 65, wherein said controlled release composition provides a sequential release.	*Staab* teaches films where a laminate of multiple film layers, each layer is made of different polymer materials having different dissolving rates. As such, it provides a sequential release. *See* col. 9, lines 28-37. One of ordinary skill in the art would have been capable of applying this known technique taught in *Staab* to *Le Person*'s films that was ready for improvement and the results would have been predictable to one of ordinary skill in the art. MPEP § 2143 (D).
70. The process of claim 1, wherein said active is a particulate.	To the extent that the term "particulate" further limits this claim, particularly since it doesn't specify, *e.g.*, when the active is a particulate, *Staab* teaches many actives in that are particulates, *e.g.*, monoclonal antibodies at col. 6, lines 49-54. One of ordinary skill in the art would have been capable of applying this known technique taught in *Staab* to *Le Person*'s films that was ready for improvement and the results would have been predictable to one of ordinary skill in the art. MPEP § 2143 (D).
72. The process of claim 1, further comprising a step of providing a second film layer.	*Staab* teaches that the film may be a laminate of two or more layers. *See e.g.*, col. 5, lines 30-31; col. 9, lines 28-43; and Figure 2.

Table 10	
Claims of '080 Patent	*Le Person* and *Staab*
	One of ordinary skill in the art would have been capable of applying this known technique taught in *Staab* to *Le Person*'s films that was ready for improvement and the results would have been predictable to one of ordinary skill in the art. MPEP § 2143 (D).
73. The process of claim 72, wherein said second film layer is coated onto said resulting film.	The second film layer of *Staab* can be formed in a conventional manner by coating the second layer onto the film. *See e.g.*, col. 5, lines 51-58. One of ordinary skill in the art would have been capable of applying this known technique taught in *Staab* to *Le Person*'s films that was ready for improvement and the results would have been predictable to one of ordinary skill in the art. MPEP § 2143 (D).
74. The process of claim 72, wherein said second film layer is spread onto said resulting film.	The second film layer of *Staab* can be poured or cast on the first film. *See e.g.*, col. 5, lines 51-58. One of ordinary skill in the art would have been capable of applying this known technique taught in *Staab* to *Le Person*'s films that was ready for improvement and the results would have been predictable to one of ordinary skill in the art. MPEP § 2143 (D).
75. The process of claim 72, wherein said second film layer is cast onto said resulting film.	The second film layer of *Staab* can be cast on the first film. *See e.g.*, col. 5, lines 51-58 and Figure 5, which is described as having five casting lines at col. 10, lines 29-30. One of ordinary skill in the art would have been capable of applying this known technique taught in *Staab* to *Le Person*'s films that was ready for improvement and the results would have been predictable to one of ordinary skill in the art. MPEP § 2143 (D).
78. The process of claim 72, wherein said	*Staab* teaches that "[f]ully formed films can also

Table 10	
Claims of '080 Patent	*Le Person* and *Staab*
second film layer is laminated onto said resulting film.	be laminated to each other." Col. 5, lines 59-60. One of ordinary skill in the art would have been capable of applying this known technique taught in *Staab* to *Le Person*'s films that was ready for improvement and the results would have been predictable to one of ordinary skill in the art. MPEP § 2143 (D).
79. The process of claim 72, further comprising laminating said resulting film to another film.	*Staab* teaches that "[f]ully formed films can also be laminated to each other." Col. 5, lines 59-60. The laminate can be made with the first and/or a third layer. *See e.g.*, col. 9, lines 28-43 and Figure 2. One of ordinary skill in the art would have been capable of applying this known technique taught in *Staab* to *Le Person*'s films that was ready for improvement and the results would have been predictable to one of ordinary skill in the art. MPEP § 2143 (D).
80. The process of claim 72, wherein said second film comprises an active.	*Staab* teaches that two films can be used which dissolve at different rates, so that *e.g.*, a first film can deliver an active immediately and a second deliver the active over an extended period of time. Col. 5, lines 41-46. *See also* Example 2, col. 13, lines 13-42, wherein both the first and second film include contraceptive. One of ordinary skill in the art would have been capable of applying this known technique taught in *Staab* to *Le Person*'s films that was ready for improvement and the results would have been predictable to one of ordinary skill in the art. MPEP § 2143 (D).
81. The process of claim 72, wherein said active in said second film is different than said active in said resulting film.	*Staab* teaches films where the active in the second film is different from the active in the first film. For example, referring to Figure 2 of *Staab*:

Table 10	
Claims of '080 Patent	*Le Person* and *Staab*
	"A first film layer 13 is made of, for example, a faster dissolving polymer material for release of a drug material 14a. A second film layer 15 is made of slower dissolving polymer material for release of more drug or another drug material 14b in combination, for example, a spermicide and an anti-infective or anti-inflammatory medication. …" Col. 9, lines 28-43 and Figure 2. One of ordinary skill in the art would have been capable of applying this known technique taught in *Staab* to *Le Person*'s films that was ready for improvement and the results would have been predictable to one of ordinary skill in the art. MPEP § 2143 (D).
82. A process for making a film having a substantially uniform distribution of components, comprising the steps of: (a) forming a flowable polymer matrix comprising a polymer selected from the group consisting of a water-soluble polymer, a water swellable polymer and combinations thereof, a solvent and an active selected from the group consisting of bioactive actives, pharmaceutical actives, drugs, medicaments and combinations thereof, said matrix having a substantially uniform distribution of said active; (b) casting said flowable polymer matrix; (c) evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film within about 10 minutes or fewer to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-	*See* the detailed explanation of the anticipation of claim 82 by *Le Person* in Table 8. *Staab* also teaches films made of dissolvable polymer material (*e.g.*, PEO and/or HPMC, both of which are identified as water soluble polymers in the '080 Patent at col. 15, lines 49-51), wherein the films also contain an active such as a drug or medication (*See* the Abstract). *Staab* teaches that "[t]he agent material is evenly distributed throughout the film, so as the film slowly dissolves, it releases the agent material in the proper dosage…" *See* col. 5, line 68 to col. 6, line 3. *Staab* discloses that "the polymer solids, water, or other solvent, contraceptive [*i.e.*, an active]… are admixed in the proper concentrations and the mixture heated to the appropriated temperature for dissolution and formation of a uniform blend to take place." *See* col. 7, lines 38-42. As such, *Staab* teaches formation a flowable polymer

Table 10	
Claims of '080 Patent	*Le Person* and *Staab*
elastic film; and (d) forming a resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained.	matrix. *Staab* also discloses that "[t]he device of the invention thus is composed of a biologically compatible material that has been blended homogeneously" with the drug. *See* col. 6, lines 6-10. The disclosure of a film with active material "evenly distributed throughout" meets the instantly claimed limitation of substantially uniform distribution of components. *Staab* discloses that that the active is evenly distributed throughout the film. *See* col. 5, line 68 through col. 6, line 1. Additionally, the film prepared in Example 1 each contains 19 mg benzalkonium chloride and about 190 mg in weight. *See* col. 11, lines 49-51. Thus, *Staab* discloses and demonstrates that its resulting films are formed while maintaining the substantially uniform distribution of active. It would have been obvious for one skilled in the art to combine the teachings of *Le Person* and *Staab* as a matter of commercial scale up to prepare a film with a desired property, *e.g.*, substantial uniformity of active and to meet FDA requirements.
83. The process of claim 82, wherein said water-soluble polymer comprises polyethylene oxide.	*See* the detailed explanation for claim 4 in this Table.
84. The process of claim 82, wherein said polymer comprises a polymer selected from the group consisting of cellulose, a cellulose derivative, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyvinyl copolymers, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl	*See* the detailed explanation for claim 5 in this Table.

Table 10	
Claims of '080 Patent	*Le Person* and *Staab*
cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof, alone or in combination with polyethylene oxide.	
89. The process of claim 82, wherein said solvent is selected from the group consisting of water, polar organic solvent, and combinations thereof.	*See* the detailed explanation for claim 10 in this Table.
91. The process of claim 82, wherein said active is selected from the group consisting of bioactive active, pharmaceutical actives, drugs, medicaments and combinations thereof.	*See* the detailed explanation for claim 12 in this Table.
92. The process of claim 82, wherein the active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous	*See* the detailed explanation for claim 13 in this Table.

Table 10	
Claims of '080 Patent	*Le Person* and *Staab*
system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, anti-tumor drugs, anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, anti-convulsants, neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, anti-asthmatics, cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.	

Table 10	
Claims of '080 Patent	*Le Person* and *Staab*
93. The process of claim 82, wherein said active is selected from the group consisting of cosmetic actives, antigens, allergens, spores, microorganisms, *See*ds, mouthwash components, flavors, fragrances, enzymes, preservatives, sweetening agents, colorants, spices, vitamins and combinations thereof.	*See* the detailed explanation for claim 14 in this Table.
94. The process of claim 82, wherein said active is a bioactive active.	*See* the detailed explanation for claim 15 in this Table.
95. The process of claim 82, wherein said active is a biological response modifier.	*See* the detailed explanation for claim 16 in this Table.
100. The process of claim 82, wherein said active is a protein.	*See* the detailed explanation for claim 21 in this Table.
103. The process of claim 82, wherein said active is an antihistamine.	*See* the detailed explanation for claim 24 in this Table.
104. The process of claim 82, wherein said active is an anti-tussive.	*See* the detailed explanation for claim 25 in this Table.
111. The process of claim 82, wherein said active is a biological response modifier.	*See* the detailed explanation for claim 32 in this Table.
123. The process of claim 82, wherein said active is an antibiotic.	*See* the detailed explanation for claim 44 in this Table.
124. The process of claim 82, wherein said active is an anesthetic.	*See* the detailed explanation for claim 45 in this Table.
125. The process of claim 82, wherein said active is a contraceptive.	*See* the detailed explanation for claim 46 in this Table.
133. The process of claim 82, wherein said active is a hormone.	*See* the detailed explanation for claim 54 in this Table.
134. The process of claim 82, wherein said	*See* the detailed explanation for claim 55 in this

Table 10	
Claims of '080 Patent	*Le Person* and *Staab*
active is a decongestant.	Table.
138. The process of claim 82, wherein said active is selected from the group consisting of an analgesic, an anti-inflammatory, an antihistamine, a decongestant, a cough suppressant and combinations thereof.	*See* the detailed explanation for claim 59 in this Table.
142. The process of claim 82, wherein said active is taste-masked.	*See* the detailed explanation for claim 63 in this Table.
143. The process of claim 82, wherein said active is taste-masked using a flavor.	*See* the detailed explanation for claim 64 in this Table.
144. The process of claim 82, wherein said active is coated with a controlled release composition.	*See* the detailed explanation for claim 65 in this Table.
145. The process of claim 144, wherein said controlled release composition provides an immediate release.	*See* the detailed explanation for claim 66 in this Table.
146. The process of claim 144, wherein said controlled release composition provides a delayed release.	*See* the detailed explanation for claim 67 in this Table.
147. The process of claim 144, wherein said controlled release composition provides a sustained release.	*See* the detailed explanation for claim 68 in this Table.
148. The process of claim 144, wherein said controlled release composition provides a sequential release.	*See* the detailed explanation for claim 69 in this Table.
149. The process of claim 82, wherein said active is a particulate.	*See* the detailed explanation for claim 70 in this Table.
151. The process of claim 82, further comprising a step of providing a second film	*See* the detailed explanation for claim 72 in this Table.

Table 10	
Claims of '080 Patent	*Le Person* and *Staab*
layer.	
152. The process of claim 151, wherein said second film layer is coated onto said resulting film.	*See* the detailed explanation for claim 73 in this Table.
153. The process of claim 151, wherein said second film layer is spread onto said resulting film.	*See* the detailed explanation for claim 74 in this Table.
154. The process of claim 151, wherein said second film layer is cast onto said resulting film.	*See* the detailed explanation for claim 75 in this Table.
157. The process of claim 151, wherein said second film layer is laminated onto said resulting film.	*See* the detailed explanation for claim 78 in this Table.
158. The process of claim 151, further comprising laminating said resulting film to another film.	*See* the detailed explanation for claim 79 in this Table.
159. The process of claim 151, wherein said second film comprises an active.	*See* the detailed explanation for claim 80 in this Table.
160. The process of claim 151, wherein said active in said second film is different than said active in said resulting film.	*See* the detailed explanation for claim 81 in this Table.
161. A process for making a film capable of being administered to a body surface having a substantially uniform distribution of components, comprising the steps of: (a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and an active, said matrix having a substantially uniform distribution of said active; (b) casting said flowable polymer matrix; (c) evaporating at least a portion of said solvent from said flowable polymer	Claim 161 is substantially similar to claim 82, but additionally recites that the film is "capable of being administered to a body surface" (preamble) and the last step "(e) administering said resulting film to a body surface." *See* claim 82 in this Table for the detailed discussion of *Le Person*'s and *Chen's* disclosure of the recited process. With respect to the preamble recitation of a film "capable" of being administered to a body surface, *Staab* additionally discloses films "capable" of being administered to a body surface

Table 10	
Claims of '080 Patent	*Le Person* and *Staab*
matrix to form a visco-elastic film within about 10 minutes or fewer to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film; (d) forming a resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained; and (e) administering said resulting film to a body surface.	and administering such films to a body surface, *e.g.*, at col. 7, lines 3-8. *Le Person* also discloses films made from the same materials and made by the same methods claimed in the '080 Patent. As such the films of *Le Person* are as "capable" of being administered to a body surface as the films of claims 82 and 161. Moreover, application of the films of *Le Person* to the skin is clearly contemplated in the Abstract. To the extent that step (a) differs between the claims, step (a) is broader in claim 161 than claim 82 and is anticipated for the same reasons disclosed above. Step (e) does not even require drug delivery, only administering the film to a body surface. As such, this claim is anticipated by *Le Person*'s disclosure of the use of the films for, *e.g.,* transdermal delivery, where the films would not only be administered to the body, but would also deliver the drug to the body. *See* Abstract, last sentence. It would have been obvious for one skilled in the art to combine the teachings of *Le Person* and *Staab* as a matter of commercial scale up to prepare a film with a desired property, *e.g.*, substantial uniformity of active and to meet FDA requirements.
162. The process of claim 161, wherein said body surface is a mucous membrane.	*Staab* teaches application of its films to the mucous membrane of the mouth or vagina. *See e.g.*, Col. 7, lines 3-9. One of ordinary skill in the art would have been capable of applying this known technique taught in *Staab* to *Le Person*'s films that was ready for improvement and the results would have been

Table 10	
Claims of '080 Patent	*Le Person* and *Staab*
	predictable to one of ordinary skill in the art. MPEP § 2143 (D).
163. The process of claim 162, wherein said mucous membrane is oral, anal, vaginal or ophthalmological.	*See* the detailed explanation for claim 162 in this Table.
164. The process of claim 161, wherein said body surface is the surface of a wound.	*Staab* teaches treating burn wounds with its films. *See* col. 7, lines 7-9. One of ordinary skill in the art would have been capable of applying this known technique taught in *Staab* to *Le Person*'s films that was ready for improvement and the results would have been predictable to one of ordinary skill in the art. MPEP § 2143 (D).
165. The process of claim 161, wherein said water-soluble polymer comprises polyethylene oxide.	*See* the detailed explanation for claim 4 in this Table.
166. The process of claim 161, wherein said polymer comprises a polymer selected from the group consisting of cellulose, a cellulose derivative, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyvinyl copolymers, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof, alone or in combination with polyethylene oxide.	*See* the detailed explanation for claim 5 in this Table.
171. The process of claim 161, wherein said solvent is selected from the group consisting of water, polar organic solvent,	*See* the detailed explanation above for claim 10.

Table 10	
Claims of '080 Patent	*Le Person* and *Staab*
and combinations thereof.	
173. The process of claim 161, wherein said active is selected from the group consisting of bioactive active, pharmaceutical actives, drugs, medicaments and combinations thereof.	*See* the detailed explanation for claim 12 in this Table.
174. The process of claim 161, wherein said active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle	*See* the detailed explanation for claim 13 in this Table.

Table 10	
Claims of '080 Patent	*Le Person* and *Staab*
relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, anti-tumor drugs, anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, anti-convulsants, neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, anti-asthmatics, cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.	
175. The process of claim 161, wherein said active is selected from the group consisting of cosmetic actives, antigens, allergens, spores, microorganisms, *See*ds, mouthwash components, flavors, fragrances, enzymes, preservatives, sweetening agents, colorants, spices, vitamins and combinations thereof.	*See* the detailed explanation with respect to claim 14 above.
176. The process of claim 161, wherein said active is a bioactive active.	*See* the detailed explanation with respect to claim 15 above.

Table 10	
Claims of '080 Patent	*Le Person* and *Staab*
177. The process of claim 161, wherein said active is a biological response modifier.	*See* the detailed explanation for claim 16 in this Table.
182. The process of claim 161, wherein said active is a protein.	*See* the detailed explanation for claim 21 in this Table.
185. The process of claim 161, wherein said active is an antihistamine.	*See* the detailed explanation for claim 24 in this Table.
186. The process of claim 161, wherein said active is an anti-tussive.	*See* the detailed explanation for claim 25 in this Table.
193. The process of claim 161, wherein said active is a biological response modifier	*See* the detailed explanation for claim 16 in this Table.
205. The process of claim 161, wherein said active is an antibiotic.	*See* the detailed explanation for claim 44 in this Table.
206. The process of claim 161, wherein said active is an anesthetic.	*See* the detailed explanation for claim 45 in this Table.
207. The process of claim 161, wherein said active is a contraceptive.	*See* the detailed explanation for claim 46 in this Table.
215. The process of claim 161, wherein said active is a hormone.	*See* the detailed explanation for claim 54 in this Table.
216. The process of claim 161, wherein said active is a decongestant.	*See* the detailed explanation for claim 55 in this Table.
220. The process of claim 161, wherein said active is selected from the group consisting of an analgesic, an anti-inflammatory, an antihistamine, a decongestant, a cough suppressant and combinations thereof.	*See* the detailed explanation for claim 59 in this Table.
224. The process of claim 161, wherein said active is taste-masked.	*See* the detailed explanation for claim 63 in this Table.

Table 10	
Claims of '080 Patent	*Le Person* and *Staab*
225. The process of claim 161, wherein said active is taste-masked using a flavor.	*See* the detailed explanation for claim 64 in this Table.
226. The process of claim 161, wherein said active is coated with a controlled release composition.	*See* the detailed explanation for claim 65 in this Table.
227. The process of claim 226, wherein said controlled release composition provides an immediate release.	*See* the detailed explanation for claim 66 in this Table.
228. The process of 226, wherein said controlled release composition provides a delayed release.	*See* the detailed explanation for claim 67 in this Table.
229. The process of claim 226, wherein said controlled release composition provides a sustained release.	*See* the detailed explanation for claim 68 in this Table.
230. The process of claim 226, wherein said controlled release composition provides a sequential release.	*See* the detailed explanation for claim 69 in this Table.
231. The process of claim 161, wherein said active is a particulate.	*See* the detailed explanation for claim 70 in this Table.
233. The process of claim 161, further comprising a step of providing a second film layer.	*See* the detailed explanation for claim 72 in this Table.
234. The process of claim 233, wherein said second film layer is coated onto said resulting film.	*See* the detailed explanation for claim 73 in this Table.
235. The process of claim 233, wherein said second film layer is spread onto said resulting film.	*See* the detailed explanation for claim 74 in this Table.
236. The process of claim 233, wherein said	*See* the detailed explanation for claim 75 in this

Table 10	
Claims of '080 Patent	*Le Person* and *Staab*
second film layer is cast onto said resulting film.	Table.
239. The process of claim 233, wherein said second film layer is laminated onto said resulting film.	*See* the detailed explanation for claim 78 in this Table.
240. The process of claim 233, further comprising laminating said resulting film to another film.	*See* the detailed explanation for claim 79 in this Table.
241. The process of claim 233, wherein said second film comprises an active.	*See* the detailed explanation for claim 80 in this Table.
242. The process of claim 233, wherein said active in said second film is different than said active in said resulting film.	*See* the detailed explanation for claim 81 in this Table.
249. The process of claim 1, wherein said resulting film provides administration of said active to an individual through the buccal cavity of said individual.	*Staab* teaches that if the drug can be applied on or in a moist area of the body, such as the mouth, then the film can be used to deliver the drug effectively. Col. 7, lines 3-8. One of ordinary skill in the art would have been capable of applying this known technique taught in *Staab* to *Le Person*'s films that was ready for improvement and the results would have been predictable to one of ordinary skill in the art. MPEP § 2143 (D).
250. The process of claim 1, wherein said resulting film provides administration of said active through gingival application of said individual.	*See* the detailed explanation for claim 249 in this Table.
251. The process of claim 1, wherein said resulting film provides administration of said active through sublingual application of said individual.	*See* the detailed explanation for claim 249 in this Table.

Table 10	
Claims of '080 Patent	*Le Person* and *Staab*
252. The process of claim 1, wherein said resulting film provides administration of said active to an individual through a mucosal membrane of said individual.	*See* the detailed explanation for claim 249 in this Table.
254. The process of claim 1, wherein said resulting film has a variation of active content of less than 10% per film unit.	The disclosure of a film with active material "evenly distributed throughout" meets the instantly claimed limitation of a variation of less than 10% of the active composition. *Staab*, col. 5, line 68 through col. 6, line 3. Also, an example shows each film prepared contains 19 mg benzalkonium chloride and about 190 mg in weight. *Staab,* col. 11, lines 49-51.
255. The process of claim 1, further comprising the step of forming a plurality of individual dosage units of substantially the same size, wherein the active content of individual dosage units has a variance of no more than 10%.	*See* claim 254 directly above regarding *Staab*'s teaching of a film having a variation of active of less than 10% per unit film. *Staab* additionally teaches forming a plurality of individual dosing units of substantially the same size. *Staab*, col. 9, lines 8-14; Figures 1-4; col. 11, lines 11-18 and 49-51. Moreover, as correctly noted by the Examiner of the '588 Patent in his February 4, 2010 Office Action at p. 5 (Exhibit K), the limitation of less than 10% variation (recited in claim 76) "is a mere obvious matter of choice dependent on the desired final product *and of little patentable consequence to the claimed process since it is not a manipulative feature or step of the claimed process*. The claimed product limitations are well-known in the ingestible or insertable film art as admitted by Applicant in its own Background at col. 2, lines 40-47 of the '080 Patent. ("Currently, as required by various world regulatory authorities, dosage forms may not vary more than 10% in the amount of active present"). It would have been obvious for one skilled in the

Table 10	
Claims of '080 Patent	*Le Person* and *Staab*
	art to combine the teachings of *Le Person* and *Staab* as a matter of commercial scale up to prepare a film with a desired property, *e.g.*, substantial uniformity of active and to meet FDA requirements.
257. The method of claim 1, wherein said at least one edible polymer, said active, and said at least one polar solvent are each ingestible materials.	*Staab* teaches the use of HPMC and water, both of which are food grade, ingestible materials. Col. 5, lines 15-28. One of ordinary skill in the art would have been capable of applying this known technique taught in *Staab* to *Le Person*'s films that was ready for improvement and the results would have been predictable to one of ordinary skill in the art. MPEP § 2143 (D).
258. The method of claim 1, wherein said resulting film is orally administrable.	*See* the detailed explanation for claim 249 in this Table.
259. The method of claim 1, wherein said active is in the form of a particle.	To the extent that the term "particle" further limits this claim, particularly since it doesn't specify, *e.g.*, when the active is a particle, *Staab* teaches actives in the form of particles, *e.g.*, monoclonal antibodies at col. 6, lines 49-54. One of ordinary skill in the art would have been capable of applying this known technique taught in *Staab* to *Le Person*'s films that was ready for improvement and the results would have been predictable to one of ordinary skill in the art. MPEP § 2143 (D).
260. The method of claim 1, wherein said matrix comprises a dispersion.	*Staab* teaches admixing polymer solids, water or other solvent and an active (*e.g.*, monoclonal antibodies at col. 6, lines 49-54) to form a uniform blend. *Staab*, col. 7, lines 37-41. Accordingly, *e.g.*, the monoclonal antibodies would be dispersed in the matrix. One of ordinary skill in the art would have been

Table 10	
Claims of '080 Patent	*Le Person* and *Staab*
	capable of applying this known technique taught in *Staab* to *Le Person*'s films that was ready for improvement and the results would have been predictable to one of ordinary skill in the art. MPEP § 2143 (D).
267. The process of claim 82, wherein said resulting film provides administration of said active to an individual through the buccal cavity of said individual.	*See* the detailed explanation for claim 249 in this Table.
268. The process of claim 82, wherein said resulting film provides administration of said active through gingival application of said individual.	*See* the detailed explanation for claim 249 in this Table.
269. The process of claim 82, wherein said resulting film provides administration of said active through sublingual application of said individual.	*See* the detailed explanation for claim 249 in this Table.
270. The process of claim 82, wherein said resulting film provides administration of said active to an individual through a mucosal membrane of said individual.	*See* the detailed explanation for claim 249 in this Table.
272. The process of claim 82, wherein said resulting film has a variation of active content of less than 10% per film unit.	*See* the detailed explanation for claim 254 in this Table.
273. The process of claim 82, further comprising the step of forming a plurality of individual dosage units of substantially the same size, wherein the active content of individual dosage units has a variance of no more than 10%.	*See* the detailed explanation for claim 255 in this Table.
275. The method of claim 82, wherein said at least one edible polymer, said active, and said at least one polar solvent are each	*See* the detailed explanation for claim 257 in this Table.

Table 10	
Claims of '080 Patent	*Le Person* and *Staab*
ingestible materials.	
276. The method of claim 82, wherein said resulting film is orally administrable.	*See* the detailed explanation for claim 249 in this Table.
277. The method of claim 82, wherein said active is in the form of a particle.	*See* the detailed explanation for claim 259 in this Table.
278. The method of claim 82, wherein said matrix comprises a dispersion.	*See* the detailed explanation for claim 260 in this Table.
285. The process of claim 161, wherein said resulting film provides administration of said active to an individual through the buccal cavity of said individual.	*See* the detailed explanation for claim 249 in this Table.
286. The process of claim 161, wherein said resulting film provides administration of said active through gingival application of said individual.	*See* the detailed explanation for claim 249 in this Table.
287. The process of claim 161, wherein said resulting film provides administration of said active through sublingual application of said individual.	*See* the detailed explanation for claim 249 in this Table.
288. The process of claim 161, wherein said resulting film provides administration of said active to an individual through a mucosal membrane of said individual.	*See* the detailed explanation for claim 249 in this Table.
290. The process of claim 161, wherein said resulting film has a variation of active content of less than 10% per film unit.	*See* the detailed explanation for claim 254 in this Table.
291. The process of claim 161, further comprising the step of forming a plurality of individual dosage units of substantially the same size, wherein the active content of individual dosage units has a variance of no	*See* the detailed explanation for claim 255 in this Table.

Table 10	
Claims of '080 Patent	*Le Person* and *Staab*
more than 10%.	
293. The method of claim 161, wherein said at least one edible polymer, said active, and said at least one polar solvent are each ingestible materials.	*See* the detailed explanation for claim 257 in this Table.
294. The method of claim 161, wherein said resulting film is orally administrable.	*See* the detailed explanation for claim 249 in this Table.
295. The method of claim 161, wherein said active is in the form of a particle.	*See* the detailed explanation for claim 259 in this Table.
296. The method of claim 161, wherein said matrix comprises a dispersion.	*See* the detailed explanation for claim 260 in this Table.
297. The method of claim 1, wherein said matrix comprises an emulsion, a colloid or a suspension.	*Staab* teaches that the matrix can include, *e.g.*, a colloid, which is obtained with mixing HPMC with water. Col. 5, lines 15-29 and col. 7, lines 37-45. One of ordinary skill in the art would have been capable of applying this known technique taught in *Staab* to *Le Person*'s films that was ready for improvement and the results would have been predictable to one of ordinary skill in the art. MPEP § 2143 (D).
298. The method of claim 82, wherein said matrix comprises an emulsion, a colloid or a suspension.	*See* the detailed explanation for claim 297 in this Table.
299. The method of claim 161, wherein said matrix comprises an emulsion, a colloid or a suspension.	*See* the detailed explanation for claim 297 in this Table.

Table 11. Proposed rejection of claims 1, 8, 9, 17, 45, 53, 71, 82, 87, 88, 96, 124, 132, 150, 161, 169, 170, 178, 206, 214, 232, 254, 272, and 290 under 35 U.S.C. § 103 as obvious over *Le Person in view of Chen*

Table 11	
Claims of '080 Patent	*Le Person and Chen*
1. A process for making a film having a substantially uniform distribution of components, comprising the steps of: (a) forming a masterbatch pre-mix comprising a solvent and a polymer selected from the group consisting of water-soluble polymers, water-swellable polymers and combinations thereof; (b) adding an active to a pre-determined amount of said masterbatch pre-mix to form a flowable polymer matrix, said matrix having a substantially uniform distribution of said active; (c) casting said flowable polymer matrix; (d) evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film within about 10 minutes or fewer to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film; and (e) forming a resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained.	*See* the detailed explanation with respect to the anticipation of claim 82 by *Le Person* in Table 8. *See* also the detailed explanation with respect to the anticipation of claim 1 by *Chen* in Table 1. *Le Person* explicitly discloses that its films are uniform at the mixing stage, during the initial evaporation, and in the final film. *See e.g. Le Person at* p. 262, col. 2, first full paragraph, and the bridging paragraph between pp. 262-263. To the extent that it is deemed that the uniformity of *Le Person* doesn't meet the "substantially uniform distribution of active" recitations in this claim, *Chen* also describes each and every step of this claim and explicitly demonstrates the uniformity of active its films to the same degree and using the same criteria as set forth in the '080 Patent. One would be motivated to combine these references to provide films with uniform distribution of active to provide a safe and effective dosage form.
8. The process of claim 5, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean	*Chen* discloses that polymers can be xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, or gellan gum. *Chen*, p. 14, lines 12-21. This claim is obvious in that all the claimed elements were known in the prior art and one

Table 11	
Claims of '080 Patent	*Le Person and Chen*
gum, dextran, gellan gum and combinations thereof.	skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art. MPEP § 2143 (A).
9. The process of claim 5, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(d-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.	*Chen* discloses that polymers can be gelatin, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, or gellan gum. *Chen*, p. 14, lines 12-21. This claim is obvious in that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art. MPEP § 2143 (A).
17. The process of claim 1, wherein said active is an opiate or opiate-derivative.	*Chen* discloses that the active agent can be hydromorphone in Table 5 on page 21. Hydromorphone is an opioid, *i.e.*, an opiate-derivative. This claim is obvious in that all the claimed

Table 11	
Claims of '080 Patent	*Le Person and Chen*
	elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art. MPEP § 2143 (A).
45. The process of claim 1, wherein said active is an anesthetic.	*Chen* discloses that the active agent can be an anesthetic at page 11, line 9. This claim is obvious in that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art. MPEP § 2143 (A).
53. The process of claim 1, wherein said active is an analgesic.	*Chen* discloses that the active agent can be an analgesic at page 10, line 24. This claim is obvious in that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art. MPEP § 2143 (A).
71. The process of claim 1, further comprising adding a degassing agent to said masterbatch premix.	The term "degassing agent" is not defined in the specification and appears only in the claims of the '080 Patent. Yet, during the prosecution of US Application No. 11/858,214, a related patent application owned by Applicant, Applicant noted, in the response to the Office Action filed December 20, 2010 (Exhibit O), that peppermint oil is one of foam reducing flavoring agents which

Table 11	
Claims of '080 Patent	*Le Person and Chen*
	"act to both flavor the film and prevent and/or **remove air** from the film-forming compositions." *See* page 3, claim 5; and page 5, last paragraph. (emphasis added) *Chen* teaches using peppermint oil as a component in its films. *See* Table 3 at page 19. As such, claim 71 is anticipated by *Chen*. To the extent that *Chen* does not explicitly disclose adding peppermint oil to its masterbatch premix, this is an obvious choice since a person of ordinary skill would be motivated to avoid gas from the outset by adding the oil to a premix. As set forth in MPEP § 2143(E), if a person of ordinary skill has good reason to pursue the known options within his or her technical grasp, and if this leads to the anticipated success, it is likely that product was not of innovation but of ordinary skill and common sense.
82. A process for making a film having a substantially uniform distribution of components, comprising the steps of: (a) forming a flowable polymer matrix comprising a polymer selected from the group consisting of a water-soluble polymer, a water swellable polymer and combinations thereof, a solvent and an active selected from the group consisting of bioactive actives, pharmaceutical actives, drugs, medicaments and combinations thereof, said matrix having a substantially uniform distribution of said active; (b) casting said flowable polymer matrix; (c) evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film within about 10 minutes or fewer to maintain said substantially uniform distribution of said	*See* the detailed explanation with respect to the anticipation of this claim by *Le Person* in Table 8. *See* also the detailed explanation with respect to the anticipation of claim 1 by *Chen* in Table 1. *Le Person* teaches that the active is homogeneously distributed throughout the wet film initially (*See* page 260, col. 1, line 4.), and then studies the migration and eventual homogenization of the active vertically (*i.e.,* throughout the thickness) of the film throughout the drying process. *See* page 262, col. 1, line 11 to col. 2, line 3. *Le Person* discloses that after 5 min of the drying, "the polymeric network is not turgescent and the meshes are densely packed. The polymer skeleton acts as a filter for the active substance [*i.e.*, a drug] when the system reequilibrates." (Page 262, col. 2, third full paragraph.) *Le Person* also explicitly

Table 11	
Claims of '080 Patent	*Le Person and Chen*
active by locking-in or substantially preventing migration of said active within said visco-elastic film; and (d) forming a resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained.	discloses that "[b]etween the 5th and 10th min of drying the heavy solvent migrates. . . active substance, slowed down in its migration, stays at the bottom of the layer." *See* the last four lines at page 262, col. 2. Of note, the heavy solvent only accounts for 2% of the wet composition of the coating. *See* page 258, Table 1. As such, within 5-10 minutes, the solvent has been sufficiently evaporated such that the substantial uniform distribution of the active is locked-in and migration is substantially prevented with the film. To the extent that it is deemed that the uniformity of *Le Person* doesn't meet the "substantially uniform distribution of active" recitation in this claim, *Chen* also describes each and every step of this claim and explicitly demonstrates the uniformity of active its films to the same degree and using the same criteria as set forth in the '080 Patent. *See* extensive discussion of uniformity of *Chen*'s films for claim 82 in Table 1. One would be motivated to combine these two references to provide films with uniform distribution of active to provide a safe and effective dosage form.
87. The process of claim 84, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.	*See* the detailed explanation above for claim 8.
88. The process of claim 84, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate,	*See* the detailed explanation above for claim 9.

Table 11	
Claims of '080 Patent	*Le Person and Chen*
hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(α-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.	
96. The process of claim 82, wherein said active is an opiate or opiate-derivative.	*See* the detailed explanation above for claim 17.
124. The process of claim 82, wherein said active is an anesthetic.	*See* the detailed explanation above for claim 45.
132. The process of claim 82, wherein said active is an analgesic.	*See* the detailed explanation above for claim 53.
150. The process of claim 82, further comprising adding a degassing agent to said flowable polymer matrix.	*See* the detailed explanation above for claim 71.
161. A process for making a film capable of being administered to a body surface having a substantially uniform distribution of components, comprising the steps of: (a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and an active, said matrix having a substantially uniform distribution of said	Claim 161 is substantially similar to claim 82, but additionally recites that the film is "capable of being administered to a body surface" (preamble) and the last step "(e) administering said resulting film to a body surface." *See* claim 82 in this Table for a detailed explanation of the obviousness of this claim by *Le Person in view of Chen*.

Table 11	
Claims of '080 Patent	*Le Person and Chen*
active; (b) casting said flowable polymer matrix; (c) evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film within about 10 minutes or fewer to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film; (d) forming a resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained; and (e) administering said resulting film to a body surface.	With respect to the preamble recitation of a film "capable" of being administered to a body surface, *Le Person* also discloses films made from the same materials and made by the same methods claimed in the '080 Patent. As such the films of *Le Person* are as "capable" of being administered to a body surface as the films of claims 82 and 161. Moreover, application of the films of *Le Person* to the skin is clearly contemplated in the Abstract. *Chen* also teaches that the films are suitable for administration to any mucosal surface, *e.g.*, the buccal cavity. *See* p. 8, lines 9-10 and Figure 1. Thus the films are clearly "capable" to being administered to a body surface. Step (e) does not even require drug delivery, only administering the film to a body surface. As such, this claim is anticipated by *Le Person*'s disclosure of the use of the films for, *e.g.,* transdermal delivery, where the films would not only be administered to the body, but would also deliver the drug to the body. *See* Abstract, last sentence. *Chen* also discloses administering the films to a body surface, *i.e.*, the oral mucosa in Examples 12 and 13.
169. The process of claim 166, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.	*See* the detailed explanation above for claim 8.
170. The process of claim 166, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate,	*See* the detailed explanation above for claim 9.

Table 11	
Claims of '080 Patent	*Le Person and Chen*
hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(α-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.	
178. The process of claim 161, wherein said active is an opiate or opiate-derivative.	*See* the detailed explanation above for claim 17.
206. The process of claim 161, wherein said active is an anesthetic.	*See* the detailed explanation above for claim 45.
214. The process of claim 161, wherein said active is an analgesic.	*See* the detailed explanation above for claim 53.
232. The process of claim 161, further comprising adding a degassing agent to said flowable polymer matrix.	*See* the detailed explanation above for claim 71.
254. The process of claim 1, wherein said resulting film has a variation of active content of less than 10% per film unit.	To the extent that films of *Le Person* do not have a variation of active content of less than 10% per film unit, *Chen* teaches this feature. *See* the explanation in Table 1.
272. The process of claim 82, wherein said resulting film has a variation of active content of less than 10% per film unit.	*See* the detailed explanation above for claim 254.

Table 11	
Claims of '080 Patent	*Le Person and Chen*
290. The process of claim 161, wherein said resulting film has a variation of active content of less than 10% per film unit.	*See* the detailed explanation above for claim 254.

D. Claim Charts Applying *Horstmann* as Sole or Primary reference

There are three independent claims in the '080 Patent, claims 1, 82, and 161. *Horstmann* anticipates all these independent claims, and further, anticipates a large number of dependent claims as set forth in detail in Table 12.

Table 12. Proposed rejection of claims 1, 5, 7-10, 12-14, 23, 63, 64, 82, 84, 86-89, 91-93, 102, 142, 143, 161, 166, 168-171, 173-175, 184, 224, 225, 249, 254, 267, 272, 285, and 290 under 35 U.S.C. § 102(b) as anticipated by *Horstmann*

Table 12	
Claims of '080 Patent	*Horstmann*
1. A process for making a film having a substantially uniform distribution of components, comprising the steps of:	*Horstmann* teaches rapidly dissolvable films for the delivery of drugs which are processed by methods that result in uniform films. *See* col. 1, lines 10-12; col. 3, lines 7-10, 20-35 and 39-47; and Abstract.
(a) forming a masterbatch pre-mix comprising a solvent and a polymer selected from the group consisting of water-soluble polymers, water-swellable polymers and combinations thereof;	*Horstmann* discloses forming a masterbatch pre-mix of components prior to adding the active. *See* Examples 1, 3 and 4. The premix includes a water soluble polymer (*e.g.*, acetylated starch)[10], and a solvent (*e.g.*, water). *See e.g.*, col. 3, line 62 through col. 4, line 6. The premix is homogenized by stirring. Examples 1, 3, and 4.

[10] Acetylated starch is a chemically modified (*i.e.*, acetylated) water-soluble amylose polymer that forms flexible, water-soluble films. It is a particularly stable against heat and acids, and is a common food additive.

Table 12	
Claims of '080 Patent	*Horstmann*
(b) adding an active to a pre-determined amount of said masterbatch pre-mix to form a flowable polymer matrix, said matrix having a substantially uniform distribution of said active;	Therapeutic agents are then added to the homogeneous pre-mix, until they are uniformly dispersed or dissolved in the matrix. *See* Examples 1, 3, and 4. The amount of the masterbatch pre-mix is pre-determined as indicated, *e.g.*, by the ingredients list providing the wet composition. *Id.*
(c) casting said flowable polymer matrix;	The resulting mixture is cast, *e.g.,* by spreading onto a siliconized paper with a coating device at a set gap width. *See e.g.,* Examples 1, 3, and 4.
(d) evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film within about 10 minutes or fewer to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film; and	*Horstmann* teaches removing at least a portion of the polar solvent from the cast matrix in 10 minutes, all of which are within the "about 10 minutes of fewer" recitation taking the broadest reasonable interpretation. *See* Example 3 and col. 4, lines 39-41. *Horstmann*'s films are viscoelastic in that they can be peeled and packaged as described in Examples 1, 3 and 4. *Horstmann* prepares its films from a coating solution with a homogeneous mixture of ingredients, which "result[s] in uniform films." *See* col. 3, lines 19-41 and Examples 1, 3 and 4. *Horstmann* performs the same process steps as here claimed.
(e) forming a resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained.	*Horstmann* discloses the step of forming a film by removing water from the matrix using the same process step recited in the instant claims. Examples 1, 3 and 4. *Horstmann* exemplifies drying cast polymer matrices with an initial amount of water of about 20%-33%. *See* Examples 1, 3 and 4. Since *Horstmann* teaches forming a matrix with far less water than many of the embodiments and examples of the '080 Patent (*See e.g.*, A-I and BA-BI and col. 14, lines 55-59), the films of *Horstmann* would necessarily have less than 10% water content because

Table 12	
Claims of '080 Patent	*Horstmann*
	Horstmann employs the same method recited in the instant claim. Indeed, the film of *Horstmann* is viscoelastic and meets the other desired properties, as it is made using the same materials and dried according to the same method recited in this claim. As set forth in MPEP 2112.01 (I): "[w]here the claimed and prior art products are identical or substantially identical in structure or composition, or **are produced by identical or substantially identical processes**, a prima facie case of either anticipation or obviousness has been established." (emphasis added) Thus, *Horstmann*'s films would be as viscoelastic within a 10 minute time period as the films of the '080 Patent, as they are **produced by identical or substantially identical processes** as the process claimed in the '080 Patent. As such, *Horstmann* anticipates this feature. *Horstmann* also discloses and demonstrates that its resulting films are formed while maintaining the substantially uniform distribution of active. *See* col. 3, lines 39-41. Additionally, as set forth in the Declaration of Dr. Cohen, a process engineer with over 45 year of experience in the field of coating and drying: In general, as a homogeneous or completely dispersed coating mixture is dried, the solvent is removed, the viscosity increases and the active would be more firmly fixed in place. When working with a homogeneous or completely dissolved coating mixture, for example, it would be difficult for a person of ordinary skill in the thin film art not to obtain a film that has uniform content of active.

Table 12	
Claims of '080 Patent	*Horstmann*
	Declaration of Dr. Cohen, ¶ 9 (Exhibit L).
5. The process of claim 1, wherein said polymer comprises a polymer selected from the group consisting of cellulose, a cellulose derivative, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyvinyl copolymers, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arrag gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof, alone or in combination with polyethylene oxide.	*Horstmann* teaches that the polymer can include, *e.g.*, polyvinyl pyrrolidone, polyvinyl alcohol, and polyethylene glycol. *See* col. 3, line 60; and col. 4, lines 1-6.
7. The process of claim 5, wherein said polymer further comprises a polymer selected from the group consisting of methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(α-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof.	*Horstmann* teaches that the polymers can include, *e.g.*, polymeric carbohydrates, poly acrylic acid and polypeptides. *See* col. 4, lines 1-6; and col. 6, line 38. Polypeptides are polyamino acids.
8. The process of claim 5, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arrag gum,	*Horstmann* teaches that the polymers can include, *e.g.*, carrageenan, dextran, tragacanth, gelatin, and gums of vegetable origin. *See* col. 3, line 65 through col. 4, line 6.

Table 12	
Claims of '080 Patent	*Horstmann*
starch, gelatin, arrageenan, locust bean gum, dextran, gellan gum and combinations thereof.	
9. The process of claim 5, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(d-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arrag gum, starch, gelatin, arrageenan, locust bean gum, dextran, gellan gum and combinations thereof.	*See* the detailed explanation for claims 7 and 8 in this Table.
10. The process of claim 1, wherein said solvent is selected from the group consisting of water, polar organic solvent, and combinations thereof.	*Horstmann* teaches that water may be used as the solvent. *See* Examples 1, 3 and 4. *Horstmann* also teaches that up to 30% wt of a polar solvent may be added in the process. *See* col. 3, lines 29-33.
12. The process of claim 1, wherein said active is selected from the group consisting of bioactive active, pharmaceutical actives, drugs, medicaments and combinations	*Horstmann* teaches that drugs can be included in its claimed sheet-like dosage units. *See* col. 3, lines 20-22.

Table 12	
Claims of '080 Patent	*Horstmann*
thereof.	
13. The process of claim 1, wherein said active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking	*Horstmann* teaches that glibenclamide can be used in its claimed invention. *See* Example 2. Glibenclamide is a well-known anti-diabetic drug.

Table 12	
Claims of '080 Patent	*Horstmann*
cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, anti-tumor drugs, anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, anti-convulsants, neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, anti-asthmatics, cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.	
14. The process of claim 1, wherein said active is selected from the group consisting of cosmetic actives, antigens, allergens, spores, microorganisms, *See*ds, mouthwash components, flavors, fragrances, enzymes, preservatives, sweetening agents, colorants, spices, vitamins and combinations thereof.	*Horstmann* teaches that confectionary, other food and cosmetics can be included in its claimed sheet-like dosage units. *See* col. 3, lines 20-22.
23. The process of claim 1, wherein said active is an anti-diabetic.	*See* the detailed explanation for claim 13 in this Table.
63. The process of claim 1, wherein said active is taste-masked.	*Horstmann* teaches that a taste-masking agent, such as peppermint oil, may be included. *See* Examples 1, 3 and 4.
64. The process of claim 1, wherein said	*Horstmann* teaches that a taste-masking agent, such as peppermint oil or honey, may be

Table 12	
Claims of '080 Patent	*Horstmann*
active is taste-masked using a flavor.	included. *See* Examples 1 and 4.
82. A process for making a film having a substantially uniform distribution of components, comprising the steps of:	*Horstmann* teaches rapidly dissolvable films for the delivery of drugs which are processed by methods that result in uniform films. *See* col. 1, lines 10-12, col. 3, lines 7-10, 20-35 and 39-47, and Abstract.
(a) forming a flowable polymer matrix comprising a polymer selected from the group consisting of a water-soluble polymer, a water swellable polymer and combinations thereof, a solvent and an active selected from the group consisting of bioactive actives, pharmaceutical actives, drugs, medicaments and combinations thereof, said matrix having a substantially uniform distribution of said active;	*Horstmann* discloses forming a flowable matrix that includes a water soluble polymer, *e.g.*, acetylated starch, a solvent, *e.g.*, water, and an active. The ingredients are uniformly dispersed or dissolved in the matrix. *See* col. 3, lines 20-29, and Example 3.
(b) casting said flowable polymer matrix;	The resulting mixture is cast, *e.g.,* by spreading onto a siliconized paper with a coating device at a set gap width. *See e.g.,* Example 3, col. 5, lines 51-53.
(c) evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film within about 10 minutes or fewer to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film; and	*Horstmann* teaches removing at least a portion of the polar solvent from the cast matrix in 10 minutes, all of which are within the "about 10 minutes of fewer" recitation taking the broadest reasonable interpretation. *See* Example 3 and col. 4, lines 39-41. *Horstmann*'s films are viscoelastic in that they can be peeled and packaged as described in Examples 1, 3 and 4. *Horstmann* prepares its films from a coating solution with a homogeneous mixture of ingredients, which "result[s] in uniform films." *See* col. 3, lines 19-41 and Examples 1, 3 and 4. *Horstmann* performs the same process steps as here claimed.

Table 12	
Claims of '080 Patent	*Horstmann*
	Also, the film of *Horstmann* is viscoelastic and meets the other desired properties, as it is made using the same materials and dried according to the same method recited in this claim. As set forth in MPEP 2112.01 (I): "[w]here the claimed and prior art products are identical or substantially identical in structure or composition, or **are produced by identical or substantially identical processes**, a prima facie case of either anticipation or obviousness has been established." (emphasis added) Thus, *Horstmann*'s films would be as viscoelastic within a 10 minute time period as the films of the '080 Patent, as they are **produced by identical or substantially identical processes** as the process claimed in the '080 Patent. As such, *Horstmann* anticipates this feature.
(d) forming a resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained.	*Horstmann* discloses the step of forming a film by removing water from the matrix using the same process step recited in the instant claims. Examples 1, 3 and 4. *Horstmann* exemplifies drying cast polymer matrices with an initial amount of water of about 20%-25%. *See* Examples 1, 3 and 4. Since *Horstmann* teaches forming a matrix with far less water than many of the embodiments and examples of the '080 Patent (*See e.g.*, A-I and BA-BI and col. 14, lines 55-59), the films of *Horstmann* would necessarily have less than 10% water content because *Horstmann* employs the same method recited in the instant claim. *Horstmann* also discloses and demonstrates that its resulting films are formed while maintaining the substantially uniform distribution of active. *See* col. 3, lines 39-41.

Table 12	
Claims of '080 Patent	*Horstmann*
	Additionally, as set forth in the Declaration of Dr. Cohen, a process engineer with over 45 year of experience in the field of coating and drying: In general, as a homogeneous or completely dispersed coating mixture is dried, the solvent is removed, the viscosity increases and the active would be more firmly fixed in place. When working with a homogeneous or completely dissolved coating mixture, for example, it would be difficult for a person of ordinary skill in the thin film art not to obtain a film that has uniform content of active. Declaration of Dr. Cohen, ¶ 9 (Exhibit L).
84. The process of claim 82, wherein said polymer comprises a polymer selected from the group consisting of cellulose, a cellulose derivative, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyvinyl copolymers, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof, alone or in combination with polyethylene oxide.	*See* the detailed explanation for claim 5 in this Table.
86. The process of claim 84, wherein said polymer further comprises a polymer selected from the group consisting of methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol	*See* the detailed explanation for claim 7 in this Table.

Table 12	
Claims of '080 Patent	*Horstmann*
copolymers, polydioxanones, polyoxalates, poly(α-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof.	
87. The process of claim 84, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.	*See* the detailed explanation for claim 8 in this Table.
88. The process of claim 84, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(α-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan	*See* the detailed explanation for claim 9 in this Table.

Table 12	
Claims of '080 Patent	*Horstmann*
gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.	
89. The process of claim 82, wherein said solvent is selected from the group consisting of water, polar organic solvent, and combinations thereof.	*See* the detailed explanation for claim 9 in this Table.
91. The process of claim 82, wherein said active is selected from the group consisting of bioactive active, pharmaceutical actives, drugs, medicaments and combinations thereof.	*See* the detailed explanation for claim 12 in this Table.
92. The process of claim 82, wherein the active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents,	*See* the detailed explanation for claim 13 in this Table.

Table 12	
Claims of '080 Patent	*Horstmann*
enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, anti-tumor drugs, anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, anti-convulsants, neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, anti-asthmatics, cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.	
93. The process of claim 82, wherein said active is selected from the group consisting of cosmetic actives, antigens, allergens, spores, microorganisms, *See*ds, mouthwash	*See* the detailed explanation for claim 14 in this Table.

Table 12	
Claims of '080 Patent	*Horstmann*
components, flavors, fragrances, enzymes, preservatives, sweetening agents, colorants, spices, vitamins and combinations thereof.	
102. The process of claim 82, wherein said active is an anti-diabetic.	*See* the detailed explanation for claim 23 in this Table.
142. The process of claim 82, wherein said active is taste-masked.	*See* the detailed explanation for claim 63 in this Table.
143. The process of claim 82, wherein said active is taste-masked using a flavor.	*See* the detailed explanation for claim 64 in this Table.
161. A process for making a film capable of being administered to a body surface having a substantially uniform distribution of components, comprising the steps of: (a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and an active, said matrix having a substantially uniform distribution of said active; (b) casting said flowable polymer matrix; (c) evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film within about 10 minutes or fewer to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film; (d) forming a resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained; and (e) administering said resulting film to a	Claim 161 is substantially similar to claim 82, but additionally recites that the film is "capable of being administered to a body surface" (preamble) and the last step "(e) administering said resulting film to a body surface." *See* claim 82 in this Table for the detailed discussion of *Horstmann*'s disclosure of the recited process. With respect to the preamble recitation of a film "capable" of being administered to a body surface, *Horstmann* discloses films made from the same materials and made by the same methods claimed in the '080 Patent. As such the films of *Horstmann* are as "capable" of being administered to a body surface as the films of claims 82 and 161. Moreover, administration of the films of *Horstmann* to a body surface, *e.g.*, mouth and teeth is discussed in Examples 1-4 and col. 3, lines 20-23. To the extent that step (a) differs between the claims, step (a) is broader in claim 161 than claim 82 and is anticipated for the same reasons disclosed above. Step (e) does not require drug delivery, only administering the film to a body surface. As

Table 12	
Claims of '080 Patent	*Horstmann*
body surface.	such, this claim is anticipated by *Horstmann*'s disclosure of the use of the films for, *e.g.*, toothpaste in Example 3. Administration of drugs to the body is also clearly taught at, *e.g.*, col. 3, lines 20-29, where the films would not only be administered to the body, but would also deliver the drug to the body.
166. The process of claim 161, wherein said polymer comprises a polymer selected from the group consisting of cellulose, a cellulose derivative, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyvinyl copolymers, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof, alone or in combination with polyethylene oxide.	*See* the detailed explanation for claim 5 in this Table.
168. The process of claim 166, wherein said polymer further comprises a polymer selected from the group consisting of methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(α-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and	*See* the detailed explanation for claim 7 in this Table.

Table 12	
Claims of '080 Patent	*Horstmann*
copolymers thereof.	
169. The process of claim 166, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.	*See* the detailed explanation for claim 8 in this Table.
170. The process of claim 166, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(α-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.	*See* the detailed explanation for claim 9 in this Table.
171. The process of claim 161, wherein said solvent is selected from the group	*See* the detailed explanation for claim 10 in this

Table 12	
Claims of '080 Patent	*Horstmann*
consisting of water, polar organic solvent, and combinations thereof.	Table.
173. The process of claim 161, wherein said active is selected from the group consisting of bioactive active, pharmaceutical actives, drugs, medicaments and combinations thereof.	*See* the detailed explanation for claim 12 in this Table.
174. The process of claim 161, wherein said active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle	*See* the detailed explanation for claim 13 in this Table.

Table 12	
Claims of '080 Patent	*Horstmann*
relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, anti-tumor drugs, anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, anti-convulsants, neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, anti-asthmatics, cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.	
175. The process of claim 161, wherein said active is selected from the group consisting of cosmetic actives, antigens, allergens, spores, microorganisms, *See*ds, mouthwash components, flavors, fragrances, enzymes, preservatives, sweetening agents, colorants, spices, vitamins and combinations thereof.	*See* the detailed explanation for claim 14 in this Table.
184. The process of claim 161, wherein said active is an anti-diabetic.	*See* the detailed explanation for claim 23 in this Table.
224. The process of claim 161, wherein said	*See* the detailed explanation for claim 63 in this

Table 12	
Claims of '080 Patent	*Horstmann*
active is taste-masked.	Table.
225. The process of claim 161, wherein said active is taste-masked using a flavor.	*See* the detailed explanation for claim 64 in this Table.
249. The process of claim 1, wherein said resulting film provides administration of said active to an individual through the buccal cavity of said individual.	*Horstmann* teaches that its formulations disintegrate in the mouth within 10 minutes. *See* col. 3, lines 44-46.
254. The process of claim 1, wherein said resulting film has a variation of active content of less than 10% per film unit.	This limitation is met by the homogenous films of *Horstmann*, which were made by the same basic methods recited in this claim. *Horstmann* also discloses its films are uniform. *See* col. 3, lines 39-41.
267. The process of claim 82, wherein said resulting film provides administration of said active to an individual through the buccal cavity of said individual.	*See* the detailed explanation for claim 249 in this Table.
272. The process of claim 82, wherein said resulting film has a variation of active content of less than 10% per film unit.	*See* the detailed explanation for claim 254 in this Table.
285. The process of claim 161, wherein said resulting film provides administration of said active to an individual through the buccal cavity of said individual.	*See* the detailed explanation for claim 249 in this Table.
290. The process of claim 161, wherein said resulting film has a variation of active content of less than 10% per film unit.	*See* the detailed explanation for claim 254 in this Table.

Table 13. Proposed rejection of claims 1, 4, 13, 15, 17, 45, 53, 71, 82, 83, 92, 94, 96, 124, 132, 150, 161, 165, 174, 176, 178, 206, 214, and 232 under 35 USC § 103 as obvious over *Horstmann* in view of *Chen*

Table 13	
Claims of '080 Patent	*Horstmann* and *Chen*
1. A process for making a film having a substantially uniform distribution of components, comprising the steps of: (a) forming a masterbatch pre-mix comprising a solvent and a polymer selected from the group consisting of water-soluble polymers, water-swellable polymers and combinations thereof; (b) adding an active to a pre-determined amount of said masterbatch pre-mix to form a flowable polymer matrix, said matrix having a substantially uniform distribution of said active; (c) casting said flowable polymer matrix; (d) evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film within about 10 minutes or fewer to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film; and (e) forming a resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained.	*See* the detailed explanation with respect to the anticipation of this claim by *Horstmann* in Table 12. To the extent it is believed that *Horstmann* does not disclose methods that result in films having a water content of 10% or less (as recited in step (e)), *Chen* also describes each and every step of this claim and explicitly describes that the resulting films have a water content of less than 10%. Accordingly, *Chen* both evidences the inherent water content of *Horstmann* and, in the alternative, renders it obvious. *Horstmann* explicitly discloses that its films are uniform at the mixing stage and that uniformity is maintained throughout the casting and drying stage so that the final film is also uniform. *See e.g., Horstmann*, Abstract, Example 3, and col. 3, lines 29-34 and 39-41. To the extent it is deemed that the uniformity of *Horstmann* doesn't meet the "substantially uniform distribution of active" recitations in this claim, *Chen* also describes each and every step of this claim and explicitly demonstrates the uniformity of active its films to the same degree and using the same criteria as set forth in the '080 Patent. One would have been motivated to combine these two references to provide films with uniform distribution of active to provide a safe and effective dosage form.
4. The process of claim 1, wherein said water-soluble polymer comprises	*Chen* discloses where the water-soluble polymer includes one or more polyethylene oxides. *Chen*,

Table 13	
Claims of '080 Patent	*Horstmann* and *Chen*
polyethylene oxide.	p. 14, line 29. This claim is obvious in that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art. MPEP § 2143 (A).
13. The process of claim 1, wherein said active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and	To the extent it is believed that *Horstmann* does not teach the actives recited in claim 13, *Chen* teaches that active agents also include analgesics, a-adrenergic receptor blockers, anti-Alzheimer's disease medication, antianginal, antianxiety, antiarrythmics, antiarthritics, antibiotics, anticoagulants/thrombolytics, anticonvulsants/anti-Parkinson medication, anti- depressants, anti-diabetics, anti-dianheal. anti-epileptics, anti-fungal, anti-gout, anti- heartworm medication for dogs, anti-histamines, anti-hypertensives, anti-inflammatories, anti-infectives, antimigranes, anti-nasuants/anti-emetics, anti-neoplastics/anti-tumor active agents, anti-pruitics, anti-psychotics, anti-pyretics, anti-spasmodics, anti-virals, bronchial dilators/anti-asthmatics, calcium antagonists, cardiac agents, cardiotonics, central nervous system actives, contraceptives, coronary vasodilators, cough/cold remedies, dietary supplements, including vitamins and minerals, and other drugs. *See* page 10, line 23 through page 11, line 12. It would have been obvious for one skilled in the art to apply the different actives taught in *Chen* to the Hostmann's films, as all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their

Table 13	
Claims of '080 Patent	*Horstmann* and *Chen*
hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, anti-tumor drugs, anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, anti-convulsants, neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, anti-asthmatics, cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.	respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art. MPEP § 2143 (A).
15. The process of claim 1, wherein said active is a bioactive active.	To the extent that *Horstmann* does not disclose a bioactive active, *Chen* discloses that the active agent can be proteins such as insulin at page 11, line 4. The reason that the combination of *Horstmann* with *Chen* is obvious in provided in claim 13 above.

Table 13	
Claims of '080 Patent	*Horstmann* and *Chen*
17. The process of claim 1, wherein said active is an opiate or opiate-derivative.	To the extent that *Horstmann* does not disclose an opiate or opiate-derivative as an active, *Chen* discloses that the active agent can be an anesthetic. *Chen*, page 11, line 9. An opiate or opiate-derivative is one of anesthetics. The reason that the combination of *Horstmann* with *Chen* is obvious in provided in claim 13 above.
45. The process of claim 1, wherein said active is an anesthetic.	To the extent that *Horstmann* does not disclose an anesthetic as an active, *Chen* discloses that the active agent can be an anesthetic. *Chen*, page 11, line 9. The reason that the combination of *Horstmann* with *Chen* is obvious in provided in claim 13 above.
53. The process of claim 1, wherein said active is an analgesic.	To the extent that *Horstmann* does not disclose an anesthetic as an analgesic, *Chen* discloses that the active agent can be an analgesic at page 10, line 24. The reason that the combination of *Horstmann* with *Chen* is obvious in provided in claim 13 above.
71. The process of claim 1, further comprising adding a degassing agent to said masterbatch premix.	The term "degassing agent" is not defined in the specification and appears only in the claims of the '080 Patent. Yet, during the prosecution of US Application No. 11/858,214, a related patent application owned by Applicant, Applicant noted, in the response to the Office Action filed December 20, 2010 (Exhibit O), that peppermint oil is one of foam reducing flavoring agents which "act to both flavor the film and prevent and/or **remove air** from the film-forming compositions." *See* page 3, claim 5; and page 5, last paragraph. (emphasis added) *Chen* teaches using peppermint oil as a component in its films. *See* Table 3 at page 19. As such, claim 71 is anticipated by *Chen*. To the extent that *Chen* does not explicitly

Table 13	
Claims of '080 Patent	*Horstmann* and *Chen*
	disclose adding peppermint oil to its masterbatch premix, this is an obvious choice since a person of ordinary skill would be motivated to avoid gas from the outset by adding the oil to a premix. As set forth in MPEP § 2143(E), if a person of ordinary skill has good reason to pursue the known options within his or her technical grasp, and if this leads to the anticipated success, it is likely that product was not of innovation but of ordinary skill and common sense.
82. A process for making a film having a substantially uniform distribution of components, comprising the steps of: (a) forming a flowable polymer matrix comprising a polymer selected from the group consisting of a water-soluble polymer, a water swellable polymer and combinations thereof, a solvent and an active selected from the group consisting of bioactive actives, pharmaceutical actives, drugs, medicaments and combinations thereof, said matrix having a substantially uniform distribution of said active; (b) casting said flowable polymer matrix; (c) evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film within about 10 minutes or fewer to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film; and (d) forming a resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially	*See* the detailed explanation with respect to claim 1 in this Table.

Table 13	
Claims of '080 Patent	*Horstmann* and *Chen*
preventing migration of said active is maintained.	
83. The process of claim 82, wherein said water-soluble polymer comprises polyethylene oxide.	*See* the detailed explanation for claim 4 in this Table.
92. The process of claim 82, wherein the active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity	*See* the detailed explanation for claim 13 in this Table.

Table 13	
Claims of '080 Patent	*Horstmann* and *Chen*
management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, anti-tumor drugs, anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, anti-convulsants, neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, anti-asthmatics, cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.	
94. The process of claim 82, wherein said active is a bioactive active.	*See* the detailed explanation for claim 15 in this Table.
96. The process of claim 82, wherein said active is an opiate or opiate-derivative.	*See* the detailed explanation for claim 17 in this Table.
124. The process of claim 82, wherein said active is an anesthetic.	*See* the detailed explanation for claim 45 in this Table.
132. The process of claim 82, wherein said	*See* the detailed explanation for claim 53 in this

Table 13	
Claims of '080 Patent	*Horstmann* and *Chen*
active is an analgesic.	Table.
150. The process of claim 82, further comprising adding a degassing agent to said flowable polymer matrix.	*See* the detailed explanation for claim 71 in this Table.
161. A process for making a film capable of being administered to a body surface having a substantially uniform distribution of components, comprising the steps of: (a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and an active, said matrix having a substantially uniform distribution of said active; (b) casting said flowable polymer matrix; (c) evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film within about 10 minutes or fewer to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film; (d) forming a resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained; and (e) administering said resulting film to a body surface.	*See* the detailed explanation with respect to claim 1 in this Table.
165. The process of claim 161, wherein said water-soluble polymer comprises polyethylene oxide.	*See* the detailed explanation for claim 4 in this Table.
174. The process of claim 161, wherein said active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics,	*See* the detailed explanation for claim 13 in this Table.

Table 13	
Claims of '080 Patent	*Horstmann* and *Chen*
anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-	

Table 13	
Claims of '080 Patent	*Horstmann* and *Chen*
anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, anti-tumor drugs, anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, anti-convulsants, neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, anti-asthmatics, cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.	
176. The process of claim 161, wherein said active is a bioactive active.	*See* the detailed explanation for claim 15 in this Table.
178. The process of claim 161, wherein said active is an opiate or opiate-derivative.	*See* the detailed explanation for claim 17 in this Table.
206. The process of claim 161, wherein said active is an anesthetic.	*See* the detailed explanation for claim 45 in this Table.
214. The process of claim 161, wherein said active is an analgesic.	*See* the detailed explanation for claim 53 in this Table.
232. The process of claim 161, further comprising adding a degassing agent to said flowable polymer matrix.	*See* the detailed explanation for claim 71 in this Table.

E. Proposed Rejection of claim 82 under 35 USC § 101 as Statutory Double Patenting in view of claim 25 of Parent US Patent No. 7,666,337

Typically, rejections in a reexamination proceeding are based on "prior art" patents and publications. There are exceptions, however. MPEP § 2258. The issue of double patenting is appropriate for consideration in reexamination, both as a basis for ordering reexamination and during subsequent examination on the merits. MPEP § 2258 (I)(D), *citing, In re Lonardo*, 119 F.3d 960, 43 USPQ2d 1262 (Fed. Cir. 1997).

As a preliminary matter, "[b]efore consideration can be given to the issue of double patenting, two or more patents or applications must have at least one common inventor and/or be either commonly assigned/owned or non-commonly assigned/owned but subject to a joint research agreement…." MPEP § 804. In the instant case, the '337 Patent and the '080 Patent are commonly owned and share the same four inventors. Accordingly, consideration of double patenting is appropriate between these two patents. MPEP § 804.[11]

The MPEP § 804(II)(A) provides the framework for determining whether a statutory basis exists for a double patenting rejection:

> In determining whether a statutory basis for a double patenting rejection exists, the question to be asked is: Is the same invention being claimed twice? 35 U.S.C. § 101 prevents two patents from issuing on the same invention. "Same invention" means identical subject matter. *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1984); *In re Vogel,* 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957).
>
> A reliable test for double patenting under 35 U.S.C. § 101 is whether a claim in the application could be literally infringed without literally infringing a corresponding claim in the patent. *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970). Is there an embodiment of the invention that falls within the scope of one claim, but not the other? If there is such an embodiment, then identical subject matter is not defined by both claims and statutory double patenting would not exist. For example, the invention defined by a claim

[11] Indeed, an obviousness-type double patenting rejection was made during the prosecution of this case over the '080 Patent, and a terminal disclaimer filed to obviate it. The terminal disclaimer, however, cannot be filed to obviate a statutory double patenting rejection under 35 USC § 101. MPEP § 804.

> reciting a compound having a "halogen" substituent is not identical to or substantively the same as a claim reciting the same compound except having a "chlorine" substituent in place of the halogen because "halogen" is broader than "chlorine." On the other hand, claims may be differently worded and still define the same invention. Thus, a claim reciting a widget having a length of "36 inches" defines the same invention as a claim reciting the same widget having a length of "3 feet."
>
> If it is determined that the same invention is being claimed twice, 35 U.S.C. § 101 precludes the grant of the second patent regardless of the presence or absence of a terminal disclaimer. *Id.*

Although the original Examiner of the '080 Patent did present a nonstatutory obviousness-type double patenting rejection over the '337 Patent, he may have missed the instant statutory double patenting rejection because there are some wording differences that – although they result in the same invention being claimed – may have been difficult to analyze given the extraordinarily large numbers of claims presented in the '080 Patent. For the sake of convenience, a redlined version of claim 82 of the '080 Patent is provided below in comparison to claim 25 of the '337 Patent:

> [[25.]] 82. A process for making a film having a substantially uniform distribution of components, comprising the steps of:
>
> (a) forming a flowable polymer matrix comprising a polymer selected from the group consisting of a water-soluble polymer, a water swellable polymer and combinations thereof, a solvent and an active[[,]] selected from the group consisting of bioactive actives, pharmaceutical actives, drugs, medicaments and combinations thereof, said matrix having a substantially uniform distribution of said active;
>
> (b) casting said flowable polymer matrix;
>
> (c) evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film within about 10 minutes or fewer to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film; and
>
> (d) forming a resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially

> uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained.

A copy of the '337 Patent is attached as Exhibit P.

With respect to step (a), a brief review of Applicant's own specification demonstrates that there is no difference between the scope of the following recitations:

'337 Patent Claim 25 Language	'080 Patent Claim 82 Language
a flowable polymer matrix comprising a water-soluble polymer	a flowable polymer matrix comprising a polymer selected from the group consisting of a water-soluble polymer, a water swellable polymer and combinations thereof

While, at first blush, the recitation of claim 25 of the '337 Patent might appear to be narrower than the recitation of claim 82, a brief review of the specification clarifies that Applicant has defined the term "water soluble polymer" to be coextensive with the term "water swellable polymer":

> As used herein the phrase "water soluble polymer" and variants thereof refer to a polymer that is at least partially soluble in water, and desirably fully or predominantly soluble in water, or absorbs water. Polymers that absorb water are often referred to as being water swellable polymers.
>
> The '080 Patent, col. 15, lines 62-66. (emphasis added).

Since Applicant has chosen to be its own lexicographer, Applicant must abide by its own definition and usage. "Where an explicit definition is provided by the applicant for a term, that definition will control interpretation of the term as it is used in the claim." MPEP § 2111.01, citing, *Toro Co. v. White Consolidated Industries Inc.*, 199 F.3d 1295, 1301, 53 USPQ2d 1065, 1069 (Fed. Cir. 1999). In the present case, the scope of the flowable polymer matrix recitation appears to be identical in both claims.

Again, as is well stated in the MPEP: A reliable test for double patenting under 35 U.S.C. § 101 is whether a claim in the application could be literally infringed without literally

infringing a corresponding claim in the patent. *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970). Is there an embodiment of the invention that falls within the scope of one claim, but not the other? In the present case, given the specification the Applicant's own definition, the answer is "no".[12]

Similarly, with respect to the active recited in both claims, while different words are used, no difference in scope can be discerned:

'337 Patent Claim 25 Language	'080 Patent Claim 82 Language
an active	an active selected from the group consisting of bioactive actives, pharmaceutical actives, drugs, medicaments and combinations thereof,

In this case, Applicant has merely collected a group of terms to recite a Markush of actives that is co-extensive with the term "active". One of skill in the art would understand that "bioactive actives, pharmaceutical actives, drugs, medicaments and combinations thereof" is coextensive with "actives." Again, employing the test set forth in the MPEP § 804(II)(A), there is no embodiment of the invention that would fall within one claim and not the other. Accordingly, the claims define the same invention.

[12] The fact that claim 82 of the '080 Patent recites both terms "and combinations thereof" does not negate Applicant's own definition and usage. This is because "[a]lthough claims of issued patents are interpreted in light of the specification, prosecution history, prior art and other claims, this is not the mode of claim interpretation to be applied during examination. During examination, the claims must be interpreted as broadly as their terms reasonably allow." MPEP § 2111.01, citing, *In re American Academy of Science Tech Center*, 367 F.3d 1359, 1369, 70 USPQ2d 1827, 1834 (Fed. Cir. 2004). Accordingly, for the purposes of reexamination, such interpretation is not appropriate. Instead, the Examiner must apply the broadest reasonable interpretation. MPEP §§ 2111, 2258(I)(G) and 2658(I).

Finally, the only other wording difference between these claims is the recitation of "substantially uniform" as opposed to "uniform" when referring to the distribution of the active in steps (a), (c), and (d).

'337 Patent Claim 25 Language	'080 Patent Claim 82 Language
uniform distribution of said active	substantially uniform distribution of said active

Again, while at first blush, the recitations appear to differ in scope, there is significant information provided in the specification that indicates that these terms are co-extensive. As stated in the MPEP § 804, "claims may be differently worded and still define the same invention."

First, no distinction between the terms "substantially uniform" and "uniform" as applied to active variation is made or defined by the '080 Patent specification. Other than appearing many times in the '080 Patent claims, the term "substantially uniform" only appears once in the specification in the Summary of the Invention. Col. 4, line 51.

Second, Applicant has without ambiguity disavowed a claim scope – in both patents - where the uniformity of its films exceeds a 10% variation in its active content. Specifically, Applicant emphasizes, when distinguishing the inventive films from those in the prior art, that government regulatory agencies worldwide, including the U.S. Food and Drug Administration require no more than 10% variation in the amount of active present. *See* the '080 Patent, col. 2, lines 40-46; and the '337 Patent, col. 2, lines 38-44. "When applied to dosage units based on films, this virtually mandates that uniformity in the film be present." *Id.* Applicant chose to make these statements to distinguish the uniformity its films from the lack of uniformity of the prior art films. Col. 2, lines 7-47. "For this reason, dosage forms formed by processed such as Fuchs, would not likely meet the stringent standards of government or regulatory agencies, such as the U.S. Federal Drug Administration (FDA)…." Col. 2, lines 37-41. Applicant has clearly disavowed variance of more than 10% of active in distinguishing its inventive films from those

in the art. Accordingly, the term "substantially uniform distribution of active" – recited in the claims – at best, means a variation of less than 10%, as the remaining scope has been disavowed. This is the broadest reasonable interpretation of the claims, as is required in a reexamination proceeding.

At the same time, Applicant has also chosen to define what "uniformity" means when referring to distribution of active in the films of the present invention. It is defined as the presence of no more than 10% variance.

> ….Furthermore, such consideration with proper material selection provides the compositions of the present invention, including a pharmaceutical and/or cosmetic dosage form or film product having no more than a 10% variance of a pharmaceutical and/or cosmetic active per unit area. ***In other words, the uniformity of the present invention is determined by the presence of no more than a 10% by weight of pharmaceutical and/or cosmetic variance throughout the matrix***. Desirably, the variance is less than 5% by weight, less than 2% by weight, less than 1% by weight, or less than 0.5% by weight.
>
> The '080 Patent, col. 15, lines 32-42; and the '337 Patent, col. 15, lines 32-42 (emphasis added).

That is, under the broadest reasonable interpretation of the claims, the terms "uniformity" and "substantial uniformity" have both been defined and employed in the '080 Patent to mean less than 10% variation. These terms are co-extensive and there are no embodiments that fall within one claim and not the other.[13]

Finally, it is noted that remaining steps (b), (c), and (d) are identical except for the same recitation of "substantially uniform" dealt with directly above.

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[13] It is noted that although claim 254 -- added with 45 other new claims after the claims were examined – claims a variation of active content of no more than 10%. This should not be deemed by Examiner as an indication that claim 82 is broader in the context of a reexamination. This is because "[a]lthough claims of issued patents are interpreted in light of the specification, prosecution history, prior art and other claims, this is not the mode of claim interpretation to be applied during examination. During examination, the claims must be interpreted as broadly as their terms reasonably allow." MPEP § 2111.01, citing, *In re American Academy of Science Tech Center*, 367 F.3d 1359, 1369, 70 USPQ2d 1827, 1834 (Fed. Cir. 2004).

Accordingly, claim 82 of the '080 Patent and claim 25 of the '337 Patent are coextensive. In other words, they claim the same invention.

For at least these reasons set forth above and further discussed in the tables below, Requester respectfully submits that this Request demonstrates a reasonable likelihood of prevailing with respect to at least one of the claims challenged in this Request, and, as such, requests an order of *Inter Partes* Reexamination for all claims, *i.e.*, claims 1-299 of the '080 Patent.

F. Summary of Invalidity over the Prior Art

Requester submits that all of the claims for which reexamination are sought are unpatentable, for the reasons cited above. Requester respectfully requests that the Examiner address all of the asserted reasons why the claims should be rejected in this reexamination and apply each reason that the Examiner concludes are supported under the facts and law. Requester understands that under Patent Office practice, the Examiner is not to refuse to adopt a rejection properly proposed by a Requester, as being cumulative to other rejections applied, so that the Requester's proposed rejections are addressed, and the parties' respective rights to appeal are preserved. MPEP § 2660 III. Requester further understands that the Examiner should respond to each argument raised in the request, as well as address any issues proper for reexamination that the Examiner becomes aware of independent of the request. *Id.*

Requester appreciates the Examiner's consideration of the proposed rejections and arguments presented above and below. Requester recognizes that this reexamination presents a number of issues.

Requester has identified and discussed in detail sufficient prior art to provide the Patent Office a good understanding of the state of the art, without unduly burdening the Office with cumulative information. Similarly, Requester has attempted to set forth a number of examples of how the prior art renders unpatentable the claims sought to be reexamined, without setting forth every possible anticipation or obviousness argument that could be presented, depending on what

claim constructions and arguments Applicant might attempt to present. Requester expressly reserves its right to apply additional prior art and additional applications of prior art, depending on what argument and amendments Applicant might present. Requester also expressly reserves the right to cite and apply any additional art that it might discover as relevant to the issued claims or any amended claims, as the reexamination proceeds.

V. Conclusion

In view of the above, Requester has demonstrated a likelihood of prevailing with respect to at least one claim of the '080 Patent. Requester respectfully requests that this Request for Reexamination be granted and that the claims for which reexamination are requested, be rejected.

The undersigned stands ready to do anything she can do to assist the Office in its consideration, including providing the Office with an electronic copy of all or a portion of this Request. The undersigned welcomes a call or an email, should the Office have any requests or questions.

If there are any additional fees due in connection with the filing of this paper, please charge the fees to our deposit account No. 50-4876.

Respectfully submitted,

Dated: September 10, 2012

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LIST OF EXHIBITS

EXHIBIT A

US007897080B2

(12) **United States Patent**
Yang et al.

(10) **Patent No.: US 7,897,080 B2**
(45) **Date of Patent: *Mar. 1, 2011**

(54) **POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM**

(75) Inventors: **Robert K. Yang**, Flushing, NY (US); **Richard C. Fuisz**, McLean, VA (US); **Gary L. Myers**, Kingsport, TN (US); **Joseph M. Fuisz**, Washington, DC (US)

(73) Assignee: **MonoSol Rx, LLC**, Portage, IN (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **12/614,928**

(22) Filed: **Nov. 9, 2009**

(65) **Prior Publication Data**

US 2010/0092545 A1 Apr. 15, 2010

Related U.S. Application Data

(63) Continuation of application No. 10/856,176, filed on May 28, 2004, now Pat. No. 7,666,337, and a continuation-in-part of application No. 10/768,809, filed on Jan. 30, 2004, now Pat. No. 7,357,891, and a continuation-in-part of application No. PCT/US02/32575, filed on Oct. 11, 2002, and a continuation-in-part of application No. PCT/US02/32594, filed on Oct. 11, 2002, and a continuation-in-part of application No. PCT/US02/32542, filed on Oct. 11, 2002.

(60) Provisional application No. 60/473,902, filed on May 28, 2003, provisional application No. 60/443,741, filed on Jan. 30, 2003, provisional application No. 60/328,868, filed on Oct. 12, 2001, provisional application No. 60/386,937, filed on Jun. 7, 2002, provisional application No. 60/414,276, filed on Sep. 27, 2002, provisional application No. 60/371,940, filed on Apr. 11, 2002.

(51) **Int. Cl.**
B29C 39/14 (2006.01)

(52) **U.S. Cl.** **264/172.19**; 264/212; 264/217; 264/211.2; 264/234; 264/319; 264/344

(58) **Field of Classification Search** ..... None
See application file for complete search history.

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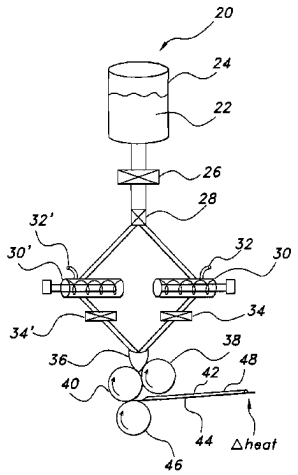
Primary Examiner—Edmund H. Lee
(74) *Attorney, Agent, or Firm*—Hoffmann & Baron, LLP

(57) **ABSTRACT**

The invention relates to the film products and methods of their preparation that demonstrate a non-self-aggregating uniform heterogeneity. Desirably, the films disintegrate in water and may be formed by a controlled drying process, or other process that maintains the required uniformity of the film. The films contain a polymer component, which includes polyethylene oxide optionally blended with hydrophilic cellulosic polymers. Desirably, the films also contain a pharmaceutical and/or cosmetic active agent with no more than a 10% variance of the active agent pharmaceutical and/or cosmetic active agent per unit area of the film.

299 Claims, 34 Drawing Sheets



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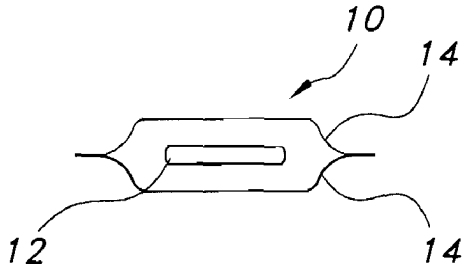


FIG. 1

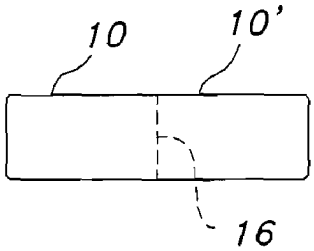


FIG. 2

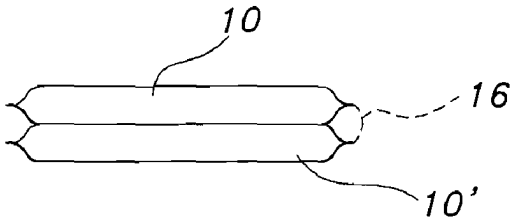
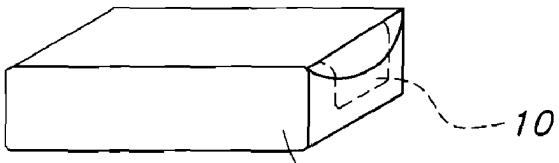


FIG. 3



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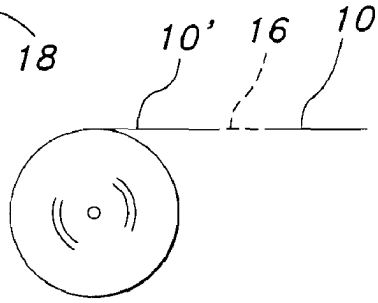


FIG. 5

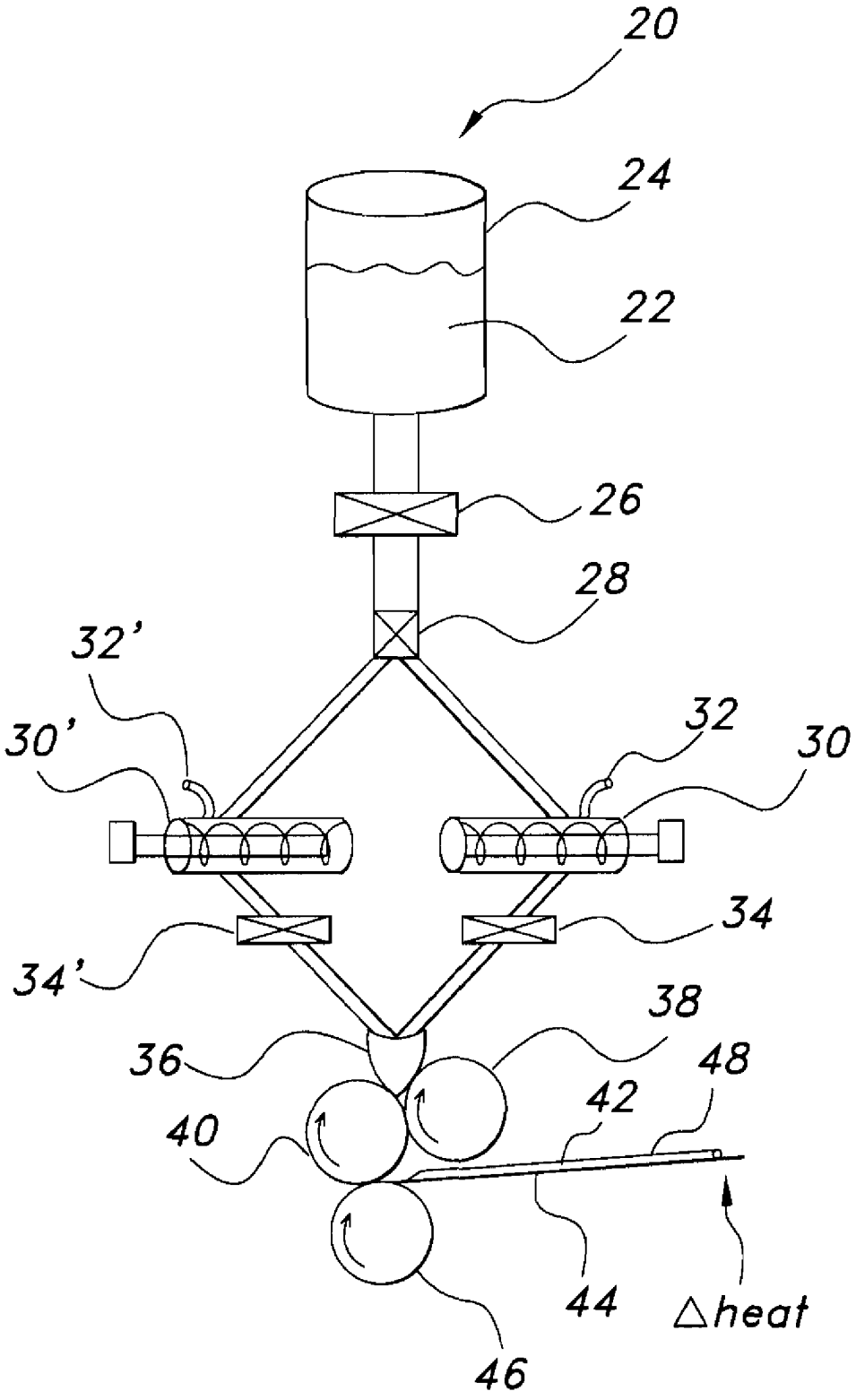


FIG. 6

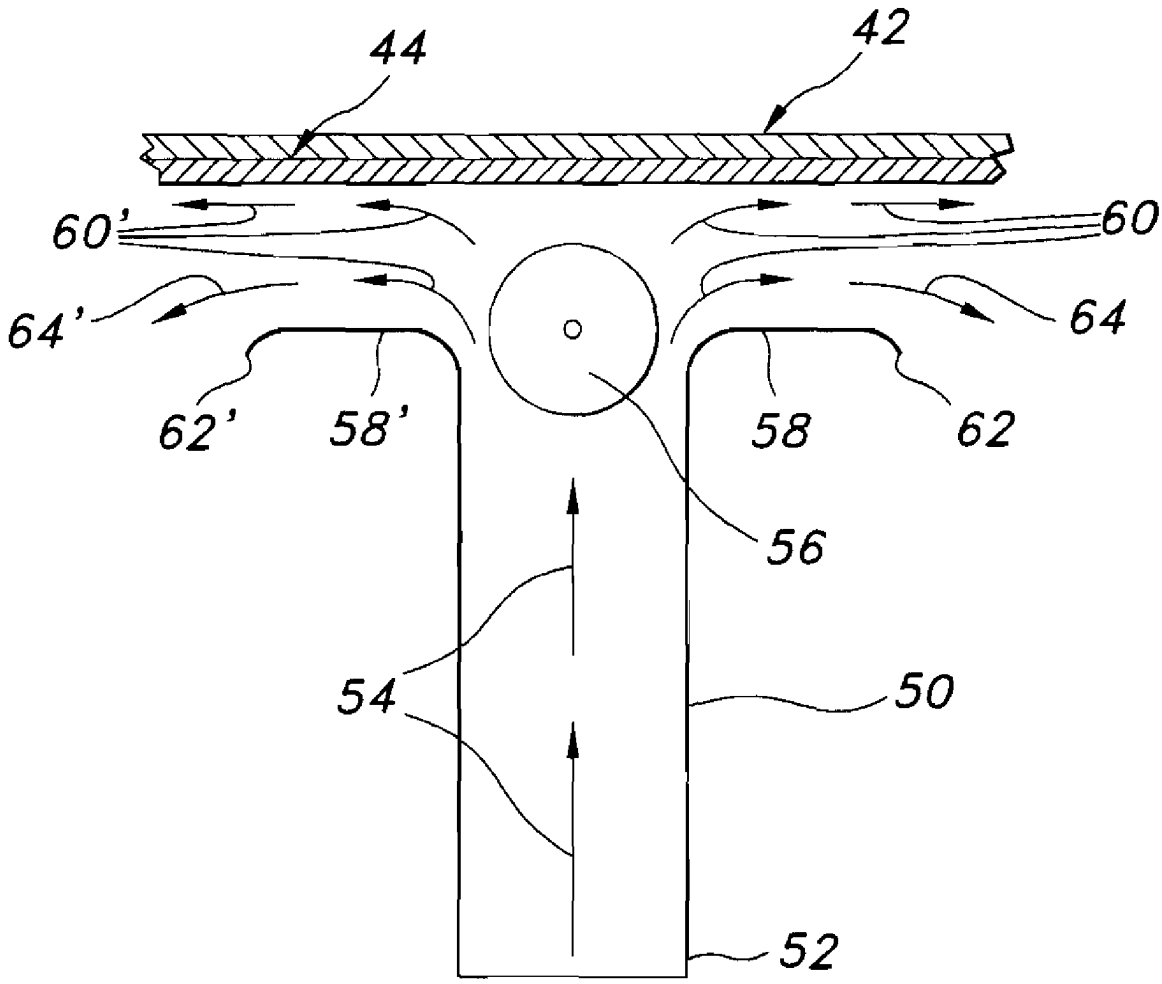


FIG. 7

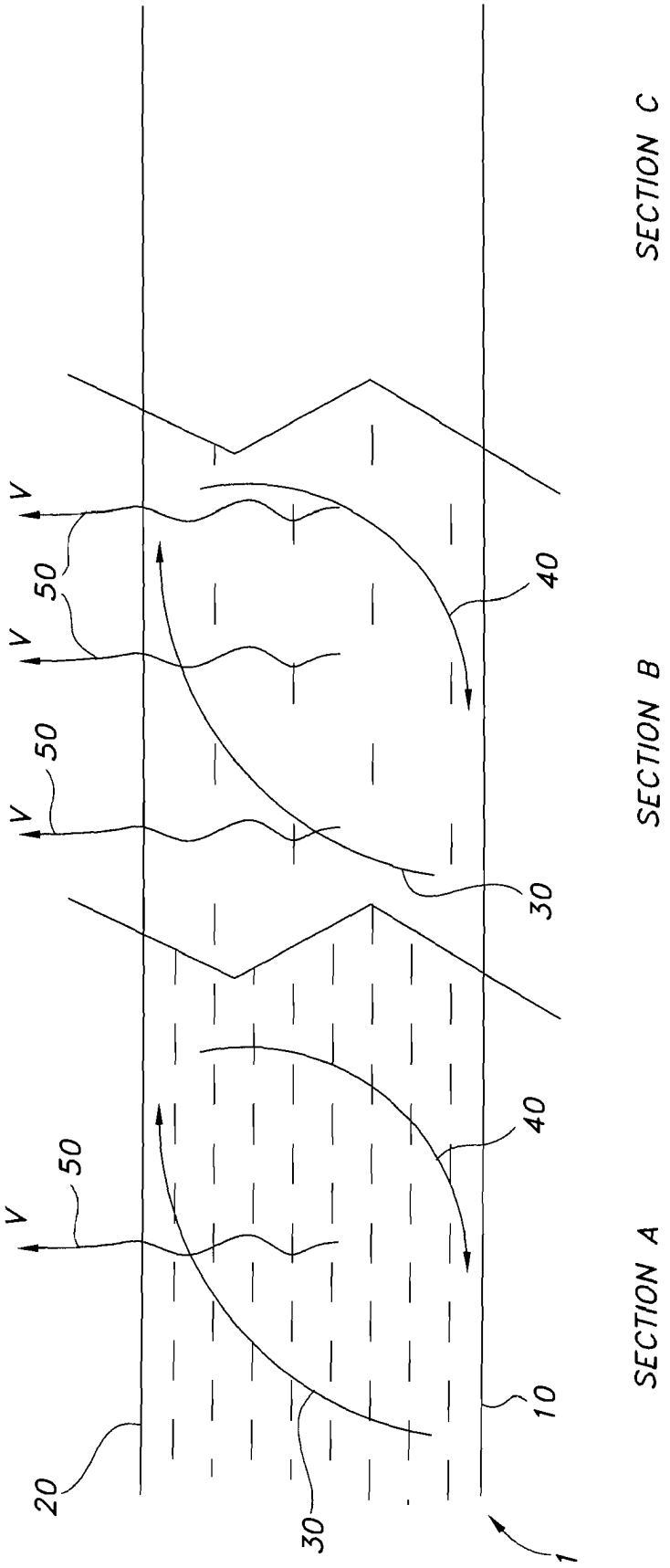


FIG. 8

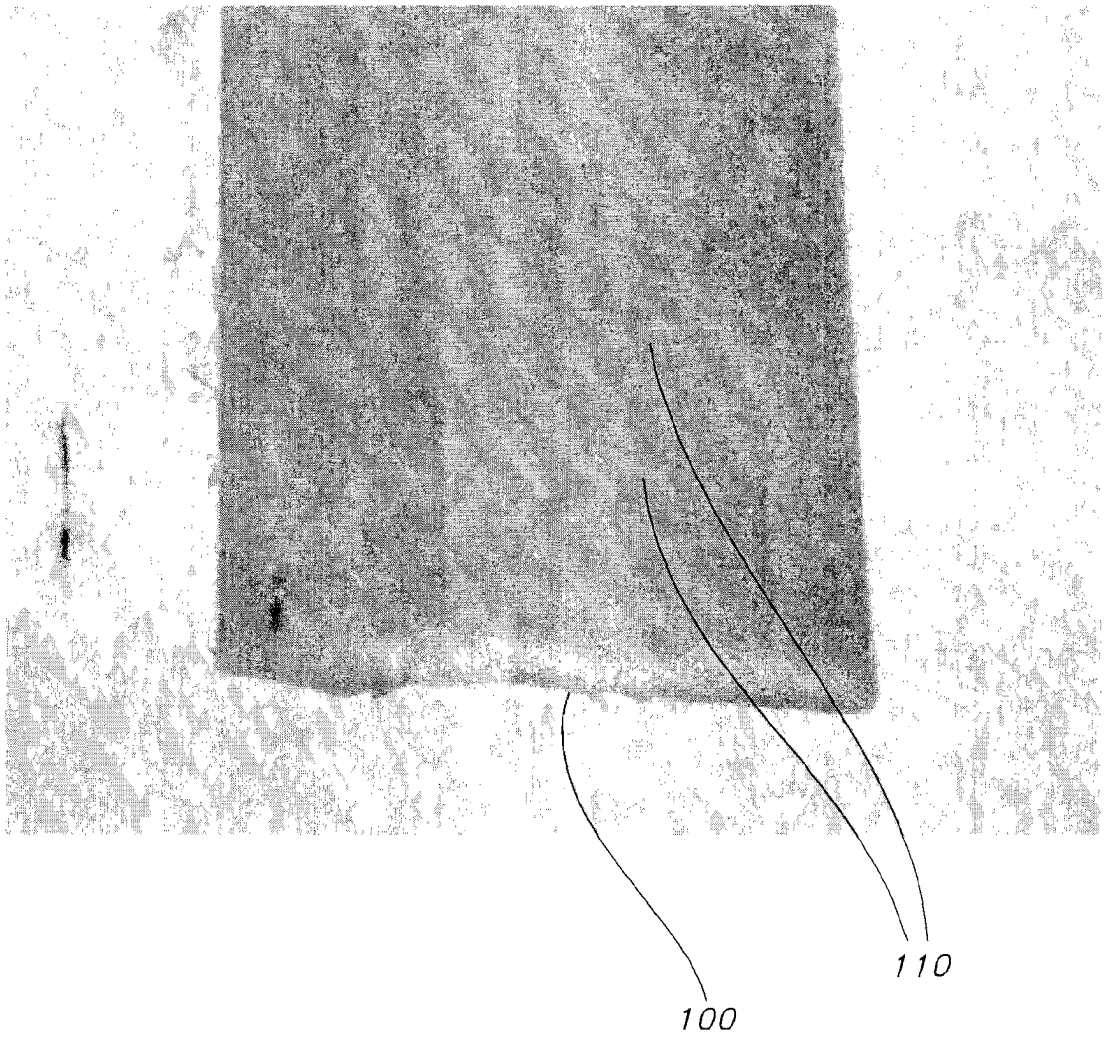


FIG. 9

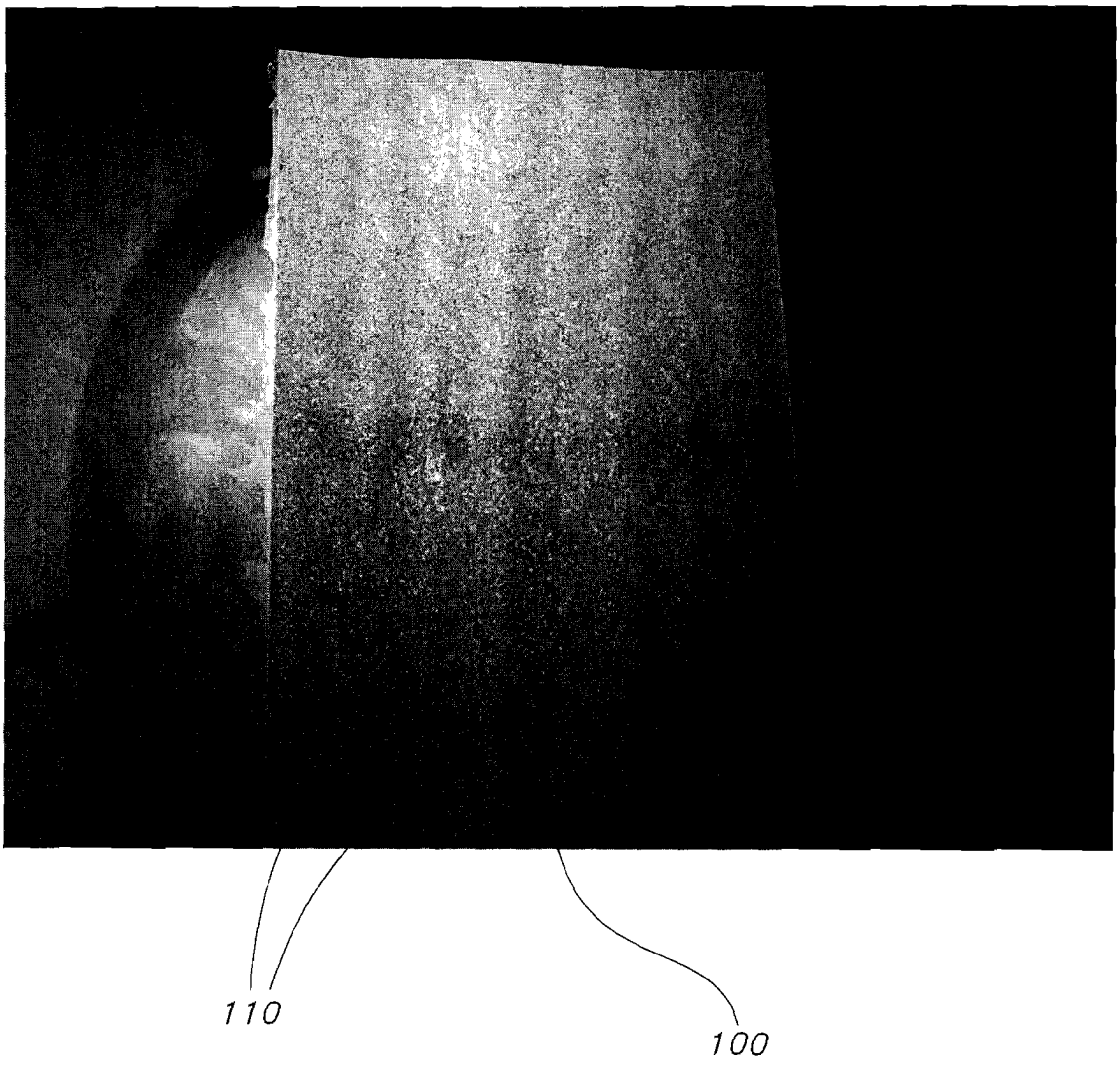


FIG. 10

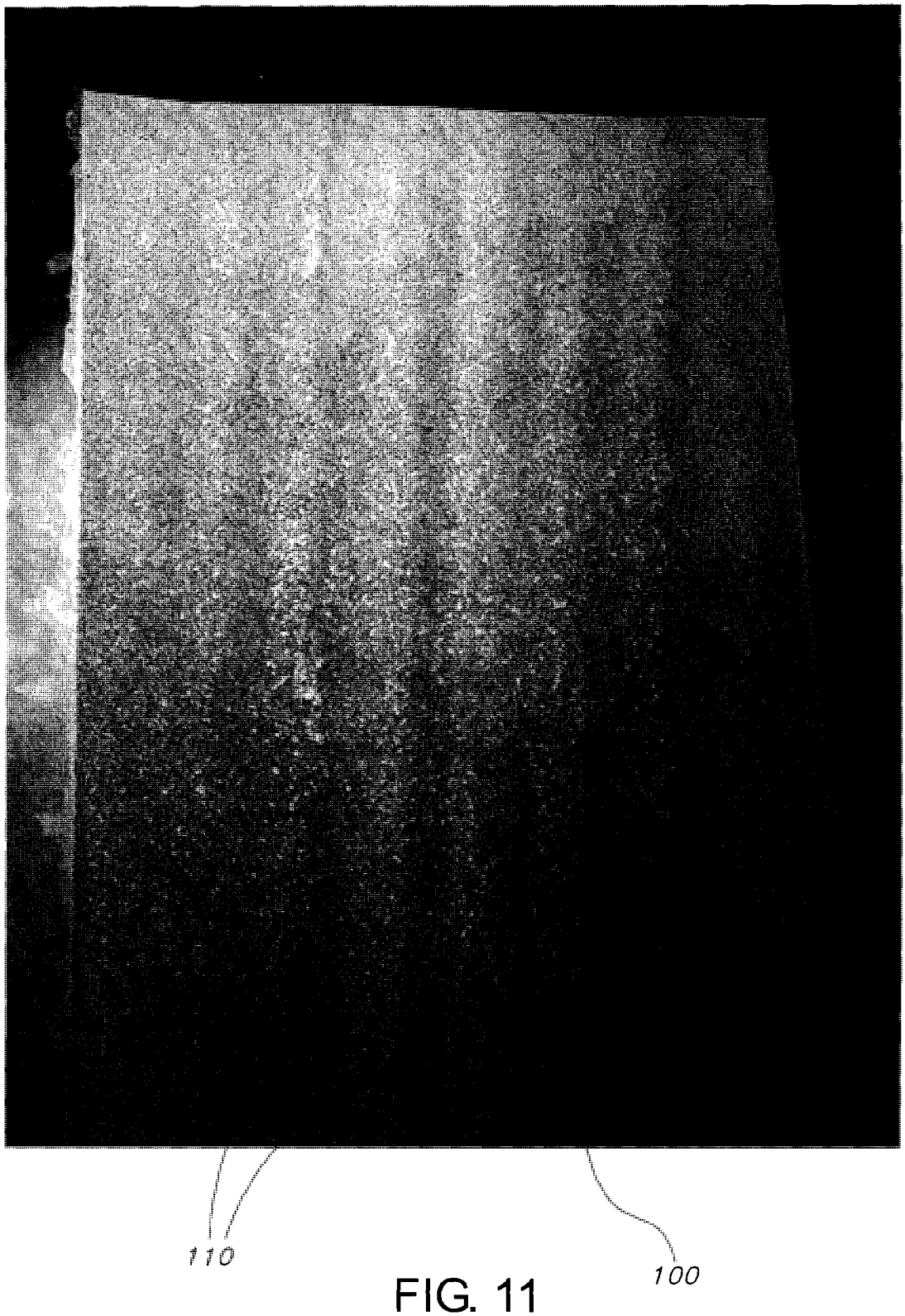


FIG. 11

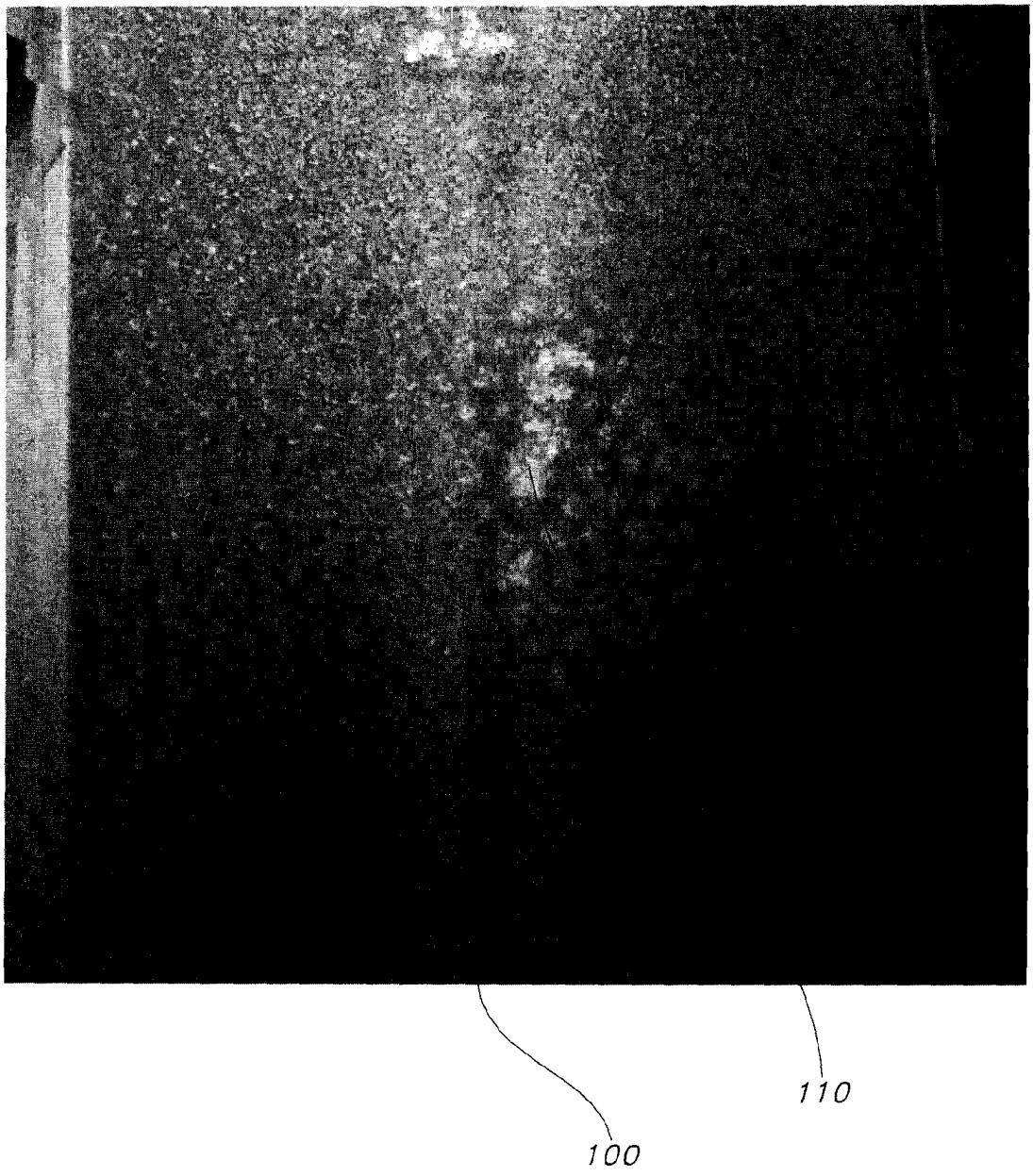


FIG. 12

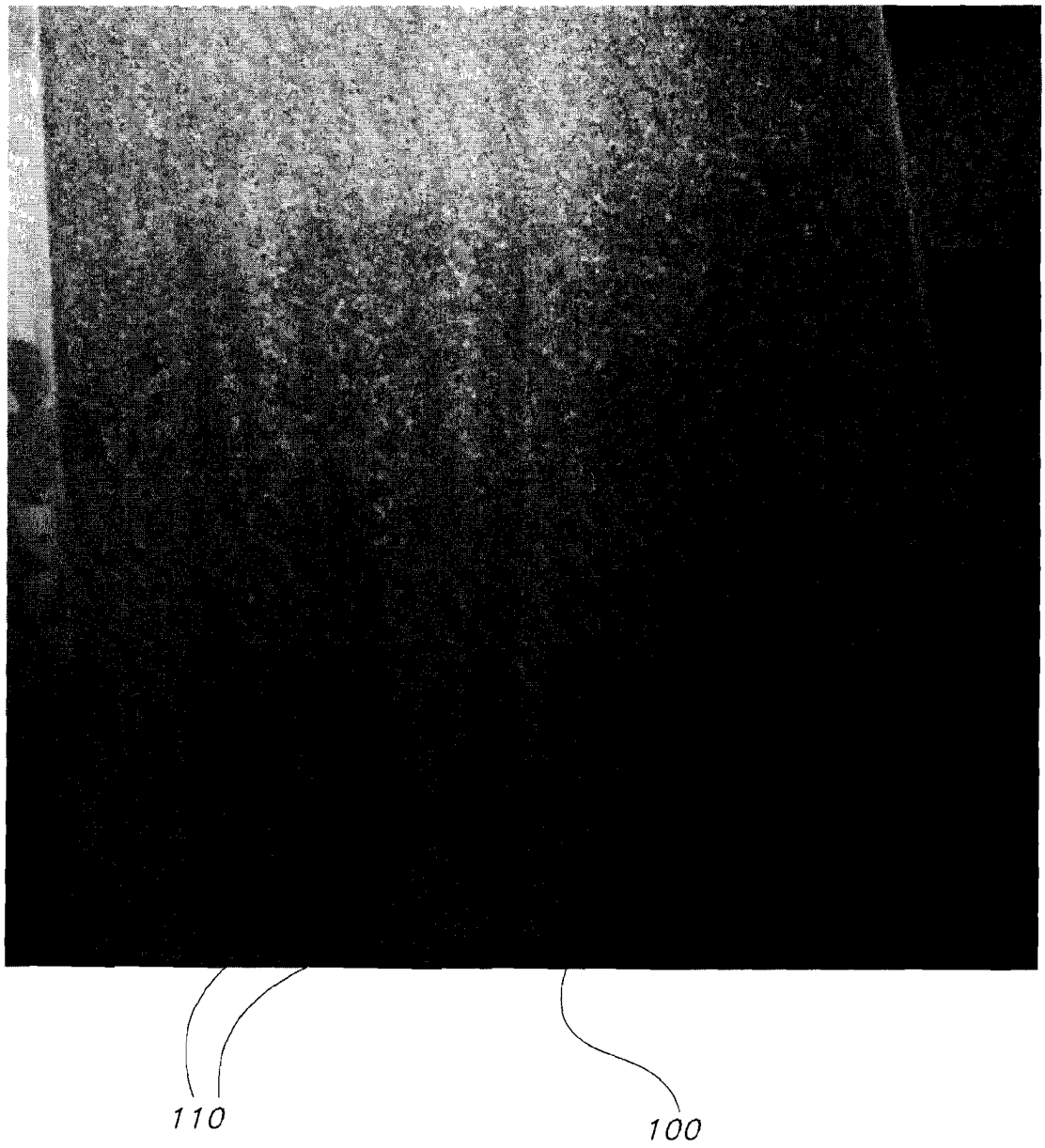


FIG. 13

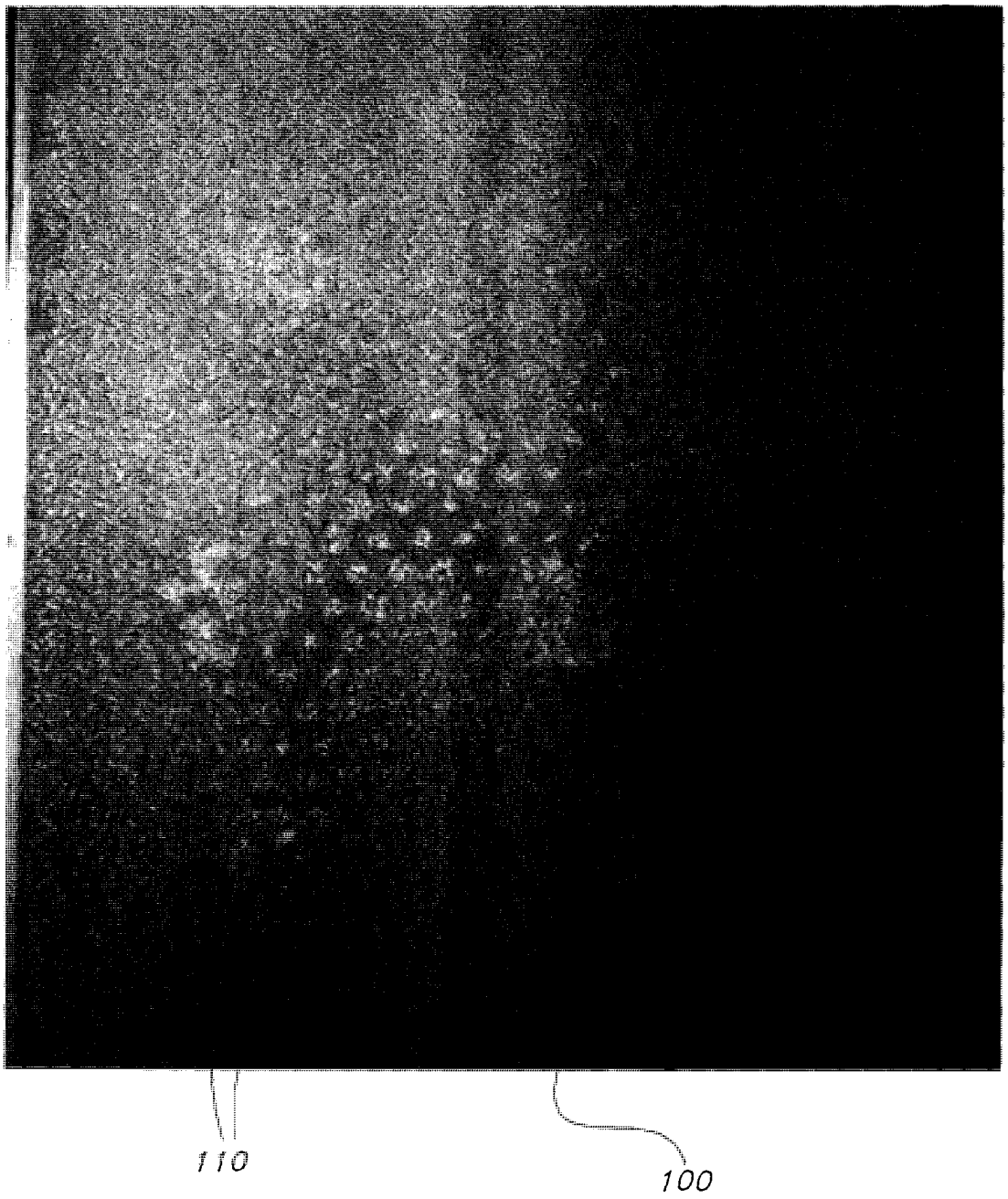


FIG. 14

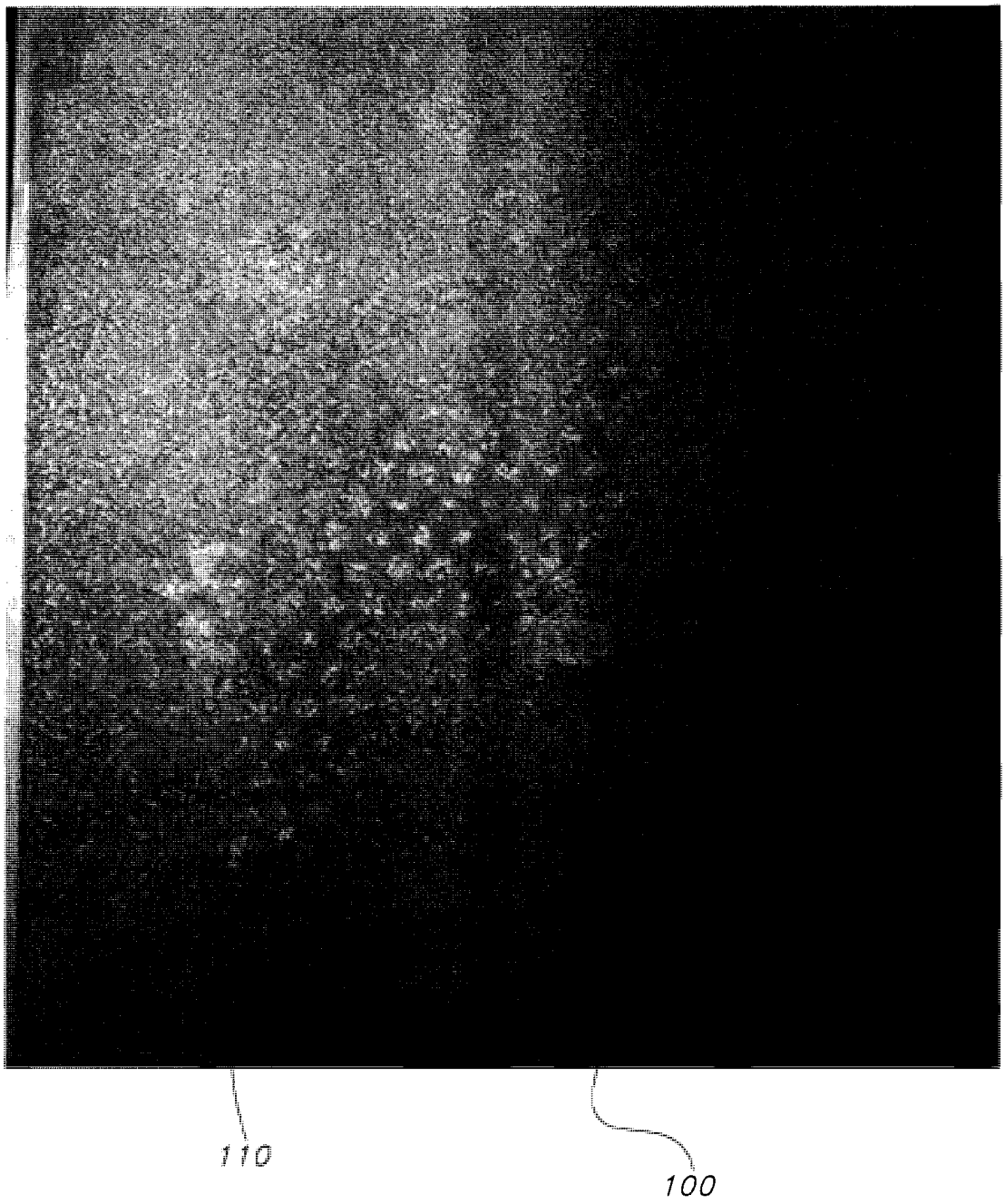


FIG. 15

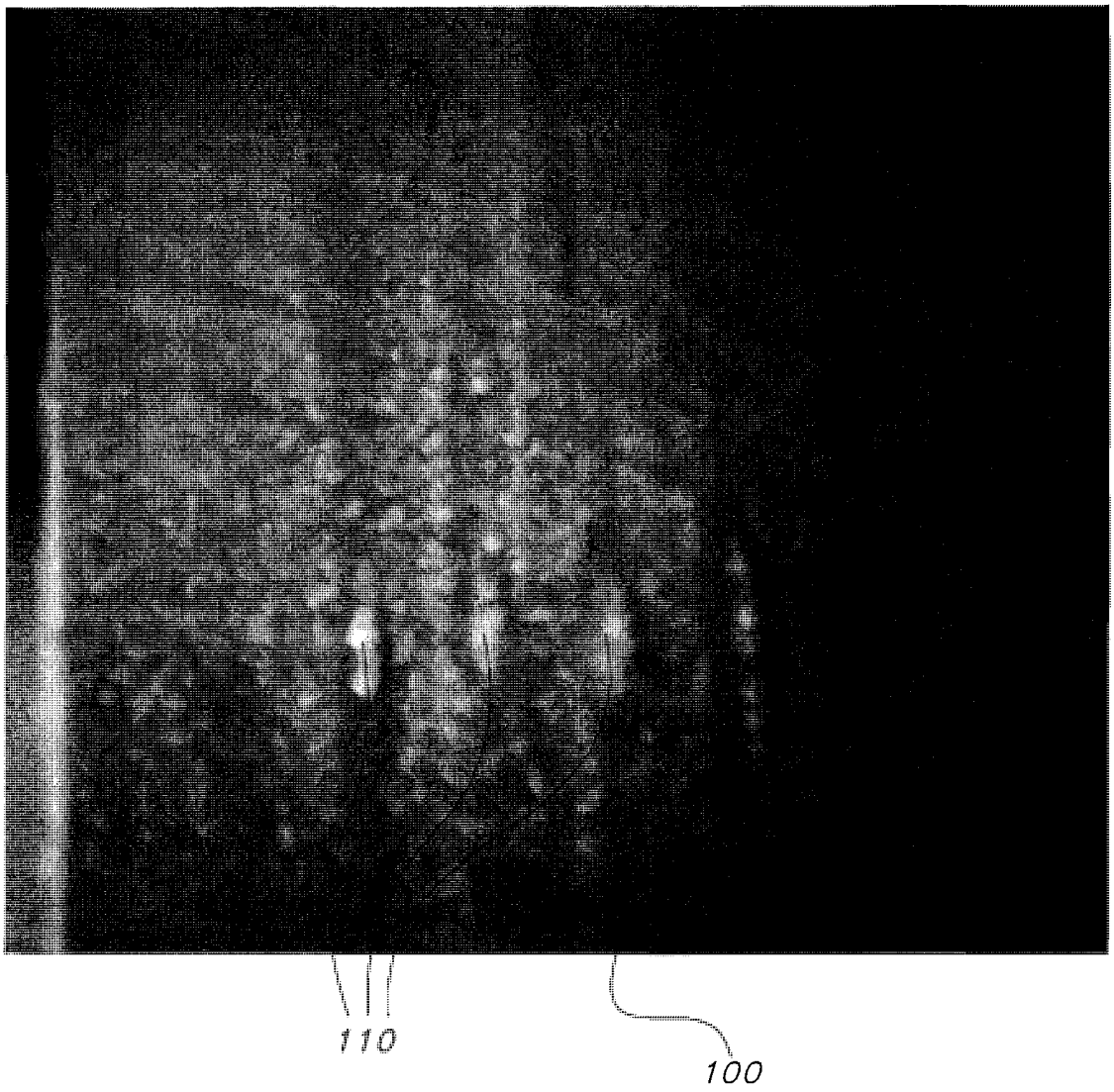


FIG. 16

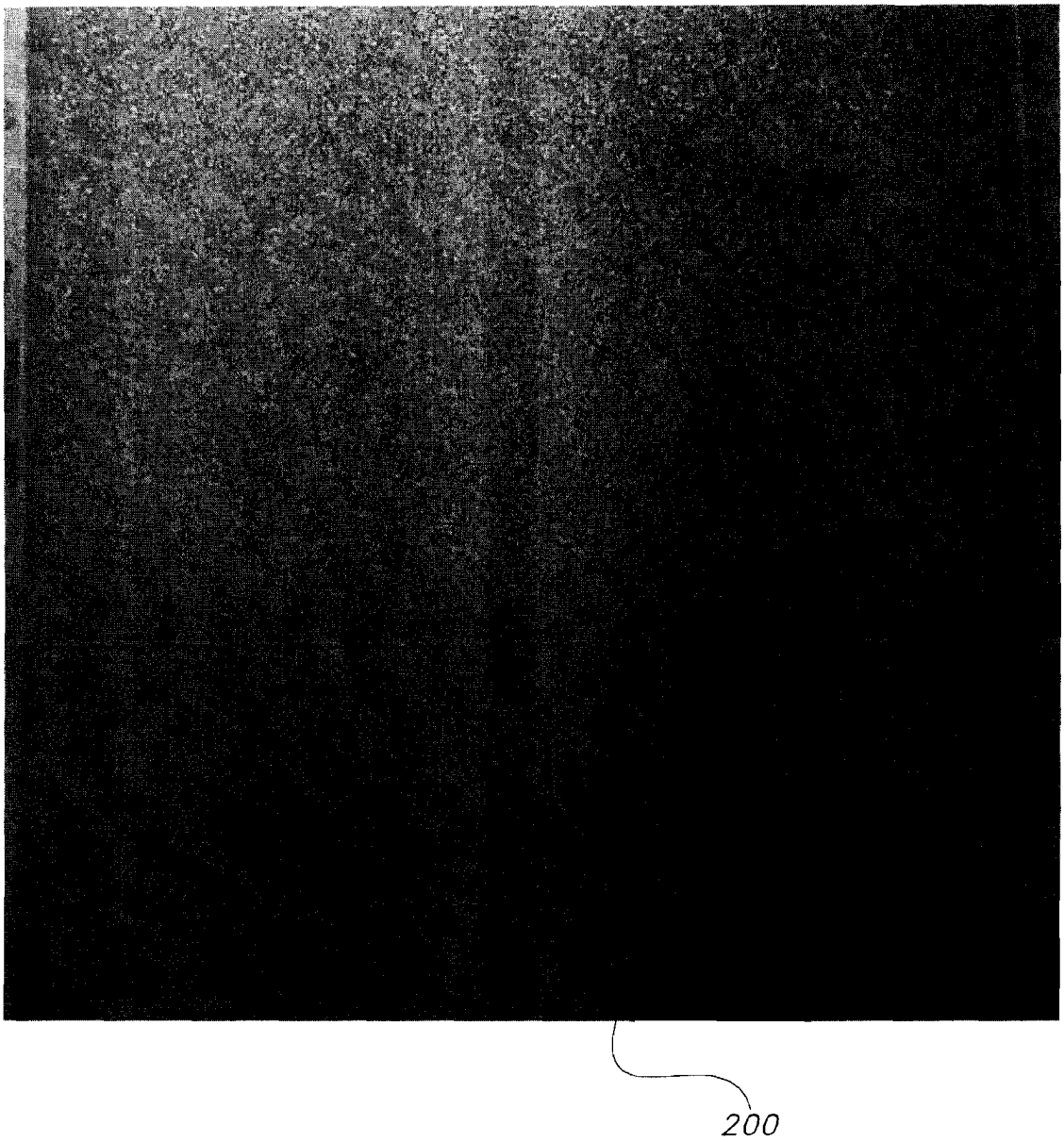


FIG. 17

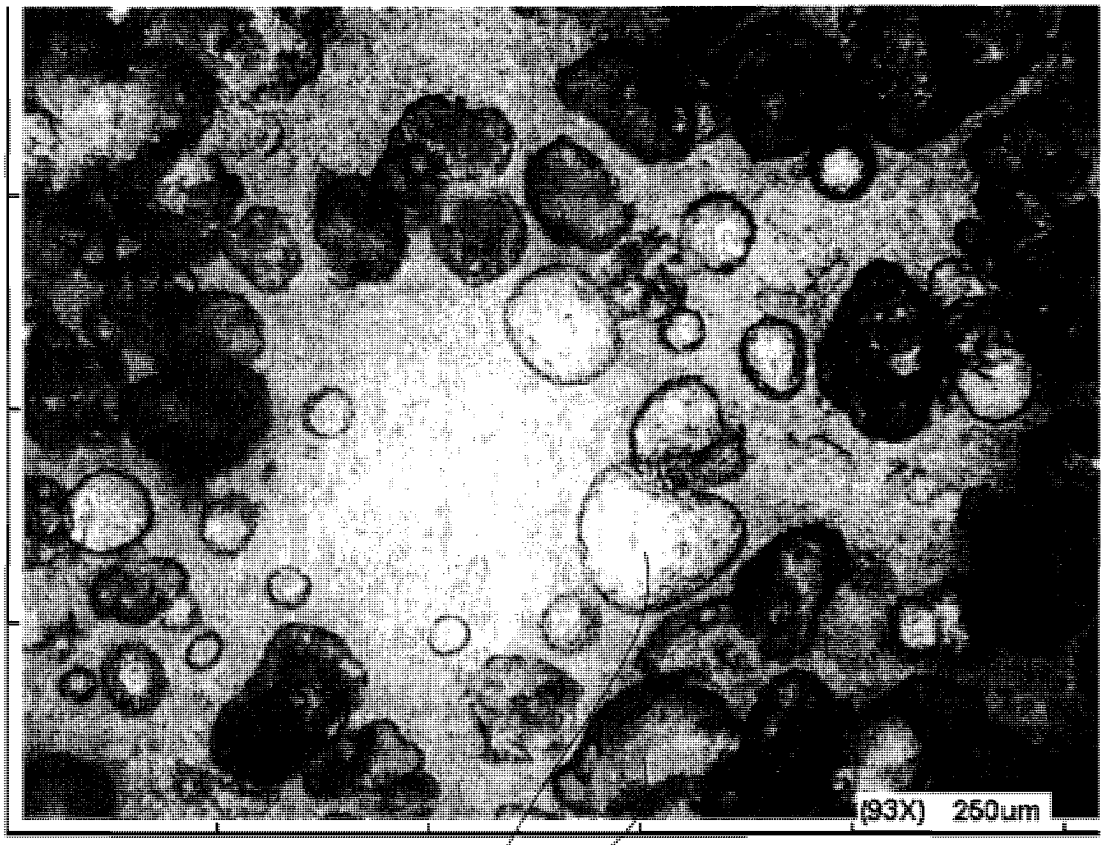
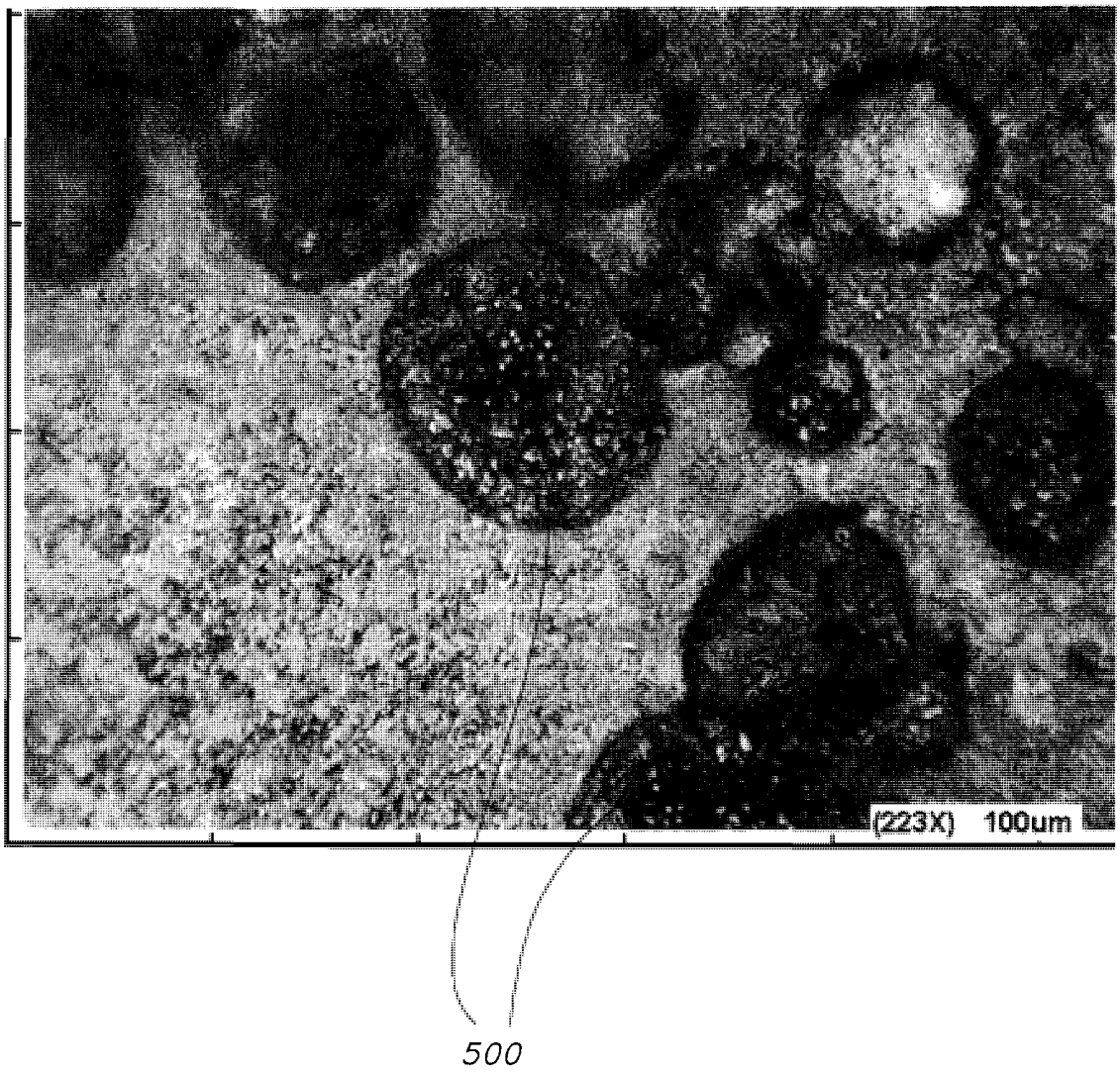


FIG. 18



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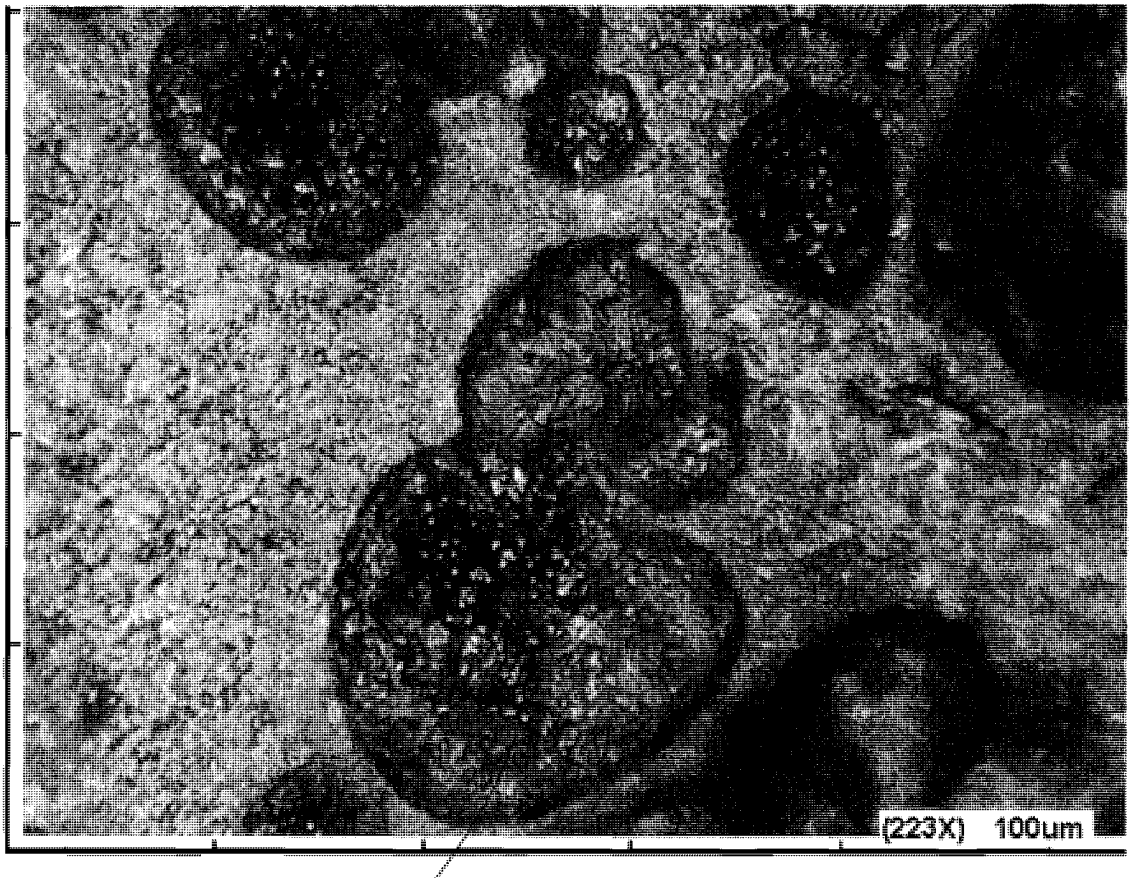


FIG. 20

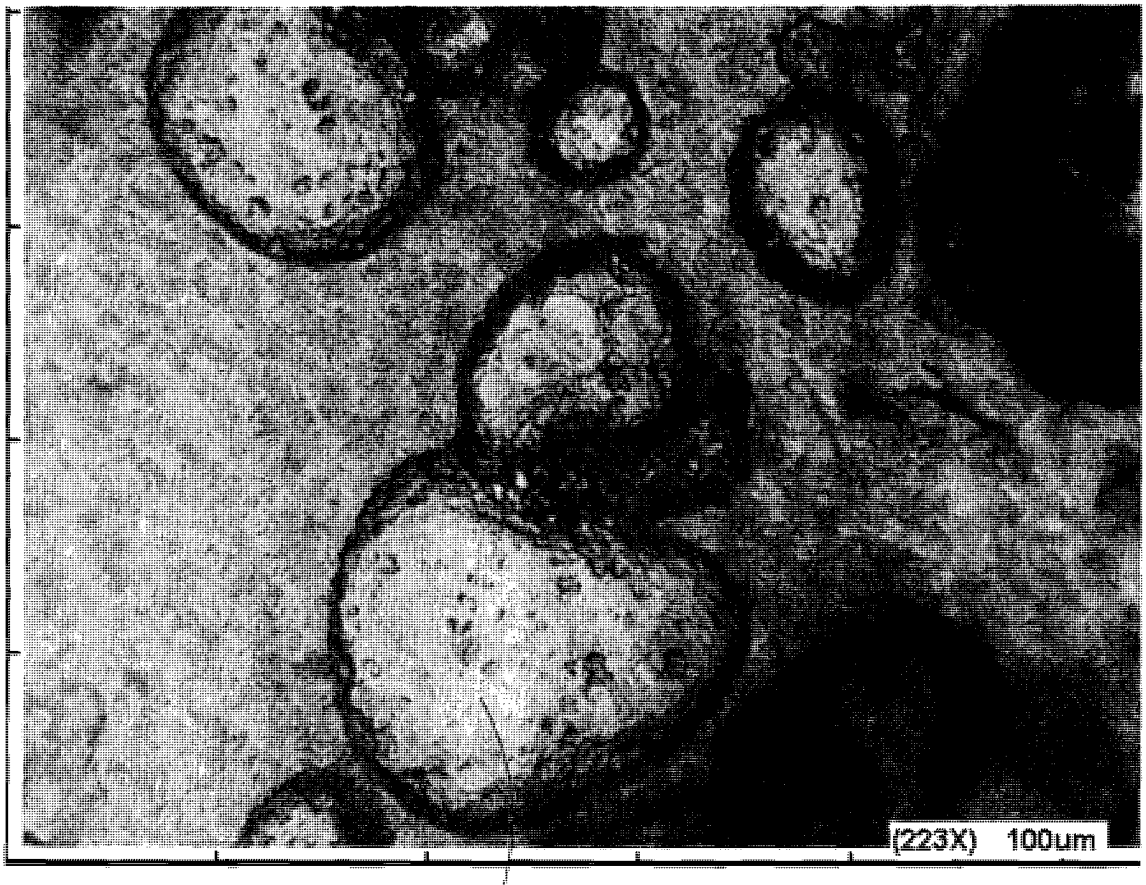


FIG. 21

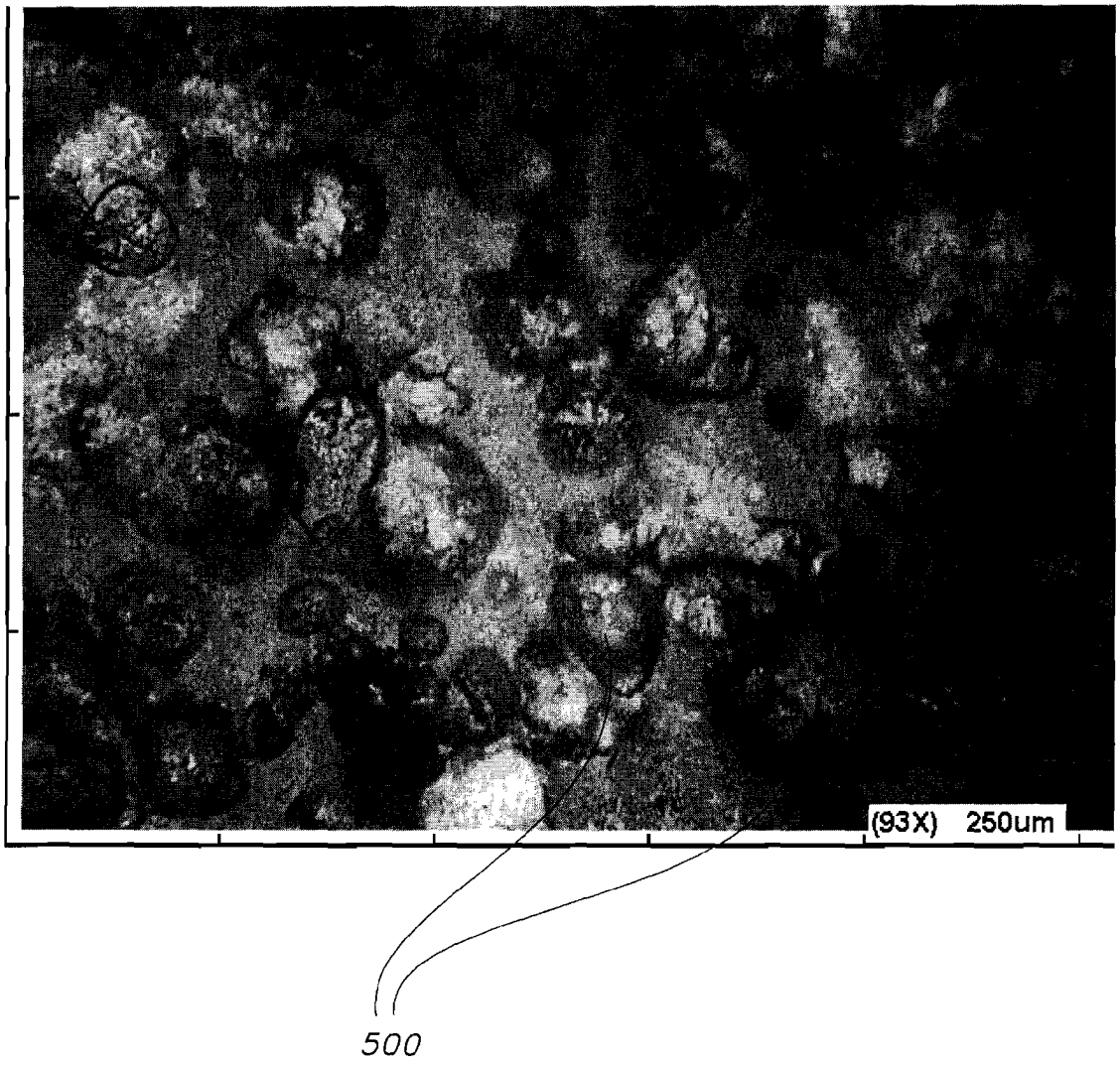


FIG. 22

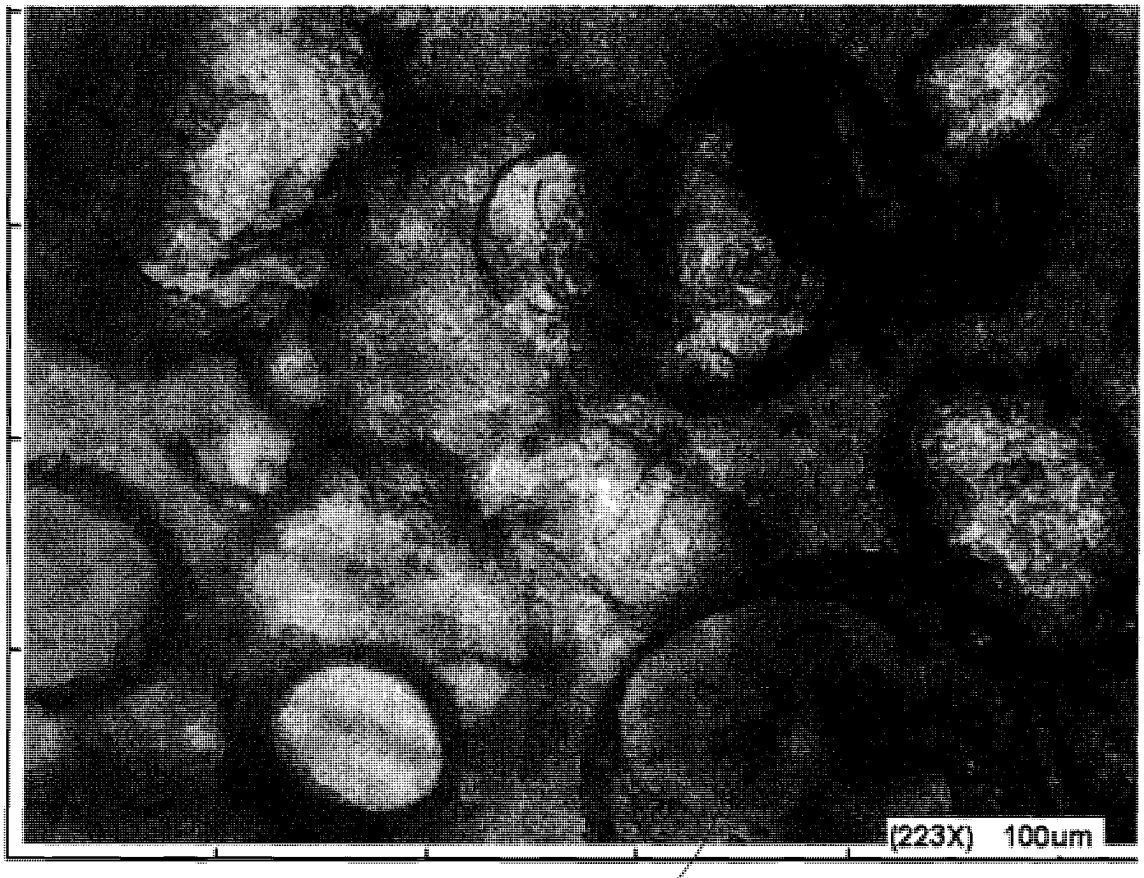


FIG. 23

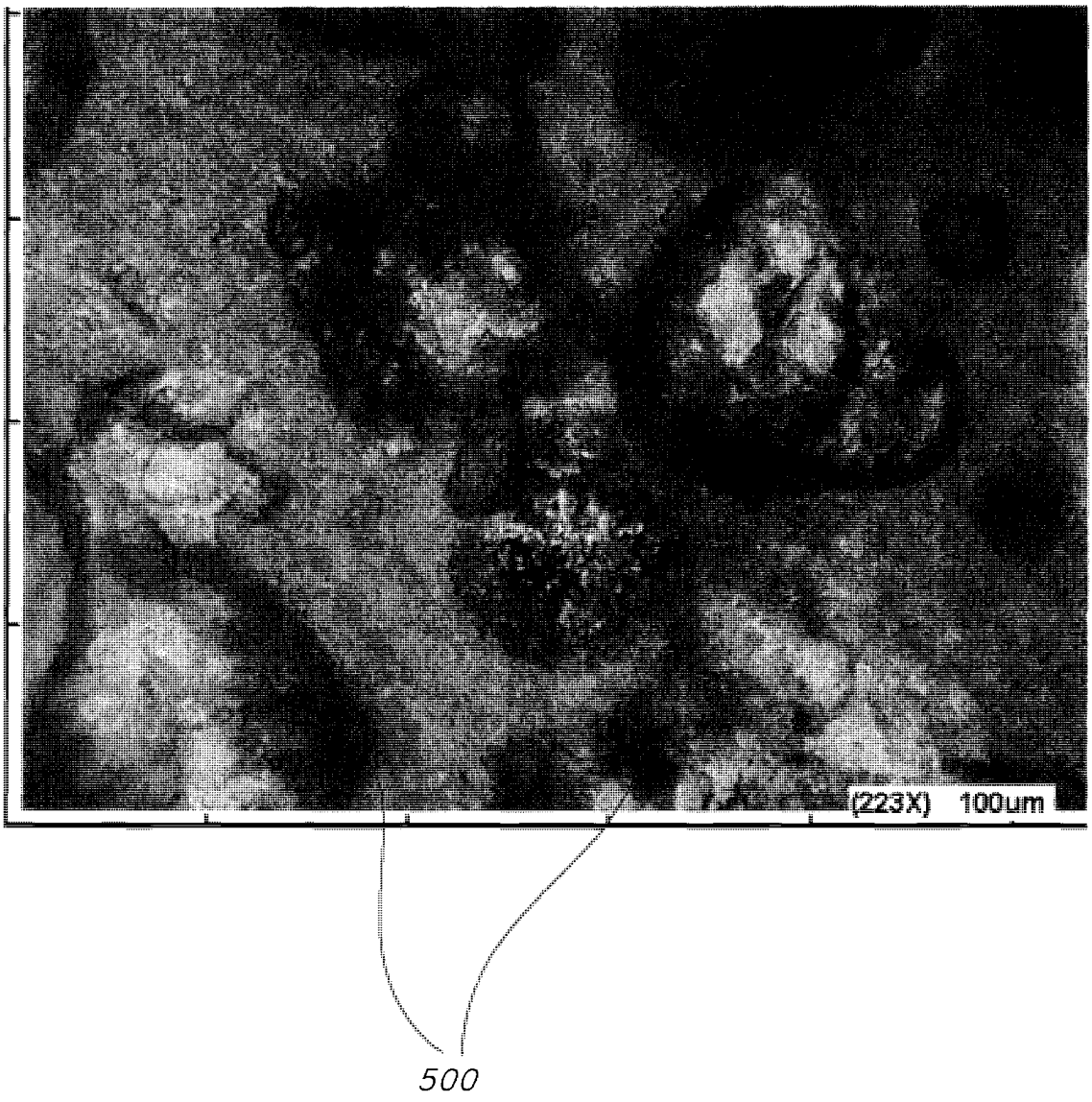


FIG. 24

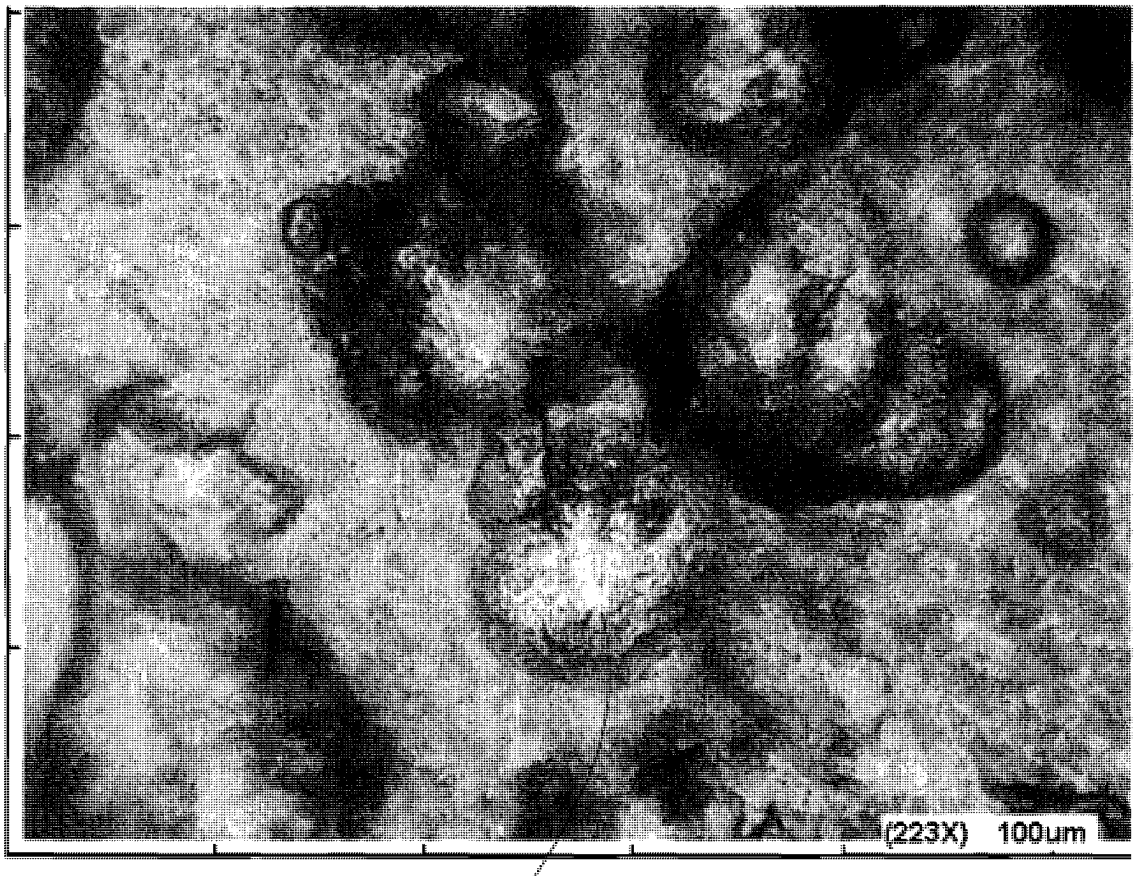


FIG. 25

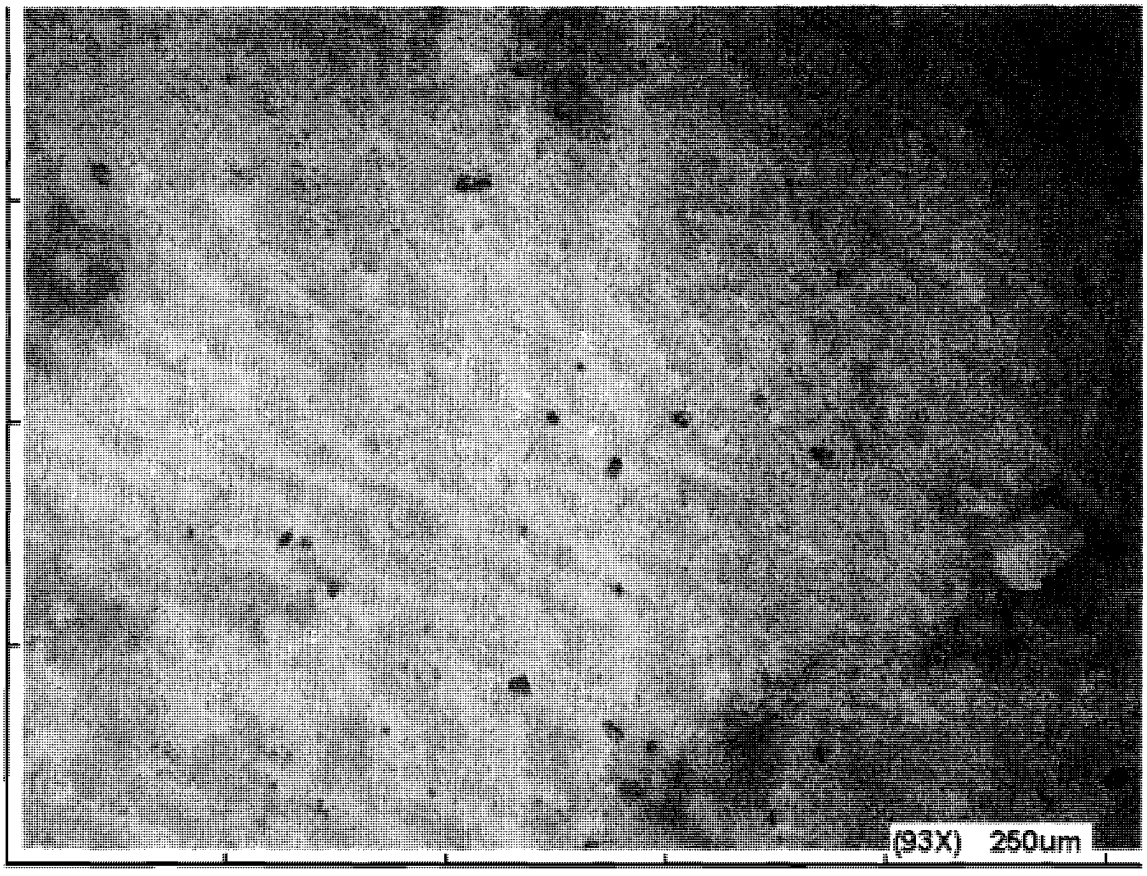


FIG. 26

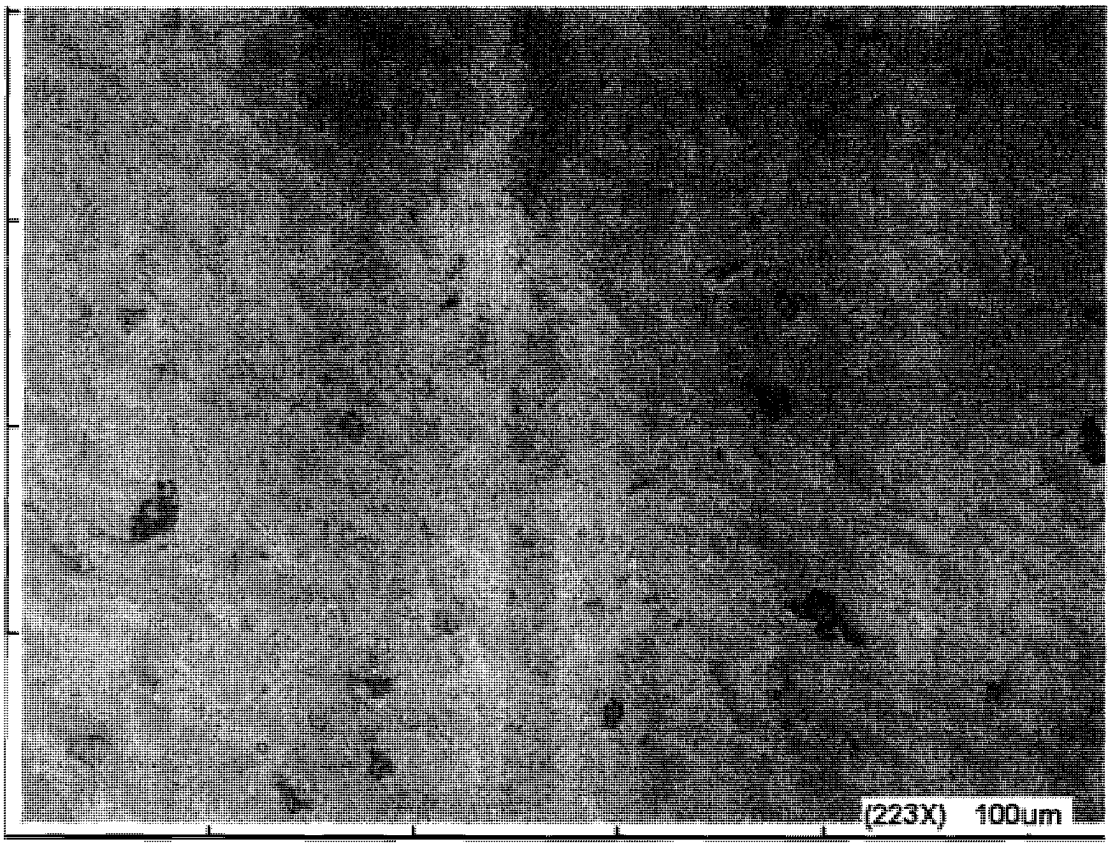


FIG. 27

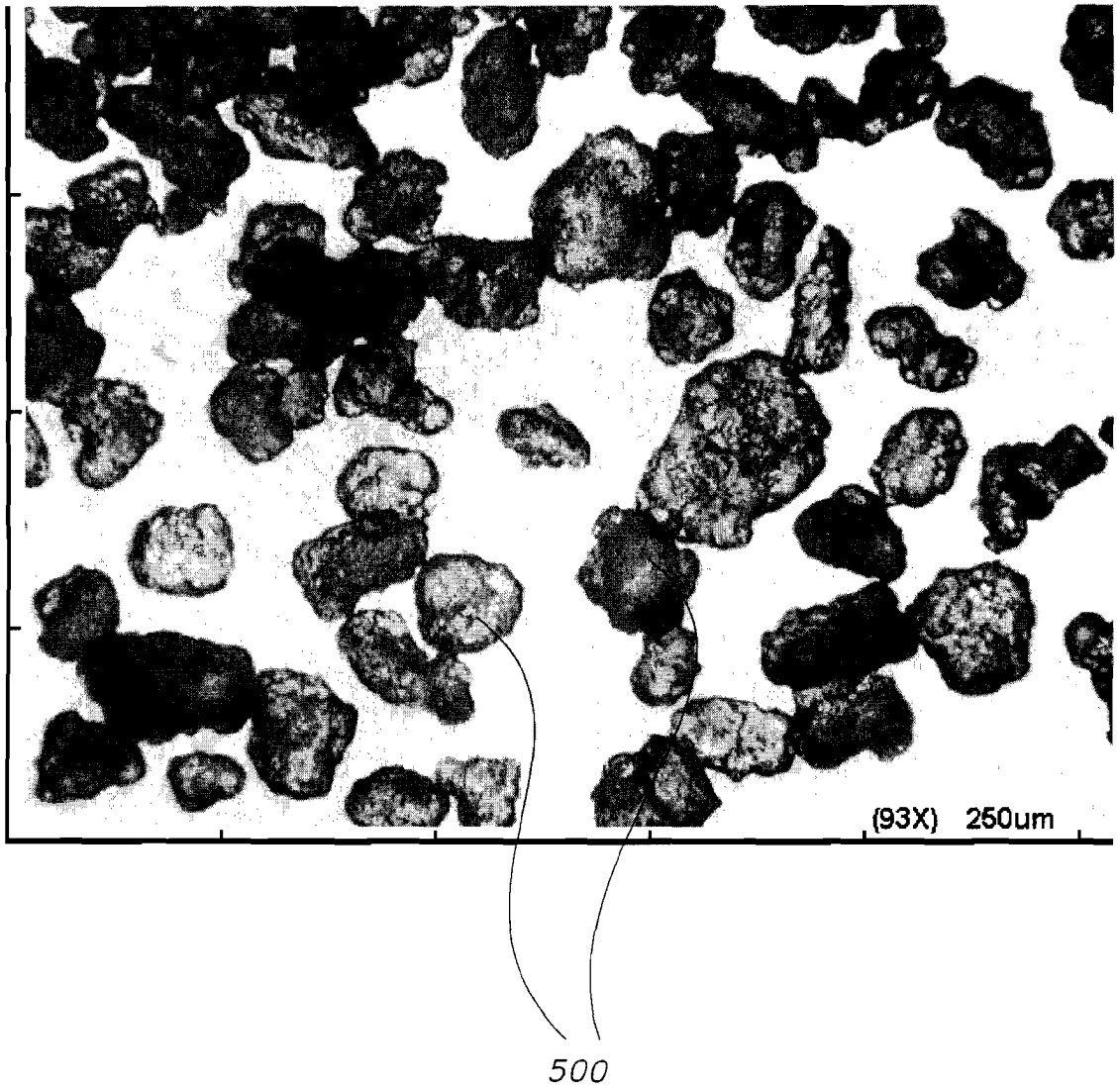


FIG. 28

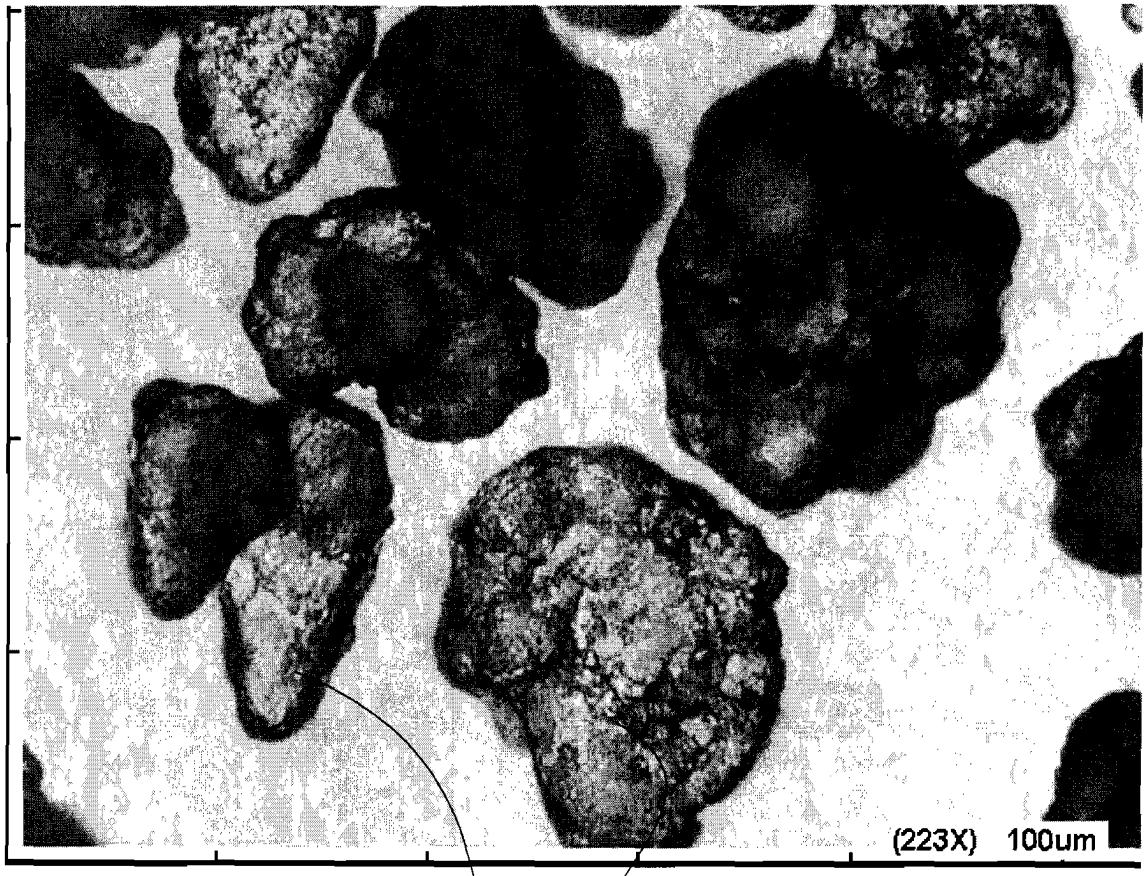


FIG. 29

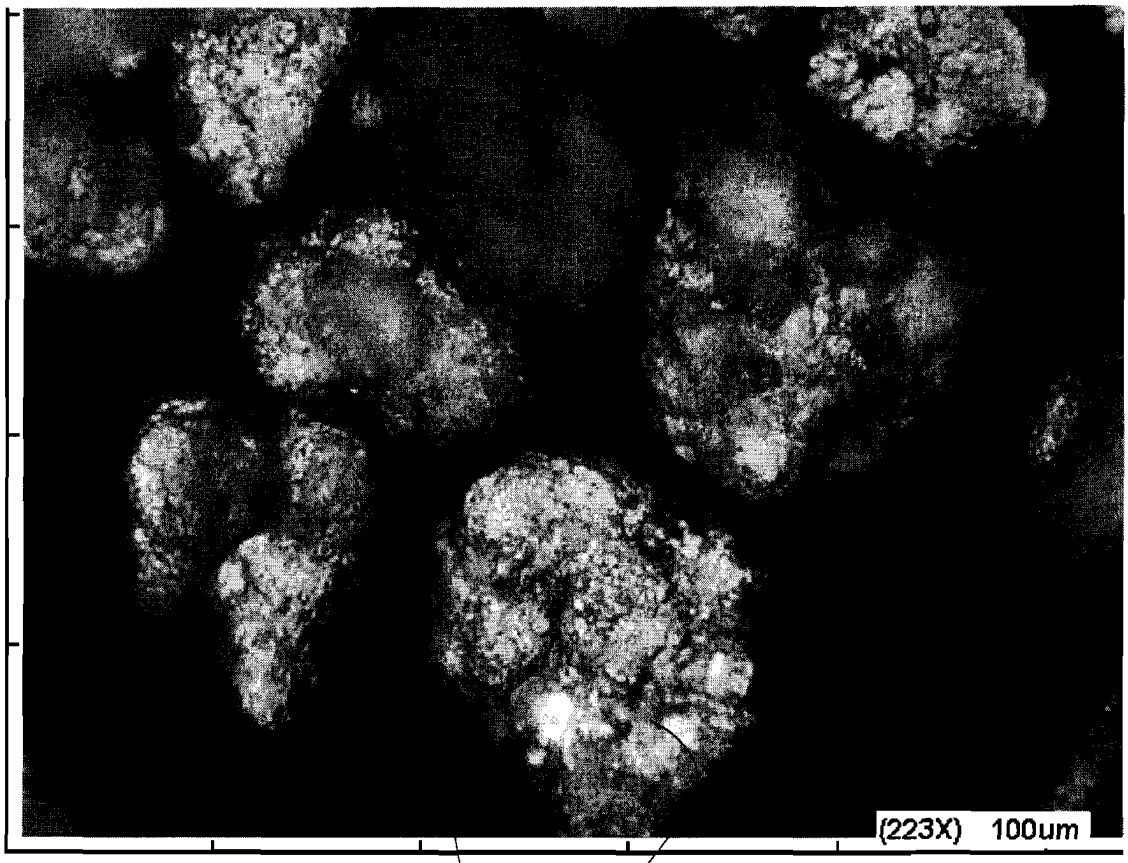


FIG. 30

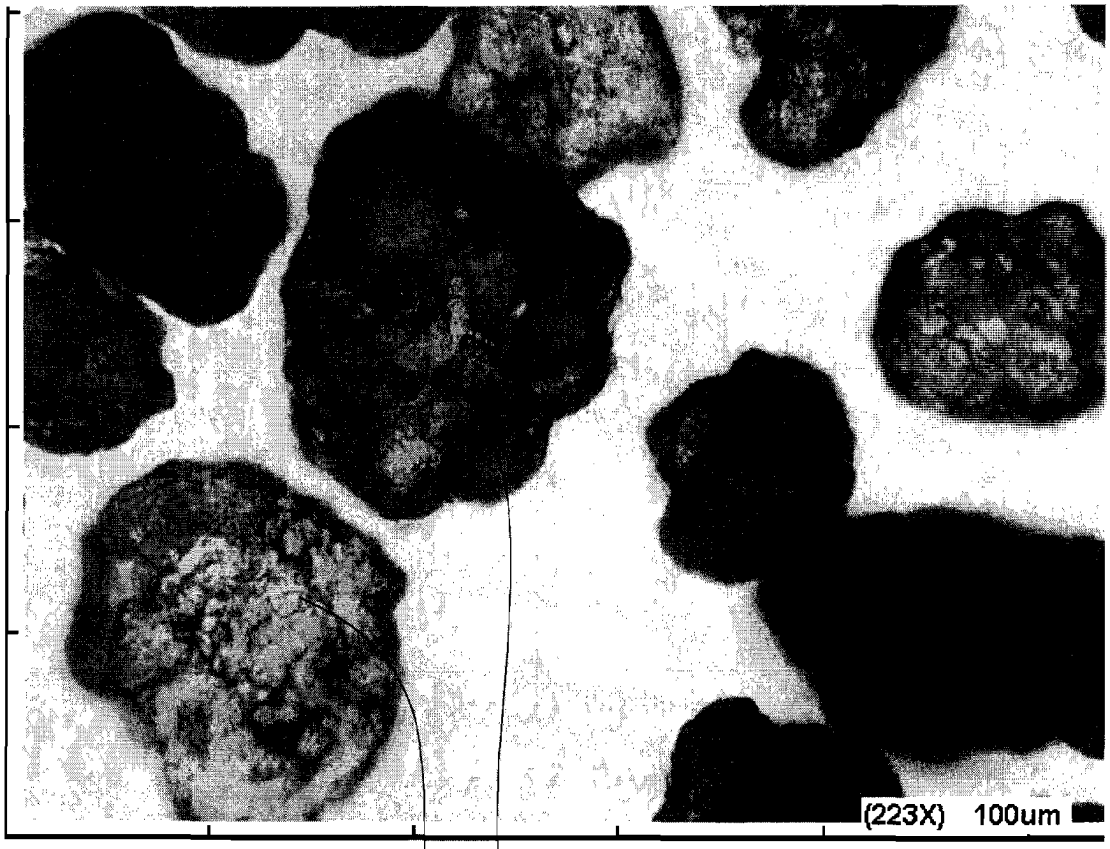
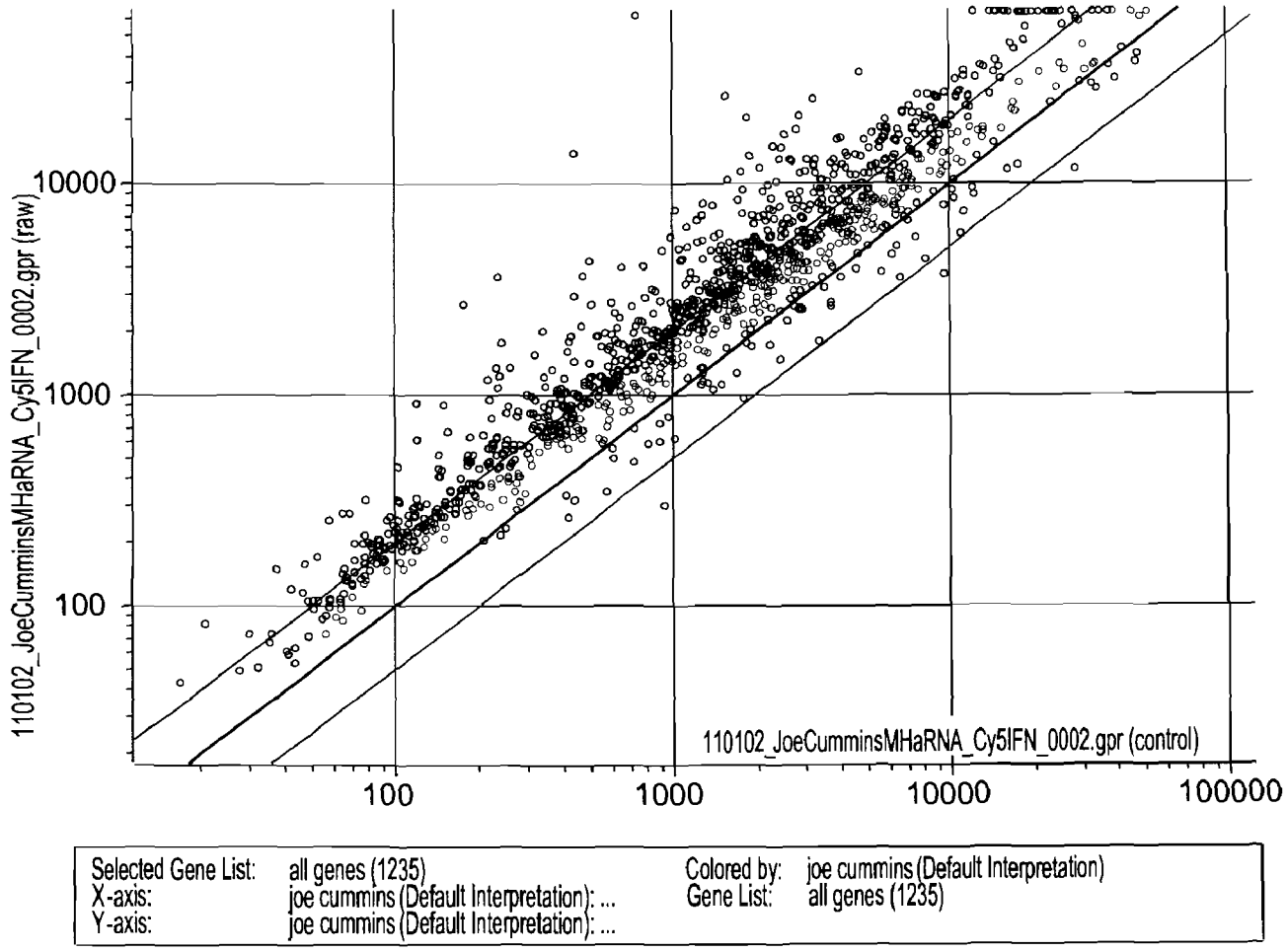
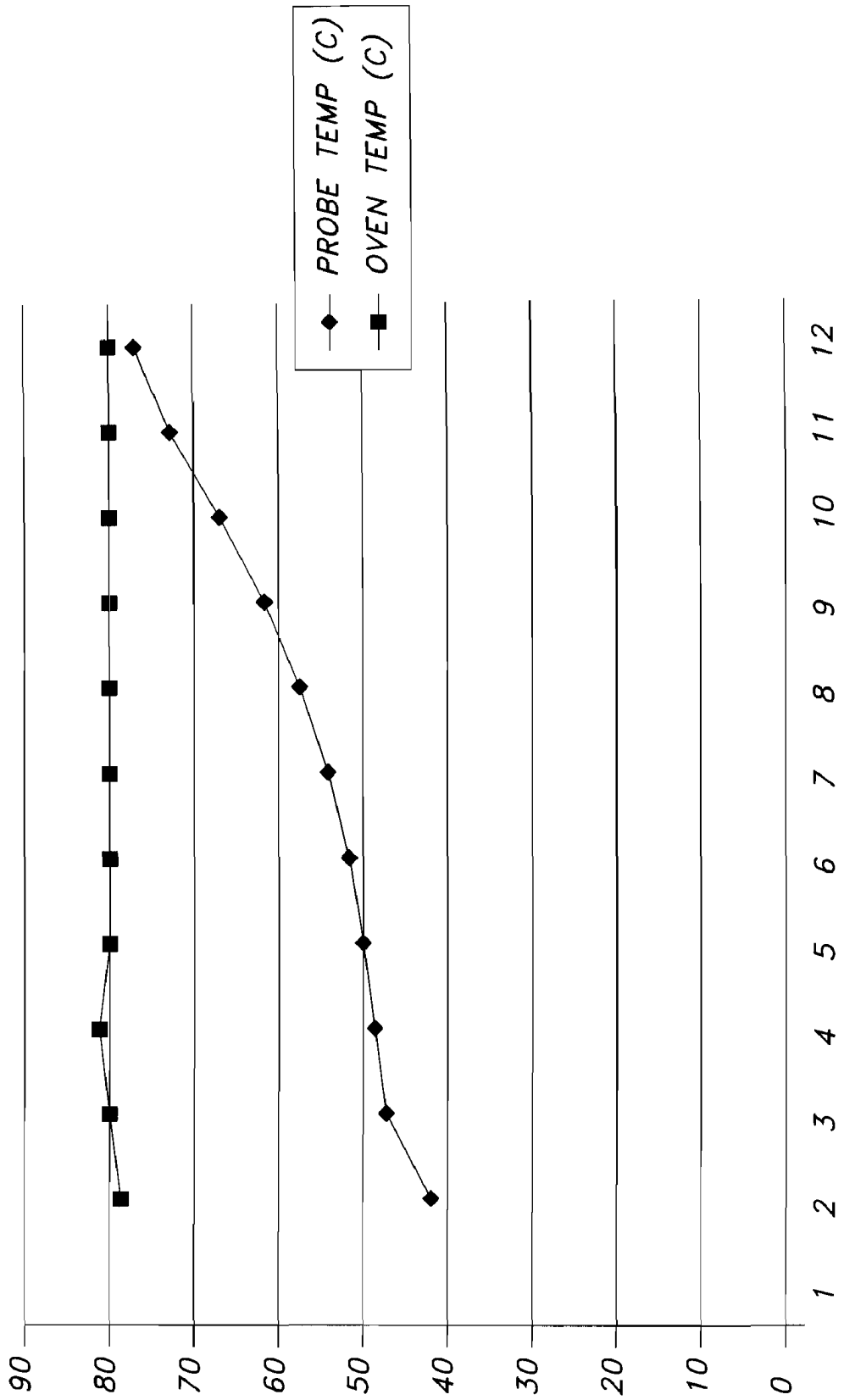


FIG. 31



Normalized to GAPDH, most of the ISGs are induced.

FIG. 32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OVEN TEMP (C)
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40
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0
1
2
3
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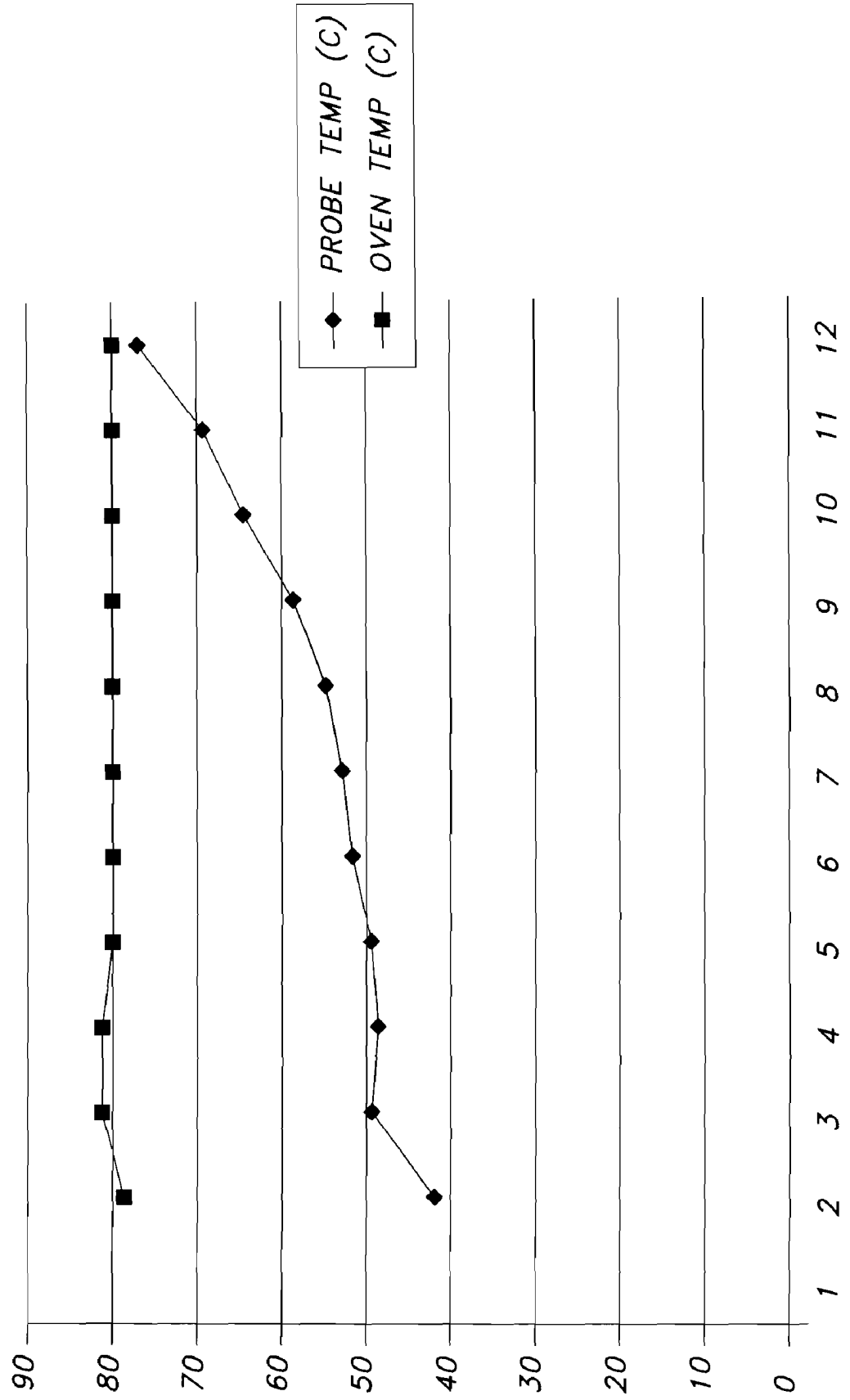
5
6
7
8
9
10
11
12

FIG. 33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OVEN TEMP (C)
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FIG. 34

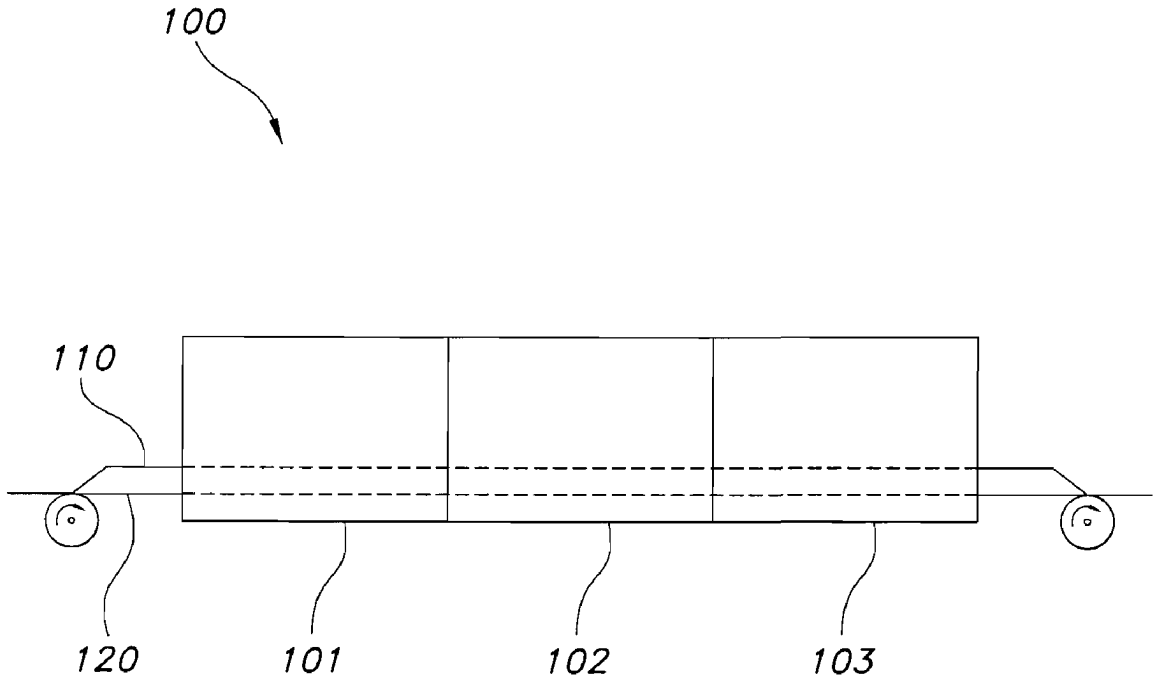


FIG. 35

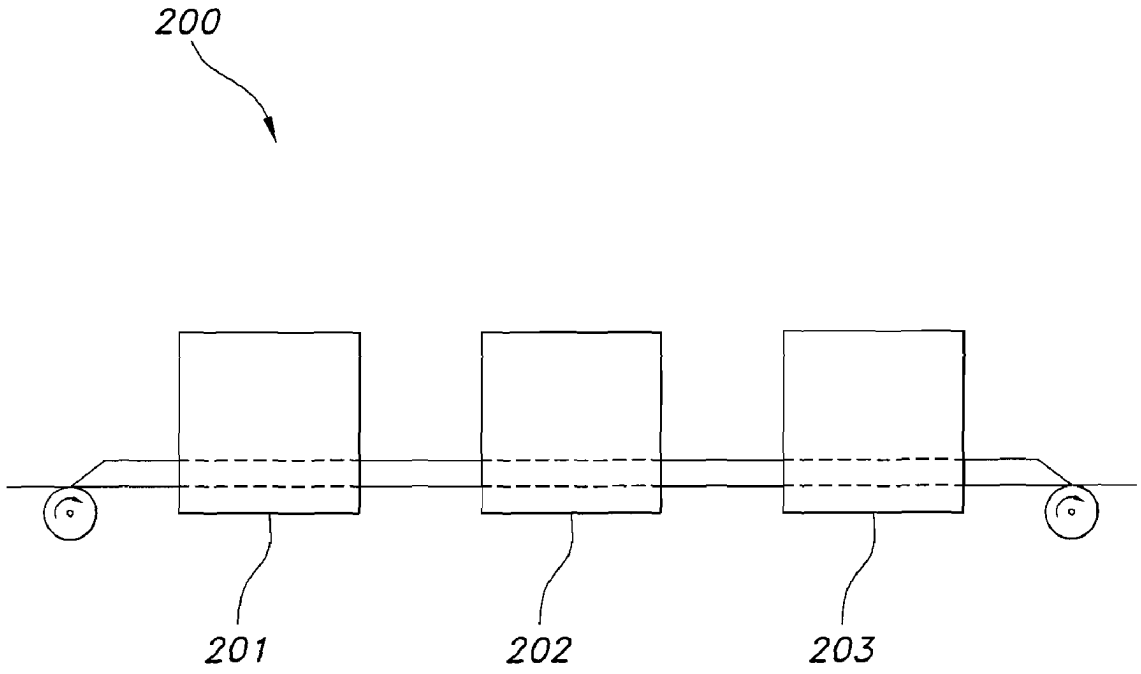


FIG. 36

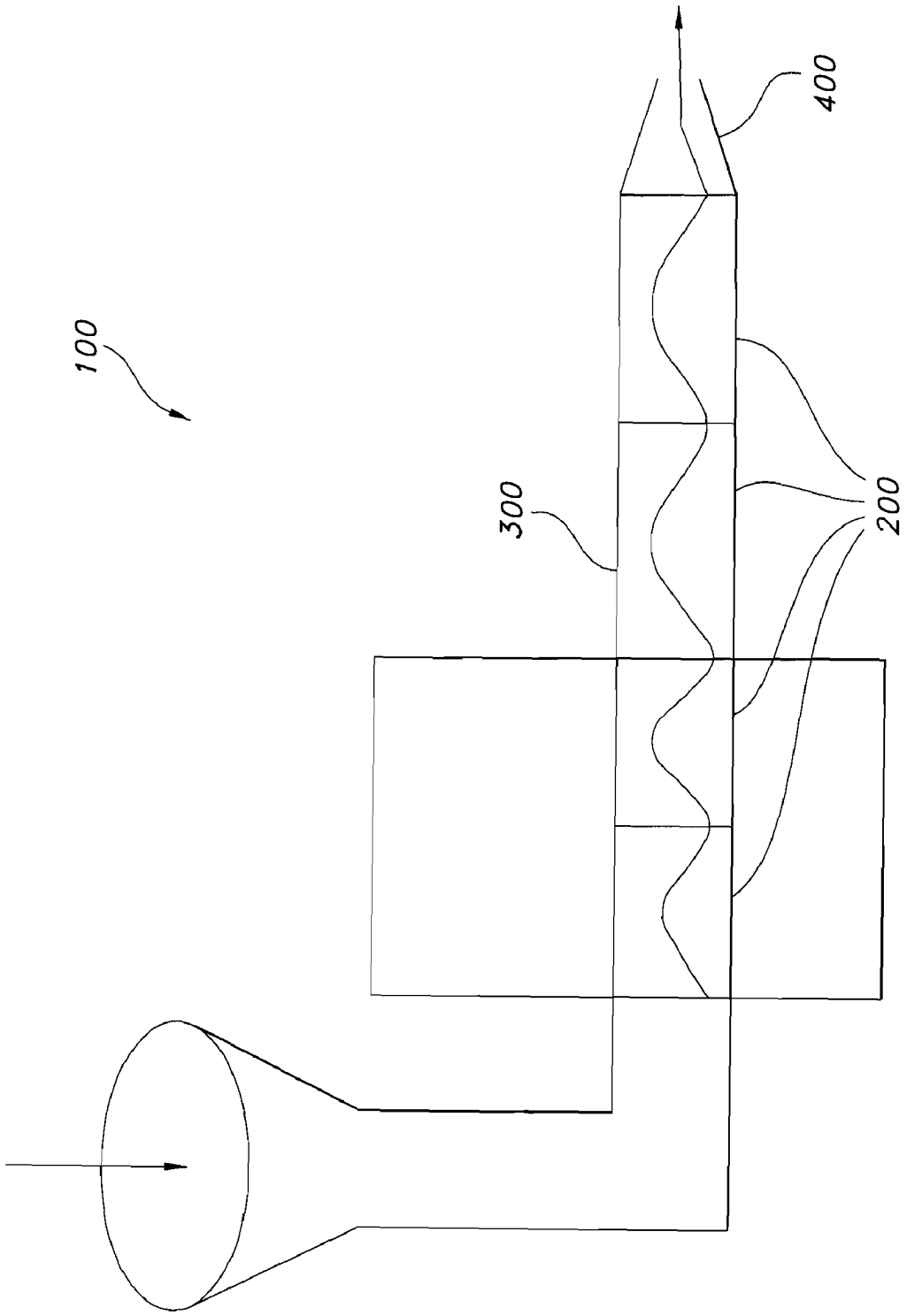


FIG. 37

FIG. 38

Ex.	Polymer Component Reference	% Solids of solution	Viscosity (cp) at 5 rpm	% moisture	Film thickness (mils)	Film strength	Tear Resistance	Tendency to go to roof of mouth	180° bend test	Film molding	Dis-solution (sec)	Rating of dissolution in mouth	Time in oven (min)
EI	PEO/PVP (60/40)	45.0	14800	2.21	3.8	Adequate	Excellent	Low	Passed	No	3	Fast to Moderate	9
EJ	PEO/PVP (40/60)	50.0	6600	2.86	4	Weak	Low to moderate	High	Passed	No	3	Fast	8
EK	PEO/Starch (80/20)	40.0	3440	2.27	4.5	Adequate to good	Excellent	High	Passed	No	3	Fast to Moderate	8
EL	PEO/CMC (80/20)	37.5	121,200	1.96	4.1	Good	Excellent	High	Passed	No	5	Slow	9
EM	PEO/CMC (60/40)	30.0	82,000	4.21	3.45	Weak	Good	High	Passed	No	3	Slow to Moderate	9
EN	PEO/CMC (40/60)	30.0	185,000	3.07	3.5	Adequate	Very low	High	Failed	No	4	Slow	9
EO	PEO/HPC (80/20)	37.5	21,200	1.65	4	Good	Excellent	High	Passed	No	4	Fast	8
EP	PEO/HPC (60/40)	37.5	17,000	2.84	3.8	Adequate	Excellent	High	Passed	No	4	Fast	9
EQ	PEO/HPC (40/60)	42.5	43,400	2.83	4.5	Poor to adequate	Poor to good	High	Passed	No	7	Fast to Moderate	7
ER	PEO/HPC (20/80)	42.5	46,400	2.33	4.4	Adequate to good	Poor	Low	Passed	No	14-15	Slow	9
ES	PEO/HPMC (80/20)	37.5	29,000	2.14	4.4	Adequate	Good	High	Passed	Yes	4	Fast to Moderate	8
ET	PEO/HPMC (60/40)	37.5	47,000	2.37	3.9	Poor to adequate	Slight	High	Passed	Yes	3	Fast to Moderate	9
EU	PEO/HPMC (40/60)	35.0	54,800	3.55	4.5	Adequate to good	Low	Low	Passed	Yes	8	Slow	8
EV	PEO/HPMC (20/80)	35.0	96,600	4.43	4.5	Good	Low	Low	Passed	No	22	Slow	10
EW	PEO/PVA (80/20)	37.5	41,600	2.92	9	Weak	Moderate	High	Passed	No	3	Moderate	10

POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. application Ser. No. 10/856,176, filed May 28, 2004 now U.S. Pat. No. 7,666,337, which claims the benefit of U.S. Provisional Application No. 60/473,902, filed May 28, 2003 and is a continuation-in-part of U.S. application Ser. No. 10/768,809, filed Jan. 30, 2004 now U.S. Pat. No. 7,357,891, which claims benefit to U.S. Provisional Application No. 60/443,741 filed Jan. 30, 2003 and is a continuation-in-part of:

(a) PCT/US02/32575 filed Oct. 11, 2002, which claims priority to: (1) U.S. application Ser. No. 10/074,272, filed Feb. 14, 2002 which claims benefit to U.S. Provisional Application No. 60/328,868, filed Oct. 12, 2001 and (2) U.S. Provisional Application No. 60/386,937, filed Jun. 7, 2002;

(b) PCT/US02/32594, filed Oct. 11, 2002, which claims priority to: (1) U.S. Provisional Application No. 60/414,276, filed Sep. 27, 2002, (2) U.S. application Ser. No. 10/074,272, filed Feb. 14, 2002, which claims benefit to U.S. Provisional Application No. 60/328,868, filed Oct. 12, 2001 and (3) U.S. Provisional Application No. 60/386,937, filed Jun. 7, 2002; and

(c) PCT/US02/32542, filed Oct. 11, 2002, which claims priority to: (1) U.S. Provisional Application No. 60/371,940, filed Apr. 11, 2002, (2) U.S. application Ser. No. 10/074,272, filed Feb. 14, 2002, which claims benefit to U.S. Provisional Application No. 60/328,868, filed Oct. 12, 2001 and (3) U.S. Provisional Application No. 60/386,937, filed Jun. 7, 2002.

FIELD OF THE INVENTION

The invention relates to rapidly dissolving films and methods of their preparation. The films contain a polymer component, which includes polyethylene oxide optionally blended with cellulosic polymers. The films may also contain an active ingredient that is evenly distributed throughout the film. The even or uniform distribution is achieved by controlling one or more parameters, and particularly the elimination of air pockets prior to and during film formation and the use of a drying process that reduces aggregation or conglomeration of the components in the film as it forms into a solid structure.

BACKGROUND OF THE RELATED TECHNOLOGY

Active ingredients, such as drugs or pharmaceuticals, may be prepared in a tablet form to allow for accurate and consistent dosing. However, this form of preparing and dispensing medications has many disadvantages including that a large proportion of adjuvants that must be added to obtain a size able to be handled, that a larger medication form requires additional storage space, and that dispensing includes counting the tablets which has a tendency for inaccuracy. In addition, many persons, estimated to be as much as 28% of the population, have difficulty swallowing tablets. While tablets may be broken into smaller pieces or even crushed as a means of overcoming swallowing difficulties, this is not a suitable solution for many tablet or pill forms. For example, crushing or destroying the tablet or pill form to facilitate ingestion, alone or in admixture with food, may also destroy the controlled release properties.

As an alternative to tablets and pills, films may be used to carry active ingredients such as drugs, pharmaceuticals, and the like. However, historically films and the process of making drug delivery systems therefrom have suffered from a number of unfavorable characteristics that have not allowed them to be used in practice.

Films that incorporate a pharmaceutically active ingredient are disclosed in expired U.S. Pat. No. 4,136,145 to Fuchs, et al. ("Fuchs"). These films may be formed into a sheet, dried and then cut into individual doses. The Fuchs disclosure alleges the fabrication of a uniform film, which includes the combination of water-soluble polymers, surfactants, flavors, sweeteners, plasticizers and drugs. These allegedly flexible films are disclosed as being useful for oral, topical or enteral use. Examples of specific uses disclosed by Fuchs include application of the films to mucosal membrane areas of the body, including the mouth, rectal, vaginal, nasal and ear areas.

Examination of films made in accordance with the process disclosed in Fuchs, however, reveals that such films suffer from the aggregation or conglomeration of particles, i.e., self-aggregation, making them inherently non-uniform. This result can be attributed to Fuchs' process parameters, which although not disclosed likely include the use of relatively long drying times, thereby facilitating intermolecular attractive forces, convection forces, air flow and the like to form such agglomeration.

The formation of agglomerates randomly distributes the film components and any active present as well. When large dosages are involved, a small change in the dimensions of the film would lead to a large difference in the amount of active per film. If such films were to include low dosages of active, it is possible that portions of the film may be substantially devoid of any active. Since sheets of film are usually cut into unit doses, certain doses may therefore be devoid of or contain an insufficient amount of active for the recommended treatment. Failure to achieve a high degree of accuracy with respect to the amount of active ingredient in the cut film can be harmful to the patient. For this reason, dosage forms formed by processes such as Fuchs, would not likely meet the stringent standards of governmental or regulatory agencies, such as the U.S. Federal Drug Administration ("FDA"), relating to the variation of active in dosage forms. Currently, as required by various world regulatory authorities, dosage forms may not vary more than 10% in the amount of active present. When applied to dosage units based on films, this virtually mandates that uniformity in the film be present.

The problems of self-aggregation leading to non-uniformity of a film were addressed in U.S. Pat. No. 4,849,246 to Schmidt ("Schmidt"). Schmidt specifically pointed out that the methods disclosed by Fuchs did not provide a uniform film and recognized that that the creation of a non-uniform film necessarily prevents accurate dosing, which as discussed above is especially important in the pharmaceutical area. Schmidt abandoned the idea that a mono-layer film, such as described by Fuchs, may provide an accurate dosage form and instead attempted to solve this problem by forming a multi-layered film. Moreover, his process is a multi-step process that adds expense and complexity and is not practical for commercial use.

Other U.S. patents directly addressed the problems of particle self-aggregation and non-uniformity inherent in conventional film forming techniques. In one attempt to overcome non-uniformity, U.S. Pat. No. 5,629,003 to Horstmann et al. and U.S. Pat. No. 5,948,430 to Zerbe et al. incorporated additional ingredients, i.e. gel formers and polyhydric alcohols respectively, to increase the viscosity of the film prior to drying in an effort to reduce aggregation of the components in

the film. These methods have the disadvantage of requiring additional components, which translates to additional cost and manufacturing steps. Furthermore, both methods employ the use the conventional time-consuming drying methods such as a high-temperature air-bath using a drying oven, drying tunnel, vacuum drier, or other such drying equipment. The long length of drying time aids in promoting the aggregation of the active and other adjuvant, notwithstanding the use of viscosity modifiers. Such processes also run the risk of exposing the active, i.e., a drug, or vitamin C, or other components to prolonged exposure to moisture and elevated temperatures, which may render it ineffective or even harmful.

In addition to the concerns associated with degradation of an active during extended exposure to moisture, the conventional drying methods themselves are unable to provide uniform films. The length of heat exposure during conventional processing, often referred to as the "heat history", and the manner in which such heat is applied, have a direct effect on the formation and morphology of the resultant film product. Uniformity is particularly difficult to achieve via conventional drying methods where a relatively thicker film, which is well-suited for the incorporation of a drug active, is desired. Thicker uniform films are more difficult to achieve because the surfaces of the film and the inner portions of the film do not experience the same external conditions simultaneously during drying. Thus, observation of relatively thick films made from such conventional processing shows a non-uniform structure caused by convection and intermolecular forces and requires greater than 10% moisture to remain flexible. The amount of free moisture can often interfere over time with the drug leading to potency issues and therefore inconsistency in the final product.

Conventional drying methods generally include the use of forced hot air using a drying oven, drying tunnel, and the like. The difficulty in achieving a uniform film is directly related to the rheological properties and the process of water evaporation in the film-forming composition. When the surface of an aqueous polymer solution is contacted with a high temperature air current, such as a film-forming composition passing through a hot air oven, the surface water is immediately evaporated forming a polymer film or skin on the surface. This seals the remainder of the aqueous film-forming composition beneath the surface, forming a barrier through which the remaining water must force itself as it is evaporated in order to achieve a dried film. As the temperature outside the film continues to increase, water vapor pressure builds up under the surface of the film, stretching the surface of the film, and ultimately ripping the film surface open allowing the water vapor to escape. As soon as the water vapor has escaped, the polymer film surface reforms, and this process is repeated, until the film is completely dried. The result of the repeated destruction and reformation of the film surface is observed as a "ripple effect" which produces an uneven, and therefore non-uniform film. Frequently, depending on the polymer, a surface will seal so tightly that the remaining water is difficult to remove, leading to very long drying times, higher temperatures, and higher energy costs.

Other factors, such as mixing techniques, also play a role in the manufacture of a pharmaceutical film suitable for commercialization and regulatory approval. Air can be trapped in the composition during the mixing process or later during the film making process, which can leave voids in the film product as the moisture evaporates during the drying stage. The film frequently collapse around the voids resulting in an uneven film surface and therefore, non-uniformity of the final film product. Uniformity is still affected even if the voids in the film caused by air bubbles do not collapse. This situation also provides a non-uniform film in that the spaces, which are not uniformly distributed, are occupying area that would otherwise be occupied by the film composition. None of the above-mentioned patents either addresses or proposes a solution to the problems caused by air that has been introduced to the film.

Therefore, there is a need for methods and compositions for film products, which use a minimal number of materials or components, and which provide a substantially non-self-aggregating uniform heterogeneity throughout the area of the films. Desirably, such films are produced through a selection of a polymer or combination of polymers that will provide a desired viscosity, a film-forming process such as reverse roll coating, and a controlled, and desirably rapid, drying process which serves to maintain the uniform distribution of non-self-aggregated components without the necessary addition of gel formers or polyhydric alcohols and the like which appear to be required in the products and for the processes of prior patents, such as the aforementioned Horstmann and Zerbe patents. Desirably, the films will also incorporate compositions and methods of manufacture that substantially reduce or eliminate air in the film, thereby promoting uniformity in the final film product.

SUMMARY OF THE INVENTION

The present invention is directed to rapid-dissolve film products containing at least one water-soluble polymer including polyethylene oxide alone or in combination with a hydrophilic cellulosic polymer, wherein the film product is free of added plasticizers.

Another embodiment of the rapid-dissolve film product includes at least one water-soluble polymer containing about 20% to 100% by weight polyethylene oxide, about 0% to 80% by weight hydroxypropylmethyl cellulose, and about 0% to 80% by weight hydroxypropyl cellulose; an active component; sucralose; precipitated calcium carbonate;

at least one flavoring; simethicone; water; and at least one colorant, wherein the film product is free of added plasticizers, surfactants, and polyalcohols.

Yet another embodiment of the present invention is directed to an edible water-soluble delivery system in the form of a film composition, which contains at least one water-soluble polymer comprising polyethylene oxide alone or in combination with a polymer selected from the group consisting of hydroxypropylmethyl cellulose and hydroxypropyl cellulose, wherein the edible water-soluble delivery system is essentially free of organic solvents, plasticizers, surfactants, and polyalcohols.

The present invention is also directed to processes for making a film having a substantially uniform distribution of components, including the steps of: (a) combining at least one water-soluble polymer comprising polyethylene oxide alone or in combination with a hydrophilic cellulosic polymer, a solvent, and an active component to form a matrix with a uniform distribution of the components; (b) forming a film from the matrix; and (c) drying the film, wherein the film is free of added plasticizers.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** shows a side view of a package containing a unit dosage film of the present invention.

FIG. **2** shows a top view of two adjacently coupled packages containing individual unit dosage forms of the present invention, separated by a tearable perforation.

FIG. **3** shows a side view of the adjacently coupled packages of FIG. **2** arranged in a stacked configuration.

FIG. **4** shows a perspective view of a dispenser for dispensing the packaged unit dosage forms, dispenser containing the packaged unit dosage forms in a stacked configuration.

FIG. **5** is a schematic view of a roll of coupled unit dose packages of the present invention.

FIG. **6** is a schematic view of an apparatus suitable for preparation of a pre-mix, addition of an active, and subsequent formation of the film.

FIG. **7** is a schematic view of an apparatus suitable for drying the films of the present invention.

FIG. **8** is a sequential representation of the drying process of the present invention.

FIG. **9** is a photographic representation of a film dried by conventional drying processes.

FIG. **10** is a photographic representation of a film dried by conventional drying processes.

FIG. **11** is a photographic representation of a film dried by conventional drying processes.

FIG. **12** is a photographic representation of a film dried by conventional drying processes.

FIG. **13** is a photographic representation of a film dried by conventional drying processes.

FIG. **14** is a photographic representation of a film dried by conventional drying processes.

FIG. **15** is a photographic representation of a film dried by conventional drying processes.

FIG. **16** is a photographic representation of a film dried by conventional drying

FIG. **17** is a photographic representation of a film dried by the inventive drying process.

FIG. **18** is a photomicrographic representation of a film containing fat coated particles dried by the inventive drying process.

FIG. **19** is a photomicrographic representation of a film containing fat coated particles dried by the inventive drying process.

FIG. **20** is a photomicrographic representation of a film containing fat coated particles dried by the inventive drying process.

FIG. **21** is a photomicrographic representation of a film containing fat coated particles dried by the inventive drying process.

FIG. **22** is a photomicrographic representation of a film containing fat coated particles dried by the inventive drying process.

FIG. **23** is a photomicrographic representation of a film containing fat coated particles dried by the inventive drying process.

FIG. **24** is a photomicrographic representation of a film containing fat coated particles dried by the inventive drying process.

FIG. **25** is a photomicrographic representation of a film containing fat coated particles dried by the inventive drying process.

FIG. **26** is a photomicrographic representation of fat coated particles not in film, heated for 9 minutes at 80° C.

FIG. **27** is a photomicrographic representation of fat coated particles not in film, heated for 9 minutes at 80° C.

FIG. **28** is a photomicrographic representation of fat coated particles at room temperature prior to processing.

FIG. **29** is a photomicrographic representation of fat coated particles at room temperature prior to processing.

FIG. **30** is a photomicrographic representation of fat coated particles at room temperature prior to processing.

FIG. **31** is a photomicrographic representation of fat coated particles at room temperature prior to processing.

FIG. **32** is a graphical representation of a microarray on the blood of a human after ingestion by the human of a film of the present invention containing a bovine derived protein.

FIG. **33** is a graphical representation of the temperature differential between the inside and outside of a film of the present invention during drying.

FIG. **34** is a graphical representation of the temperature differential between the inside and outside of a film of the present invention during drying.

FIG. **35** is a schematic representation of a continuously-linked zone drying apparatus in accordance with the present invention.

FIG. **36** is a schematic representation of a separate zone drying apparatus in accordance with the present invention.

FIG. **37** is a schematic representation of a extrusion device for use in producing films of the present invention.

FIG. **38** provides a table of various compositions of the invention, as well as certain properties.

DETAILED DESCRIPTION OF THE INVENTION

For the purposes of the present invention the term non-self-aggregating uniform heterogeneity refers to the ability of the films of the present invention, which are formed from one or more components in addition to a polar solvent, to provide a substantially reduced occurrence of, i.e. little or no, aggregation or conglomeration of components within the film as is normally experienced when films are formed by conventional drying methods such as a high-temperature air-bath using a drying oven, drying tunnel, vacuum drier, or other such drying equipment. The term heterogeneity, as used in the present invention, includes films that will incorporate a single component, such as a polymer, as well as combinations of components, such as a polymer and an active. Uniform heterogeneity includes the substantial absence of aggregates or conglomerates as is common in conventional mixing and heat drying methods used to form films.

Furthermore, the films of the present invention have a substantially uniform thickness, which is also not provided by the use of conventional drying methods used for drying water-based polymer systems. The absence of a uniform thickness detrimentally affects uniformity of component distribution throughout the area of a given film.

The film products of the present invention are produced by a combination of a properly selected polymer and a polar solvent, optionally including an active ingredient as well as other fillers known in the art. These films provide a non-self-aggregating uniform heterogeneity of the components within them by utilizing a selected casting or deposition method and a controlled drying process. Examples of controlled drying processes include, but are not limited to, the use of the apparatus disclosed in U.S. Pat. No. 4,631,837 to Magoon ("Magoon"), herein incorporated by reference, as well as hot air impingement across the bottom substrate and bottom heating plates. Another drying technique for obtaining the films of the present invention is controlled radiation drying, in the absence of uncontrolled air currents, such as infrared and radio frequency radiation (i.e. microwaves).

The objective of the drying process is to provide a method of drying the films that avoids complications, such as the noted "rippling" effect, that are associated with conventional drying methods and which initially dry the upper surface of the film, trapping moisture inside. In conventional oven drying methods, as the moisture trapped inside subsequently evaporates, the top surface is altered by being ripped open and

then reformed. These complications are avoided by the present invention, and a uniform film is provided by drying the bottom surface of the film first or otherwise preventing the formation of polymer film formation (skin) on the top surface of the film prior to drying the depth of the film. This may be achieved by applying heat to the bottom surface of the film with substantially no top air flow, or alternatively by the introduction of controlled microwaves to evaporate the water or other polar solvent within the film, again with substantially no top air flow. Yet alternatively, drying may be achieved by using balanced fluid flow, such as balanced air flow, where the bottom and top air flows are controlled to provide a uniform film. In such a case, the air flow directed at the top of the film should not create a condition which would cause movement of particles present in the wet film, due to forces generated by the air currents. Additionally, air currents directed at the bottom of the film should desirably be controlled such that the film does not lift up due to forces from the air. Uncontrolled air currents, either above or below the film, can create non-uniformity in the final film products. The humidity level of the area surrounding the top surface may also be appropriately adjusted to prevent premature closure or skinning of the polymer surface.

This manner of drying the films provides several advantages. Among these are the faster drying times and a more uniform surface of the film, as well as uniform distribution of components for any given area in the film. In addition, the faster drying time allows viscosity to quickly build within the film, further encouraging a uniform distribution of components and decrease in aggregation of components in the final film product. Desirably, the drying of the film will occur within about ten minutes or fewer, or more desirably within about five minutes or fewer.

The present invention yields exceptionally uniform film products when attention is paid to reducing the aggregation of the compositional components. By avoiding the introduction of and eliminating excessive air in the mixing process, selecting polymers and solvents to provide a controllable viscosity and by drying the film in a rapid manner from the bottom up, such films result.

The products and processes of the present invention rely on the interaction among various steps of the production of the films in order to provide films that substantially reduce the self-aggregation of the components within the films. Specifically, these steps include the particular method used to form the film, making the composition mixture to prevent air bubble inclusions, controlling the viscosity of the film forming composition and the method of drying the film. More particularly, a greater viscosity of components in the mixture is particularly useful when the active is not soluble in the selected polar solvent in order to prevent the active from settling out. However, the viscosity must not be too great as to hinder or prevent the chosen method of casting, which desirably includes reverse roll coating due to its ability to provide a film of substantially consistent thickness.

In addition to the viscosity of the film or film-forming components or matrix, there are other considerations taken into account by the present invention for achieving desirable film uniformity. For example, stable suspensions are achieved which prevent solid (such as drug particles) sedimentation in non-colloidal applications. One approach provided by the present invention is to balance the density of the particulate (ρ_p) and the liquid phase (ρ_1) and increase the viscosity of the liquid phase (μ). For an isolated particle, Stokes law relates the terminal settling velocity (Vo) of a rigid spherical body of radius (r) in a viscous fluid, as follows:

$$V_o=(2gr^r)(\rho_p-\rho_1)/9\mu$$

At high particle concentrations, however, the local particle concentration will affect the local viscosity and density. The viscosity of the suspension is a strong function of solids volume fraction, and particle-particle and particle-liquid interactions will further hinder settling velocity.

Stokian analyses has shown that the incorporation of a third phase, dispersed air or nitrogen, for example, promotes suspension stability. Further, increasing the number of particles leads to a hindered settling effect based on the solids volume fraction. In dilute particle suspensions, the rate of sedimentation, v, can be expressed as:

$$v/V_o=1/(1+\kappa\phi)$$

where κ=a constant, and ϕ is the volume fraction of the dispersed phase. More particles suspended in the liquid phase results in decreased velocity. Particle geometry is also an important factor since the particle dimensions will affect particle-particle flow interactions.

Similarly, the viscosity of the suspension is dependent on the volume fraction of dispersed solids. For dilute suspensions of non-interaction spherical particles, an expression for the suspension viscosity can be expressed as:

$$\mu/\mu_o=1+2.5\phi$$

where μ_o is the viscosity of the continuous phase and ϕ is the solids volume fraction. At higher volume fractions, the viscosity of the dispersion can be expressed as

$$\mu/\mu_o=1+2.5\phi+C_1\phi^2+C_2\phi^3+\ldots$$

where C is a constant.

The viscosity of the liquid phase is critical and is desirably modified by customizing the liquid composition to a viscoelastic non-Newtonian fluid with low yield stress values. This is the equivalent of producing a high viscosity continuous phase at rest. Formation of a viscoelastic or a highly structured fluid phase provides additional resistive forces to particle sedimentation. Further, flocculation or aggregation can be controlled minimizing particle-particle interactions. The net effect would be the preservation of a homogeneous dispersed phase.

The addition of hydrocolloids to the aqueous phase of the suspension increases viscosity, may produce viscoelasticity and can impart stability depending on the type of hydrocolloid, its concentration and the particle composition, geometry, size, and volume fraction. The particle size distribution of the dispersed phase needs to be controlled by selecting the smallest realistic particle size in the high viscosity medium, i.e., <500 μm. The presence of a slight yield stress or elastic body at low shear rates may also induce permanent stability regardless of the apparent viscosity. The critical particle diameter can be calculated from the yield stress values. In the case of isolated spherical particles, the maximum shear stress developed in settling through a medium of given viscosity can be given as

$$\tau_{max}=3V\mu/2r$$

For pseudoplastic fluids, the viscosity in this shear stress regime may well be the zero shear rate viscosity at the Newtonian plateau.

A stable suspension is an important characteristic for the manufacture of a pre-mix composition which is to be fed into the film casting machinery film, as well as the maintenance of this stability in the wet film stage until sufficient drying has occurred to lock-in the particles and matrix into a sufficiently solid form such that uniformity is maintained. For viscoelastic fluid systems, a rheology that yields stable suspensions for

extended time period, such as 24 hours, must be balanced with the requirements of high-speed film casting operations. A desirable property for the films is shear thinning or pseudoplasticity, whereby the viscosity decreases with increasing shear rate. Time dependent shear effects such as thixotropy are also advantageous. Structural recovery and shear thinning behavior are important properties, as is the ability for the film to self-level as it is formed.

The rheology requirements for the inventive compositions and films are quite severe. This is due to the need to produce a stable suspension of particles, for example 30-60 wt %, in a viscoelastic fluid matrix with acceptable viscosity values throughout a broad shear rate range. During mixing, pumping, and film casting, shear rates in the range of $10\text{-}10^5$ sec.$^{-1}$ may be experienced and pseudoplasticity is the preferred embodiment.

In film casting or coating, rheology is also a defining factor with respect to the ability to form films with the desired uniformity. Shear viscosity, extensional viscosity, viscoelasticity, structural recovery will influence the quality of the film. As an illustrative example, the leveling of shear-thinning pseudoplastic fluids has been derived as

$$\alpha^{(n-1/n)}=\alpha_o^{(n-1/n)}-((n-1)/(2n-1))(\tau/K)^{1/n}(2\pi/\lambda)^{(3+n)/n}h^{(2n+1)/n}t$$

where α is the surface wave amplitude, α_o is the initial amplitude, λ is the wavelength of the surface roughness, and both "n" and "K" are viscosity power law indices. In this example, leveling behavior is related to viscosity, increasing as n decreases, and decreasing with increasing K.

Desirably, the films or film-forming compositions of the present invention have a very rapid structural recovery, i.e. as the film is formed during processing, it doesn't fall apart or become discontinuous in its structure and compositional uniformity. Such very rapid structural recovery retards particle settling and sedimentation. Moreover, the films or film-forming compositions of the present invention are desirably shear-thinning pseudoplastic fluids. Such fluids with consideration of properties, such as viscosity and elasticity, promote thin film formation and uniformity.

Thus, uniformity in the mixture of components depends upon numerous variables. As described herein, viscosity of the components, the mixing techniques and the rheological properties of the resultant mixed composition and wet casted film are important aspects of the present invention. Additionally, control of particle size and particle shape are further considerations. Desirably, the size of the particulate a particle size of 150 microns or less, for example 100 microns or less. Moreover, such particles may be spherical, substantially spherical, or non-spherical, such as irregularly shaped particles or ellipsoidally shaped particles. Ellipsoidally shaped particles or ellipsoids are desirable because of their ability to maintain uniformity in the film forming matrix as they tend to settle to a lesser degree as compared to spherical particles.

A number of techniques may be employed in the mixing stage to prevent bubble inclusions in the final film. To provide a composition mixture with substantially no air bubble formation in the final product, anti-foaming or surface-tension reducing agents are employed. Additionally, the speed of the mixture is desirably controlled to prevent cavitation of the mixture in a manner which pulls air into the mix. Finally, air bubble reduction can further be achieved by allowing the mix to stand for a sufficient time for bubbles to escape prior to drying the film. Desirably, the inventive process first forms a masterbatch of film-forming components without active ingredients such as drug particles or volatile materials such as flavor oils. The actives are added to smaller mixes of the masterbatch just prior to casting. Thus, the masterbatch premix can be allowed to stand for a longer time without concern for instability in drug or other ingredients.

When the matrix is formed including the film-forming polymer and polar solvent in addition to any additives and the active ingredient, this may be done in a number of steps. For example, the ingredients may all be added together or a premix may be prepared. The advantage of a pre-mix is that all ingredients except for the active may be combined in advance, with the active added just prior to formation of the film. This is especially important for actives that may degrade with prolonged exposure to water, air or another polar solvent.

FIG. **6** shows an apparatus **20** suitable for the preparation of a pre-mix, addition of an active and subsequent formation of a film. The pre-mix or master batch **22**, which includes the film-forming polymer, polar solvent, and any other additives except a drug active is added to the master batch feed tank **24**. The components for pre-mix or master batch **22** are desirably formed in a mixer (not shown) prior to their addition into the master batch feed tank **24**. Then a pre-determined amount of the master batch is controllably fed via a first metering pump **26** and control valve **28** to either or both of the first and second mixers, **30**, **30'**. The present invention, however, is not limited to the use of two mixers, **30**, **30'**, and any number of mixers may suitably be used. Moreover, the present invention is not limited to any particular sequencing of the mixers **30**, **30'**, such as parallel sequencing as depicted in FIG. **6**, and other sequencing or arrangements of mixers, such as series or combination of parallel and series, may suitably be used. The required amount of the drug or other ingredient, such as a flavor, is added to the desired mixer through an opening, **32**, **32'**, in each of the mixers, **30**, **30'**. Desirably, the residence time of the pre-mix or master batch **22** is minimized in the mixers **30**, **30'**. While complete dispersion of the drug into the pre-mix or master batch **22** is desirable, excessive residence times may result in leaching or dissolving of the drug, especially in the case for a soluble drug. Thus, the mixers **30**, **30'** are often smaller, i.e. lower residence times, as compared to the primary mixers (not shown) used in forming the pre-mix or master batch **22**. After the drug has been blended with the master batch pre-mix for a sufficient time to provide a uniform matrix, a specific amount of the uniform matrix is then fed to the pan **36** through the second metering pumps, **34**, **34'**. The metering roller **38** determines the thickness of the film **42** and applies it to the application roller. The film **42** is finally formed on the substrate **44** and carried away via the support roller **46**.

While the proper viscosity uniformity in mixture and stable suspension of particles, and casting method are important in the initial steps of forming the composition and film to promote uniformity, the method of drying the wet film is also important. Although these parameters and properties assist uniformity initially, a controlled rapid drying process ensures that the uniformity will be maintained until the film is dry.

The wet film is then dried using controlled bottom drying or controlled microwave drying, desirably in the absence of external air currents or heat on the top (exposed) surface of the film **48** as described herein. Controlled bottom drying or controlled microwave drying advantageously allows for vapor release from the film without the disadvantages of the prior art. Conventional convection air drying from the top is not employed because it initiates drying at the top uppermost portion of the film, thereby forming a barrier against fluid flow, such as the evaporative vapors, and thermal flow, such as the thermal energy for drying. Such dried upper portions

serve as a barrier to further vapor release as the portions beneath are dried, which results in non-uniform films. As previously mentioned some top air flow can be used to aid the drying of the films of the present invention, but it must not create a condition that would cause particle movement or a rippling effect in the film, both of which would result in non-uniformity. If top air is employed, it is balanced with the bottom air drying to avoid non-uniformity and prevent film lift-up on the carrier belt. A balance top and bottom air flow may be suitable where the bottom air flow functions as the major source of drying and the top air flow is the minor source of drying. The advantage of some top air flow is to move the exiting vapors away from the film thereby aiding in the overall drying process. The use of any top air flow or top drying, however, must be balanced by a number of factors including, but not limited, to rheological properties of the composition and mechanical aspects of the processing. Any top fluid flow, such as air, also must not overcome the inherent viscosity of the film-forming composition. In other words, the top air flow cannot break, distort or otherwise physically disturb the surface of the composition. Moreover, air velocities are desirably below the yield values of the film, i.e., below any force level that can move the liquids in the film-forming compositions. For thin or low viscosity compositions, low air velocity must be used. For thick or high viscosity compositions, higher air velocities may be used. Furthermore, air velocities are desirable low so as to avoid any lifting or other movement of the film formed from the compositions.

Moreover, the films of the present invention may contain particles that are sensitive to temperature, such as flavors, which may be volatile, or drugs, proteins, or antigens, which may have a low degradation temperature. In such cases, the drying temperature may be decreased while increasing the drying time to adequately dry the uniform films of the present invention. Furthermore, bottom drying also tends to result in a lower internal film temperature as compared to top drying. In bottom drying, the evaporating vapors more readily carry heat away from the film as compared to top drying which lowers the internal film temperature. Such lower internal film temperatures often result in decreased drug degradation and decreased loss of certain volatiles, such as flavors.

During film preparation, it may be desirable to dry films at high temperatures. High heat drying produces uniform films, and leads to greater efficiencies in film production. Films containing sensitive active components, however, may face degradation problems at high temperatures. Degradation is the "decomposition of a compound . . . exhibiting well-defined intermediate products." The American Heritage Dictionary of the English Language (4^{th} ed. 2000). Degradation of an active component is typically undesirable as it may cause instability, inactivity, and/or decreased potency of the active component. For instance, if the active component is a drug or bioactive material, this may adversely affect the safety or efficacy of the final pharmaceutical product. Additionally, highly volatile materials will tend to be quickly released from this film upon exposure to conventional drying methods.

Degradation of an active component may occur through a variety of processes, such as, hydrolysis, oxidation, and light degradation, depending upon the particular active component. Moreover, temperature has a significant effect on the rate of such reactions. The rate of degradation typically doubles for every 10° C. increase in temperature. Therefore, it is commonly understood that exposing an active component to high temperatures will initiate and/or accelerate undesirable degradation reactions.

Proteins are one category of useful active ingredients that will degrade, denature, or otherwise become inactive when they are exposed to high temperatures for extended periods of time. Proteins serve a variety of functions in the body such as enzymes, structural elements, hormones and immunoglobulins. Examples of proteins include enzymes such as pancreatin, trypsin, pancrelipase, chymotrypsin, hyaluronidase, sutilains, streptokinaw, urokinase, altiplase, papain, bromelainsdiastase, structural elements such as collagen and albumin, hormones such as thyroliberin, gonadoliberin, adrenocorticottropin, corticotrophin, cosyntropin, sometrem, somatropion, prolactin, thyrotropin, somatostatin, vasopressin, felypressin, lypressin, insulin, glucagons, gastrin, pentagastrin, secretin, cholecystokinin-pancreozymin, and immunomodulators which may include polysaccharides in addition to glycoproteins including cytokines which are useful for the inhibition and prevention of malignant cell growth such as tumor growth. A suitable method for the production of some useful glycoproteins is disclosed in U.S. Pat. No. 6,281,337 to Cannon-Carlson, et al., which in incorporated herein in its entirety.

Temperatures that approach 100° C. will generally cause degradation of proteins as well as nucleic acids. For example some glycoproteins will degrade if exposed to a temperature of 70° C. for thirty minutes. Proteins from bovine extract are also known to degrade at such low temperatures. DNA also begins to denature at this temperature.

Applicants have discovered, however, that the films of the present invention may be exposed to high temperatures during the drying process without concern for degradation, loss of activity or excessive evaporation due to the inventive process for film preparation and forming. In particular, the films may be exposed to temperatures that would typically lead to degradation, denaturization, or inactivity of the active component, without causing such problems. According to the present invention, the manner of drying may be controlled to prevent deleterious levels of heat from reaching the active component.

As discussed herein, the flowable mixture is prepared to be uniform in content in accordance with the teachings of the present invention. Uniformity must be maintained as the flowable mass was formed into a film and dried. During the drying process of the present invention, several factors produce uniformity within the film while maintaining the active component at a safe temperature, i.e., below its degradation temperature. First, the films of the present invention have an extremely short heat history, usually only on the order of minutes, so that total temperature exposure is minimized to the extent possible. The films are controllably dried to prevent aggregation and migration of components, as well as preventing heat build up within. Desirably, the films are dried from the bottom. Controlled bottom drying, as described herein, prevents the formation of a polymer film, or skin, on the top surface of the film. As heat is conducted from the film bottom upward, liquid carrier, e.g., water, rises to the film surface. The absence of a surface skin permits rapid evaporation of the liquid carrier as the temperature increases, and thus, concurrent evaporative cooling of the film. Due to the short heat exposure and evaporative cooling, the film components such as drag or volatile actives remain unaffected by high temperatures. In contrast, skinning on the top surface traps liquid carrier molecules of increased energy within the film, thereby causing the temperature within the film to rise and exposing active components to high, potentially deleterious temperatures.

Second, thermal mixing occurs within the film due to bottom heating and absence of surface skinning. Thermal mixing occurs via convection currents in the film. As heat is applied to the bottom of the film, the liquid near the bottom increases

in temperature, expands, and becomes less dense. As such, this hotter liquid rises and cooler liquid takes its place. While rising, the hotter liquid mixes with the cooler liquid and shares thermal energy with it, i.e., transfers heat. As the cycle repeats, thermal energy is spread throughout the film.

Robust thermal mixing achieved by the controlled drying process of the present invention produces uniform heat diffusion throughout the film. In the absence of such thermal mixing, "hot spots" may develop. Pockets of heat in the film result in the formation of particle aggregates or danger areas within the film and subsequent non-uniformity. The formation of such aggregates or agglomerations is undesirable because it leads to non-uniform films in which the active may be randomly distributed. Such uneven distribution may lead to large differences in the amount of active per film, which is problematic from a safety and efficacy perspective.

Furthermore, thermal mixing helps to maintain a lower overall temperature inside the film. Although the film surfaces may be exposed to a temperature above that at which the active component degrades, the film interior may not reach this temperature. Due to this temperature differential, the active does not degrade.

For instance, the films of the present invention desirably are dried for 10 minutes or less. Drying the films at 80° C. for 10 minutes produces a temperature differential of about 5° C. This means that after 10 minutes of drying, the temperature of the inside of the film is 5° C. less than the outside exposure temperature. In many cases, however, drying times of less than 10 minutes are sufficient, such as 4 to 6 minutes. Drying for 4 minutes may be accompanied by a temperature differential of about 30° C., and drying for 6 minutes may be accompanied by a differential of about 25° C. Due to such large temperature differentials, the films may be dried at efficient, high temperatures without causing heat sensitive actives to degrade.

FIG. **8** is a sequential representation of the drying process of the present invention. After mechanical mixing, the film may be placed on a conveyor for continued thermal mixing during the drying process. At the outset of the drying process, depicted in Section A, the film **1** preferably is heated from the bottom **10** as it is travels via conveyor (not shown). Heat may be supplied to the film by a heating mechanism, such as, but not limited to, the dryer depicted in FIG. **7**. As the film is heated, the liquid carrier, or volatile ("V"), begins to evaporate, as shown by upward arrow **50**. Thermal mixing also initiates as hotter liquid, depicted by arrow **30**, rises and cooler liquid, depicted by arrow **40**, takes its place. Because no skin forms on the top surface **20** of the film **1**, as shown in Section B the volatile liquid continues to evaporate **50** and thermal mixing **30**/**40** continues to distribute thermal energy throughout the film. Once a sufficient amount of the volatile liquid has evaporated, thermal mixing has produced uniform heat diffusion throughout the film **1**. The resulting dried film **1** is a visco-elastic solid, as depicted in Section C. The components desirably are locked into a uniform distribution throughout the film. Although minor amounts of liquid carrier, i.e., water, may remain subsequent to formation of the visco-elastic, the film may be dried further without movement of the particles, if desired.

Furthermore, particles or particulates may be added to the film-forming composition or matrix after the composition or matrix is cast into a film. For example, particles may be added to the film **42** prior to the drying of the film **42**. Particles may be controllably metered to the film and disposed onto the film through a suitable technique, such as through the use of a doctor blade (not shown) which is a device which marginally or softly touches the surface of the film and controllably disposes the particles onto the film surface. Other suitable, but non-limiting, techniques include the use of an additional roller to place the particles on the film surface, spraying the particles onto the film surface, and the like. The particles may be placed on either or both of the opposed film surfaces, i.e., the top and/or bottom film surfaces. Desirably, the particles are securably disposed onto the film, such as being embedded into the film. Moreover, such particles are desirably not fully encased or fully embedded into the film, but remain exposed to the surface of the film, such as in the case where the particles are partially embedded or partially encased.

The particles may be any useful organoleptic agent, cosmetic agent, pharmaceutical agent, or combinations thereof. Desirably, the pharmaceutical agent is a taste-masked or a controlled-release pharmaceutical agent. Useful organoleptic agents include flavors and sweeteners. Useful cosmetic agents include breath freshening or decongestant agents, such as menthol, including menthol crystals.

Although the inventive process is not limited to any particular apparatus for the above-described desirable drying, one particular useful drying apparatus **50** is depicted in FIG. **7**. Drying apparatus **50** is a nozzle arrangement for directing hot fluid, such as but not limited to hot air, towards the bottom of the film **42** which is disposed on substrate **44**. Hot air enters the entrance end **52** of the drying apparatus and travels vertically upward, as depicted by vectors **54**, towards air deflector **56**. The air deflector **56** redirects the air movement to minimize upward force on the film **42**. As depicted in FIG. **7**, the air is tangentially directed, as indicated by vectors **60** and **60'**, as the air passes by air deflector **56** and enters and travels through chamber portions **58** and **58'** of the drying apparatus **50**. With the hot air flow being substantially tangential to the film **42**, lifting of the film as it is being dried is thereby minimized. While the air deflector **56** is depicted as a roller, other devices and geometries for deflecting air or hot fluid may suitable be used. Furthermore, the exit ends **62** and **62'** of the drying apparatus **50** are flared downwardly. Such downward flaring provides a downward force or downward velocity vector, as indicated by vectors **64** and **64'**, which tend to provide a pulling or drag effect of the film **42** to prevent lifting of the film **42**. Lifting of the film **42** may not only result in non-uniformity in the film or otherwise, but may also result in non-controlled processing of the film **42** as the film **42** and/or substrate **44** lift away from the processing equipment.

Monitoring and control of the thickness of the film also contributes to the production of a uniform film by providing a film of uniform thickness. The thickness of the film may be monitored with gauges such as Beta Gauges. A gauge may be coupled to another gauge at the end of the drying apparatus, i.e. drying oven or tunnel, to communicate through feedback loops to control and adjust the opening in the coating apparatus, resulting in control of uniform film thickness.

The film products are generally formed by combining a properly selected polymer and polar solvent, as well as any active ingredient or filler as desired. Desirably, the solvent content of the combination is at least about 30% by weight of the total combination. The matrix formed by this combination is formed into a film, desirably by roll coating, and then dried, desirably by a rapid and controlled drying process to maintain the uniformity of the film, more specifically, a non-self-aggregating uniform heterogeneity. The resulting film will desirably contain less than about 10% by weight solvent, more desirably less than about 8% by weight solvent, even more desirably less than about 6% by weight solvent and most desirably less than about 2%. The solvent may be water, a

polar organic solvent including, but not limited to, ethanol, isopropanol, acetone, methylene chloride, or any combination thereof.

In alternative embodiments, the film products of the present invention may be formed by extrusion rather than casting methods. Extrusion is particularly useful for film compositions containing polyethylene oxide-based polymer components, as discussed below. For instance, a single screw extrusion process may be employed in accordance with the present invention. According to such an extrusion process, pressure builds in the polymer melt so that it may be extruded through a die or injected into a mold.

As further explanation, a single screw extruder for use in the process of the present invention may include a barrel **300** containing a number of zones **200**, as shown in the extruder **100** depicted in FIG. **37**. These zones **200** may have varying temperatures and pressures. For instance, it may be desirable for the zones to increase in temperature as the composition proceeds through the barrel **300** to the extrusion die **400**. Any number of zones may be included in accordance with the present invention. In addition, the speed of extrusion may be controlled to produce desired film properties. For example, the extrusion composition may be held for an extended time period in the screw mixing chamber. Although this discussion is directed to single screw extrusion, other forms of extrusion are known to those skilled in the art and are considered well within the scope of the present invention.

Consideration of the above discussed parameters, such as but not limited to rheology properties, viscosity, mixing method, casting method and drying method, also impact material selection for the different components of the present invention. Furthermore, such consideration with proper material selection provides the compositions of the present invention, including a pharmaceutical and/or cosmetic dosage form or film product having no more than a 10% variance of a pharmaceutical and/or cosmetic active per unit area. In other words, the uniformity of the present invention is determined by the presence of no more than a 10% by weight of pharmaceutical and/or cosmetic variance throughout the matrix. Desirably, the variance is less than 5% by weight, less than 2% by weight, less than 1% by weight, or less than 0.5% by weight.

Film-Forming Polymers

The polymer may be water soluble, water swellable, water insoluble, or a combination of one or more either water soluble, water swellable or water insoluble polymers. The polymer may include cellulose or a cellulose derivative. Specific examples of useful water soluble polymers include, but are not limited to, polyethylene oxide (PEO), pullulan, hydroxypropylmethyl cellulose (HPMC), hydroxyethyl cellulose (HPC), hydroxypropyl cellulose, polyvinyl pyrrolidone, carboxymethyl cellulose, polyvinyl alcohol, sodium aginate, polyethylene glycol, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof. Specific examples of useful water insoluble polymers include, but are not limited to, ethyl cellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate and combinations thereof.

As used herein the phrase "water soluble polymer" and variants thereof refer to a polymer that is at least partially soluble in water, and desirably fully or predominantly soluble in water, or absorbs water. Polymers that absorb water are often referred to as being water swellable polymers. The materials useful with the present invention may be water soluble or water swellable at room temperature and other temperatures, such as temperatures exceeding room temperature. Moreover, the materials may be water soluble or water swellable at pressures less than atmospheric pressure. Desirably, the water soluble polymers are water soluble or water swellable having at least 20 percent by weight water uptake. Water swellable polymers having a 25 or greater percent by weight water uptake are also useful. Films or dosage forms of the present invention formed from such water soluble polymers are desirably sufficiently water soluble to be dissolvable upon contact with bodily fluids.

Other polymers useful for incorporation into the films of the present invention include biodegradable polymers, copolymers, block polymers and combinations thereof. Among the known useful polymers or polymer classes which meet the above criteria are: poly(glycolic acid) (PGA), poly (lactic acid) (PLA), polydioxanones, polyoxalates, poly(α-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof. Additional useful polymers include, stereopolymers of L- and D-lactic acid, copolymers of bis(p-carboxyphenoxy) propane acid and sebacic acid, sebacic acid copolymers, copolymers of caprolactone, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, copolymers of polyurethane and (poly(lactic acid), copolymers of polyurethane and poly(lactic acid), copolymers of α-amino acids, copolymers of α-amino acids and caproic acid, copolymers of α-benzyl glutamate and polyethylene glycol, copolymers of succinate and poly(glycols), polyphosphazene, polyhydroxy-alkanoates and mixtures thereof. Binary and ternary systems are contemplated.

Other specific polymers useful include those marketed under the Medisorb and Biodel trademarks. The Medisorb materials are marketed by the Dupont Company of Wilmington, Del. and are generically identified as a "lactide/glycolide co-polymer" containing "propanoic acid, 2-hydroxy-polymer with hydroxy-polymer with hydroxyacetic acid." Four such polymers include lactide/glycolide 100 L, believed to be 100% lactide having a melting point within the range of 338°-347° F. (170°-175° C.); lactide/glycolide 100 L, believed to be 100% glycolide having a melting point within the range of 437°-455° F. (225°-235° C.); lactide/glycolide 85/15, believed to be 85% lactide and 15% glycolide with a melting point within the range of 338°-347° F. (170°-175° C.); and lactide/glycolide 50/50, believed to be a copolymer of 50% lactide and 50% glycolide with a melting point within the range of 338°-347° F. (170°-175° C.).

The Biodel materials represent a family of various polyanhydrides which differ chemically.

Although a variety of different polymers may be used, it is desired to select polymers to provide a desired viscosity of the mixture prior to drying. For example, if the active or other components are not soluble in the selected solvent, a polymer that will provide a greater viscosity is desired to assist in maintaining uniformity. On the other hand, if the components are soluble in the solvent, a polymer that provides a lower viscosity may be preferred.

The polymer plays an important role in affecting the viscosity of the film. Viscosity is one property of a liquid that controls the stability of the active in an emulsion, a colloid or a suspension. Generally the viscosity of the matrix will vary from about 400 cps to about 100,000 cps, preferably from about 800 cps to about 60,000 cps, and most preferably from

about 1,000 cps to about 40,000 cps. Desirably, the viscosity of the film-forming matrix will rapidly increase upon initiation of the drying process.

The viscosity may be adjusted based on the selected active depending on the other components within the matrix. For example, if the component is not soluble within the selected solvent, a proper viscosity may be selected to prevent the component from settling which would adversely affect the uniformity of the resulting film. The viscosity may be adjusted in different ways. To increase viscosity of the film matrix, the polymer may be chosen of a higher molecular weight or crosslinkers may be added, such as salts of calcium, sodium and potassium. The viscosity may also be adjusted by adjusting the temperature or by adding a viscosity increasing component. Components that will increase the viscosity or stabilize the emulsion/suspension include higher molecular weight polymers and polysaccharides and gums, which include without limitation, alginate, carrageenan, hydroxypropyl methyl cellulose, locust bean gum, guar gum, xanthan gum, dextran, gum arabic, gellan gum and combinations thereof.

It has also been observed that certain polymers which when used alone would ordinarily require a plasticizer to achieve a flexible film, can be combined without a plasticizer and yet achieve flexible films. For example, HPMC and HPC when used in combination provide a flexible, strong film with the appropriate plasticity and elasticity for manufacturing and storage. No additional plasticizer or polyalcohol is needed for flexibility.

Additionally, polyethylene oxide (PEO), when used alone or in combination with a hydrophilic cellulosic polymer, achieves flexible, strong films. Additional plasticizers or polyalcohols are not needed for flexibility. Non-limiting examples of suitable cellulosic polymers for combination with PEO include HPC and HPMC. PEO and HPC have essentially no gelation temperature, while HPMC has a gelation temperature of 58-64° C. (Methocel EF available from Dow Chemical Co.). Moreover, these films are sufficiently flexible even when substantially free of organic solvents, which may be removed without compromising film properties. As such, if there is no solvent present, then there is no plasticizer in the films. PEO based films also exhibit good resistance to tearing, little or no curling, and fast dissolution rates when the polymer component contains appropriate levels of PEO.

To achieve the desired film properties, the level and/or molecular weight of PEO in the polymer component may be varied. Modifying the PEO content affects properties such as tear resistance, dissolution rate, and adhesion tendencies. Thus, one method for controlling film properties is to modify the PEO content. For instance, in some embodiments rapid dissolving films are desirable. By modifying the content of the polymer component, the desired dissolution characteristics can be achieved.

In accordance with the present invention, PEO desirably ranges from about 20% to 100% by weight in the polymer component. In some embodiments, the amount of PEO desirably ranges from about 1 mg to about 200 mg. The hydrophilic cellulosic polymer ranges from about 0% to about 80% by weight, or in a ratio of up to about 4:1 with the PEO, and desirably in a ratio of about 1:1.

In some embodiments, it may be desirable to vary the PEO levels to promote certain film properties. To obtain films with high tear resistance and fast dissolution rates, levels of about 50% or greater of PEO in the polymer component are desirable. To achieve adhesion prevention, i.e., preventing the film from adhering to the roof of the mouth, PEO levels of about 20% to 75% are desirable. In some embodiments, however, adhesion to the roof of the mouth may be desired, such as for administration to animals or children. In such cases, higher levels of PEO may be employed. More specifically, structural integrity and dissolution of the film can be controlled such that the film can adhere to mucosa and be readily removed, or adhere more firmly and be difficult to remove, depending on the intended use.

The molecular weight of the PEO may also be varied. High molecular weight PEO, such as about 4 million, may be desired to increase mucoadhesivity of the film. More desirably, the molecular weight may range from about 100,000 to 900,000, more desirably from about 100,000 to 600,000, and most desirably from about 100,000 to 300,000. In some embodiments, it may be desirable to combine high molecular weight (600,000 to 900,000) with low molecular weight (100,000 to 300,000) PEOs in the polymer component.

For instance, certain film properties, such as fast dissolution rates and high tear resistance, may be attained by combining small amounts of high molecular weight PEOs with larger amounts of lower molecular weight PEOs. Desirably, such compositions contain about 60% or greater levels of the lower molecular weight PEO in the PEO-blend polymer component.

To balance the properties of adhesion prevention, fast dissolution rate, and good tear resistance, desirable film compositions may include about 50% to 75% low molecular weight PEO, optionally combined with a small amount of a higher molecular weight PEO, with the remainder of the polymer component containing a hydrophilic cellulosic polymer (HPC or HPMC).

Controlled Release Films

The term "controlled release" is intended to mean the release of active at a pre-selected or desired rate. This rate will vary depending upon the application. Desirable rates include fast or immediate release profiles as well as delayed, sustained or sequential release. Combinations of release patterns, such as initial spiked release followed by lower levels of sustained release of active are contemplated. Pulsed drug releases are also contemplated.

The polymers that are chosen for the films of the present invention may also be chosen to allow for controlled disintegration of the active. This may be achieved by providing a substantially water insoluble film that incorporates an active that will be released from the film over time. This may be accomplished by incorporating a variety of different soluble or insoluble polymers and may also include biodegradable polymers in combination. Alternatively, coated controlled release active particles may be incorporated into a readily soluble film matrix to achieve the controlled release property of the active inside the digestive system upon consumption.

Films that provide a controlled release of the active are particularly useful for buccal, gingival, sublingual and vaginal applications. The films of the present invention are particularly useful where mucosal membranes or mucosal fluid is present due to their ability to readily wet and adhere to these areas.

The convenience of administering a single dose of a medication which releases active ingredients in a controlled fashion over an extended period of time as opposed to the administration of a number of single doses at regular intervals has long been recognized in the pharmaceutical arts. The advantage to the patient and clinician in having consistent and uniform blood levels of medication over an extended period of time are likewise recognized. The advantages of a variety of sustained release dosage forms are well known. However,

the preparation of a film that provides the controlled release of an active has advantages in addition to those well-known for controlled release tablets. For example, thin films are difficult to inadvertently aspirate and provide an increased patient compliance because they need not be swallowed like a tablet. Moreover, certain embodiments of the inventive films are designed to adhere to the buccal cavity and tongue, where they controllably dissolve. Furthermore, thin films may not be crushed in the manner of controlled release tablets which is a problem leading to abuse of drugs such as Oxycontin.

The actives employed in the present invention may be incorporated into the film compositions of the present invention in a controlled release form. For example, particles of drug may be coated with polymers such as ethyl cellulose or polymethacrylate, commercially available under brand names such as Aquacoat ECD and Eudragit E-100, respectively. Solutions of drug may also be absorbed on such polymer materials and incorporated into the inventive film compositions. Other components such as fats and waxes, as well as sweeteners and/or flavors may also be employed in such controlled release compositions.

The actives may be taste-masked prior to incorporation into the film composition, as set forth in co-pending PCT application titled, Uniform Films For Rapid Dissolve Dosage Form Incorporating Taste-Masking Compositions, (based on U.S. Provisional Application No. Express Mail Label No.: EU552991605 US of the same title, filed Sep. 27, 2003, Ser. No. 60/414,276 the entire subject matter of which is incorporated by reference herein.

Actives

When an active is introduced to the film, the amount of active per unit area is determined by the uniform distribution of the film. For example, when the films are cut into individual dosage forms, the amount of the active in the dosage form can be known with a great deal of accuracy. This is achieved because the amount of the active in a given area is substantially identical to the amount of active in an area of the same dimensions in another part of the film. The accuracy in dosage is particularly advantageous when the active is a medicament, i.e. a drug.

The active components that may be incorporated into the films of the present invention include, without limitation pharmaceutical and cosmetic actives, drugs, medicaments, proteins, antigens or allergens such as ragweed pollen, spores, microorganisms, seeds, mouthwash components, flavors, fragrances, enzymes, preservatives, sweetening agents, colorants, spices, vitamins and combinations thereof.

A wide variety of medicaments, bioactive active substances and pharmaceutical compositions may be included in the dosage forms of the present invention. Examples of useful drugs include ace-inhibitors, antianginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, biological response modifiers, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, anti-tumor drugs, anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, anti-convulsants, neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, terine relaxants, anti-obesity drugs, erythropoietic drugs, anti-asthmatics, cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

Examples of medicating active ingredients contemplated for use in the present invention include antacids, H_2-antagonists, and analgesics. For example, antacid dosages can be prepared using the ingredients calcium carbonate alone or in combination with magnesium hydroxide, and/or aluminum hydroxide. Moreover, antacids can be used in combination with H_2-antagonists.

Analgesics include opiates and opiate derivatives, such as oxycodone (available as Oxycontin®), ibuprofen, aspirin, acetaminophen, and combinations thereof that may optionally include caffeine.

Other preferred drugs for other preferred active ingredients for use in the present invention include anti-diarrheals such as immodium AD, anti-histamines, anti-tussives, decongestants, vitamins, and breath fresheners. Common drugs used alone or in combination for colds, pain, fever, cough, congestion, runny nose and allergies, such as acetaminophen, chlorpheniramine maleate, dextromethorphan, pseudoephedrine HCl and diphenhydramine may be included in the film compositions of the present invention.

Also contemplated for use herein are anxiolytics such as alprazolam (available as Xanax®); anti-psychotics such as clozopin (available as Clozaril®) and haloperidol (available as Haldol®); non-steroidal anti-inflammatories (NSAID's) such as dicyclofenacs (available as Voltaren®) and etodolac (available as Lodine®), anti-histamines such as loratadine (available as Claritin®), astemizole (available as Hismanal™), nabumetone (available as Relafen®), and Clemastine (available as Tavist®); anti-emetics such as granisetron hydrochloride (available as Kytril®) and nabilone (available as Cesamet™); bronchodilators such as Bentolin®, albuterol sulfate (available as Proventil®); anti-depressants such as fluoxetine hydrochloride (available as Prozac®), sertraline hydrochloride (available as Zoloft®), and paroxetine hydrochloride (available as Paxil®); anti-migraines such as Imigra®, ACE-inhibitors such as enelaprilat (available as Vasotec®), captopril (available as Capoten®) and lisinopril (available as Zestril®); anti-Alzheimer's agents, such as nicergoline; and Ca^H-antagonists such as nifedipine (available as Procardia® and Adalat®), and verapamil hydrochloride (available as Calan®).

Erectile dysfunction therapies include, but are not limited to, drugs for facilitating blood flow to the penis, and for effecting autonomic nervous activities, such as increasing

parasympathetic (cholinergic) and decreasing sympathetic (adrenersic) activities. Useful non-limiting drugs include sildenafils, such as Viagra®, tadalafils, such as Cialis®, vardenafils, apomorphines, such as Uprima®, yohimbine hydrochlorides such as Aphrodyne®, and alprostadils such as Caverject®.

The popular H_2-antagonists which are contemplated for use in the present invention include cimetidine, ranitidine hydrochloride, famotidine, nizatidine, ebrotidine, mifentidine, roxatidine, pisatidine and aceroxatidine.

Active antacid ingredients include, but are not limited to, the following: aluminum hydroxide, dihydroxyaluminum aminoacetate, aminoacetic acid, aluminum phosphate, dihydroxyaluminum sodium carbonate, bicarbonate, bismuth aluminate, bismuth carbonate, bismuth subcarbonate, bismuth subgallate, bismuth subnitrate, bismuth subsilysilate, calcium carbonate, calcium phosphate, citrate ion (acid or salt), amino acetic acid, hydrate magnesium aluminate sulfate, magaldrate, magnesium aluminosilicate, magnesium carbonate, magnesium glycinate, magnesium hydroxide, magnesium oxide, magnesium trisilicate, milk solids, aluminum mono- or di-basic calcium phosphate, tricalcium phosphate, potassium bicarbonate, sodium tartrate, sodium bicarbonate, magnesium aluminosilicates, tartaric acids and salts.

The pharmaceutically active agents employed in the present invention may include allergens or antigens, such as, but not limited to, plant pollens from grasses, trees, or ragweed; animal danders, which are tiny scales shed from the skin and hair of cats and other furred animals; insects, such as house dust mites, bees, and wasps; and drugs, such as penicillin.

An anti-oxidant may also be added to the film to prevent the degradation of an active, especially where the active is photosensitive.

Cosmetic active agents may include breath freshening compounds like menthol, other flavors or fragrances, especially those used for oral hygiene, as well as actives used in dental and oral cleansing such as quaternary ammonium bases. The effect of flavors may be enhanced using flavor enhancers like tartaric acid, citric acid, vanillin, or the like.

Also color additives can be used in preparing the films. Such color additives include food, drug and cosmetic colors (FD&C), drug and cosmetic colors (D&C), or external drug and cosmetic colors (Ext. D&C). These colors are dyes, their corresponding lakes, and certain natural and derived colorants. Lakes are dyes absorbed on aluminum hydroxide.

Other examples of coloring agents include known azo dyes, organic or inorganic pigments, or coloring agents of natural origin. Inorganic pigments are preferred, such as the oxides or iron or titanium, these oxides, being added in concentrations ranging from about 0.001 to about 10%, and preferably about 0.5 to about 3%, based on the weight of all the components.

Flavors may be chosen from natural and synthetic flavoring liquids. An illustrative list of such agents includes volatile oils, synthetic flavor oils, flavoring aromatics, oils, liquids, oleoresins or extracts derived from plants, leaves, flowers, fruits, stems and combinations thereof. A non-limiting representative list of examples includes mint oils, cocoa, and citrus oils such as lemon, orange, grape, lime and grapefruit and fruit essences including apple, pear, peach, grape, strawberry, raspberry, cherry, plum, pineapple, apricot or other fruit flavors.

The films containing flavorings may be added to provide a hot or cold flavored drink or soup. These flavorings include, without limitation, tea and soup flavorings such as beef and chicken.

Other useful flavorings include aldehydes and esters such as benzaldehyde (cherry, almond), citral i.e., alphacitral (lemon, lime), neral, i.e., beta-citral (lemon, lime), decanal (orange, lemon), aldehyde C-8 (citrus fruits), aldehyde C-9 (citrus fruits), aldehyde C-12 (citrus fruits), tolyl aldehyde (cherry, almond), 2,6-dimethyloctanol (green fruit), and 2-dodecenal (citrus, mandarin), combinations thereof and the like.

The sweeteners may be chosen from the following non-limiting list: glucose (corn syrup), dextrose, invert sugar, fructose, and combinations thereof saccharin and its various salts such as the sodium salt; dipeptide sweeteners such as aspartame; dihydrochalcone compounds, glycyrrhizin; Stevia Rebaudiana (Stevioside); chloro derivatives of sucrose such as sucralose; sugar alcohols such as sorbitol, mannitol, xylitol, and the like. Also contemplated are hydrogenated starch hydrolysates and the synthetic sweetener 3,6-dihydro-6-methy-1-1-1-1,2,3-oxathiazin-4-one-2,2-dioxide, particularly the potassium salt (acesulfame-K), and sodium and calcium salts thereof, and natural intensive sweeteners, such as Lo Han Kuo. Other sweeteners may also be used.

When the active is combined with the polymer in the solvent, the type of matrix that is formed depends on the solubilities of the active and the polymer. If the active and/or polymer are soluble in the selected solvent, this may form a solution. However, if the components are not soluble, the matrix may be classified as an emulsion, a colloid, or a suspension.

Dosages

The film products of the present invention are capable of accommodating a wide range of amounts of the active ingredient. The films are capable of providing an accurate dosage amount (determined by the size of the film and concentration of the active in the original polymer/water combination) regardless of whether the required dosage is high or extremely low. Therefore, depending on the type of active or pharmaceutical composition that is incorporated into the film, the active amount may be as high as about 300 mg, desirably up to about 150 mg or as low as the microgram range, or any amount therebetween.

The film products and methods of the present invention are well suited for high potency, low dosage drugs. This is accomplished through the high degree of uniformity of the films. Therefore, low dosage drugs, particularly more potent racemic mixtures of actives are desirable.

Anti-Foaming and De-Foaming Compositions

Anti-foaming and/or de-foaming components may also be used with the films of the present invention. These components aid in the removal of air, such as entrapped air, from the film-forming compositions. As described above, such entrapped air may lead to non-uniform films. Simethicone is one particularly useful anti-foaming and/or de-foaming agent. The present invention, however, is not so limited and other anti-foam and/or de-foaming agents may suitable be used.

As a related matter, simethicone and related agents may be employed for densification purposes. More specifically, such agents may facilitate the removal of voids, air, moisture, and similar undesired components, thereby providing denser, and thus more uniform films. Agents or components which perform this function can be referred to as densification or densifying agents. As described above, entrapped air or undesired components may lead to non-uniform films.

Simethicone is generally used in the medical field as a treatment for gas or colic in babies. Simethicone is a mixture of fully methylated linear siloxane polymers containing

repeating units of polydimethylsiloxane which is stabilized with trimethylsiloxy end-blocking unites, and silicon dioxide. It usually contains 90.5-99% polymethylsiloxane and 4-7% silicon dioxide. The mixture is a gray, translucent, viscous fluid which is insoluble in water.

When dispersed in water, simethicone will spread across the surface, forming a thin film of low surface tension. In this way, simethicone reduces the surface tension of bubbles air located in the solution, such as foam bubbles, causing their collapse. The function of simethicone mimics the dual action of oil and alcohol in water. For example, in an oily solution any trapped air bubbles will ascend to the surface and dissipate more quickly and easily, because an oily liquid has a lighter density compared to a water solution. On the other hand, an alcohol/water mixture is known to lower water density as well as lower the water's surface tension. So, any air bubbles trapped inside this mixture solution will also be easily dissipated. Simethicone solution provides both of these advantages. It lowers the surface energy of any air bubbles that trapped inside the aqueous solution, as well as lowering the surface tension of the aqueous solution. As the result of this unique functionality, simethicone has an excellent anti-foaming property that can be used for physiological processes (anti-gas in stomach) as well as any for external processes that require the removal of air bubbles from a product.

In order to prevent the formation of air bubbles in the films of the present invention, the mixing step can be performed under vacuum. However, as soon as the mixing step is completed, and the film solution is returned to the normal atmosphere condition, air will be re-introduced into or contacted with the mixture. In many cases, tiny air bubbles will be again trapped inside this polymeric viscous solution. The incorporation of simethicone into the film-forming composition either substantially reduces or eliminates the formation of air bubbles.

Simethicone may be added to the film-forming mixture as an anti-foaming agent in an amount from about 0.01 weight percent to about 5.0 weight percent, more desirably from about 0.05 weight percent to about 2.5 weight percent, and most desirably from about 0.1 weight percent to about 1.0 weight percent.

Optional Components

A variety of other components and fillers may also be added to the films of the present invention. These may include, without limitation, surfactants; plasticizers which assist in compatibilizing the components within the mixture; polyalcohols; anti-foaming agents, such as silicone-containing compounds, which promote a smoother film surface by releasing oxygen from the film; thermo-setting gels such as pectin, carageenan, and gelatin, which help in maintaining the dispersion of components; and inclusion compounds, such as cyclodextrins and caged molecules, which improve the solubility and/or stability of certain active components.

The variety of additives that can be incorporated into the inventive compositions may provide a variety of different functions. Examples of classes of additives include excipients, lubricants, buffering agents, stabilizers, blowing agents, pigments, coloring agents, fillers, bulking agents, sweetening agents, flavoring agents, fragrances, release modifiers, adjuvants, plasticizers, flow accelerators, mold release agents, polyols, granulating agents, diluents, binders, buffers, absorbents, glidants, adhesives, anti-adherents, acidulants, softeners, resins, demulcents, solvents, surfactants, emulsifiers, elastomers and mixtures thereof. These additives may be added with the active ingredient(s).

Useful additives include, for example, gelatin, vegetable proteins such as sunflower protein, soybean proteins, cotton seed proteins, peanut proteins, grape seed proteins, whey proteins, whey protein isolates, blood proteins, egg proteins, acrylated proteins, water-soluble polysaccharides such as alginates, carrageenans, guar gum, agar-agar, xanthan gum, gellan gum, gum arabic and related gums (gum ghatti, gum karaya, gum tragacanth), pectin, water-soluble derivatives of cellulose: alkylcelluloses hydroxyalkylcelluloses and hydroxyalkylalkylcelluloses, such as methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxyethylmethylcellulose, hydroxypropylmethylcellulose, hydroxybutylmethylcellulose, cellulose esters and hydroxyalkylcellulose esters such as cellulose acetate phthalate (CAP), hydroxypropylmethylcellulose (HPMC); carboxyalkylcelluloses, carboxyalkylalkylcelluloses, carboxyalkylcellulose esters such as carboxymethylcellulose and their alkali metal salts; water-soluble synthetic polymers such as polyacrylic acids and polyacrylic acid esters, polymethacrylic acids and polymethacrylic acid esters, polyvinylacetates, polyvinylalcohols, polyvinylacetatephthalates (PVAP), polyvinylpyrrolidone (PVP), PVY/vinyl acetate copolymer, and polycrotonic acids; also suitable are phthalated gelatin, gelatin succinate, crosslinked gelatin, shellac, water soluble chemical derivatives of starch, cationically modified acrylates and methacrylates possessing, for example, a tertiary or quaternary amino group, such as the diethylaminoethyl group, which may be quaternized if desired; and other similar polymers.

Such extenders may optionally be added in any desired amount desirably within the range of up to about 80%, desirably about 3% to 50% and more desirably within the range of 3% to 20% based on the weight of all components.

Further additives may be inorganic fillers, such as the oxides of magnesium aluminum, silicon, titanium, etc. desirably in a concentration range of about 0.02% to about 3% by weight and desirably about 0.02% to about 1% based on the weight of all components.

Further examples of additives are plasticizers which include polyalkylene oxides, such as polyethylene glycols, polypropylene glycols, polyethylene-propylene glycols, organic plasticizers with low molecular weights, such as glycerol, glycerol monoacetate, diacetate or triacetate, triacetin, polysorbate, cetyl alcohol, propylene glycol, sorbitol, sodium diethylsulfosuccinate, triethyl citrate, tributyl citrate, and the like, added in concentrations ranging from about 0.5% to about 30%, and desirably ranging from about 0.5% to about 20% based on the weight of the polymer.

There may further be added compounds to improve the flow properties of the starch material such as animal or vegetable fats, desirably in their hydrogenated form, especially those which are solid at room temperature. These fats desirably have a melting point of 50° C. or higher. Preferred are tri-glycerides with C_{12}-, C_{14}-, C_{16}-, C_{18}-, C_{20}- and C_{22}-fatty acids. These fats can be added alone without adding extenders or plasticizers and can be advantageously added alone or together with mono- and/or di-glycerides or phosphatides, especially lecithin. The mono- and di-glycerides are desirably derived from the types of fats described above, i.e. with C_{12}-, C_{14}-, C_{16}-, C_{18}-, C_{20}- and C_{22}-fatty acids.

The total amounts used of the fats, mono-, di-glycerides and/or lecithins are up to about 5% and preferably within the range of about 0.5% to about 2% by weight of the total composition

It is further useful to add silicon dioxide, calcium silicate, or titanium dioxide in a concentration of about 0.02% to about 1% by weight of the total composition. These compounds act as texturizing agents.

These additives are to be used in amounts sufficient to achieve their intended purpose. Generally, the combination of certain of these additives will alter the overall release profile of the active ingredient and can be used to modify, i.e. impede or accelerate the release.

Lecithin is one surface active agent for use in the present invention. Lecithin can be included in the feedstock in an amount of from about 0.25% to about 2.00% by weight. Other surface active agents, i.e. surfactants, include, but are not limited to, cetyl alcohol, sodium lauryl sulfate, the Spans™ and Tweens™ which are commercially available from ICI Americas, Inc. Ethoxylated oils, including ethoxylated castor oils, such as Cremophor® EL which is commercially available from BASF, are also useful. Carbowax™ is yet another modifier which is very useful in the present invention. Tweens™ or combinations of surface active agents may be used to achieve the desired hydrophilic-lipophilic balance ("HLB"). The present invention, however, does not require the use of a surfactant and films or film-forming compositions of the present invention may be essentially free of a surfactant while still providing the desirable uniformity features of the present invention.

As additional modifiers which enhance the procedure and product of the present invention are identified, Applicants intend to include all such additional modifiers within the scope of the invention claimed herein.

Other ingredients include binders which contribute to the ease of formation and general quality of the films. Non-limiting examples of binders include starches, pregelatinize starches, gelatin, polyvinylpyrrolidone, methylcellulose, sodium carboxymethylcellulose, ethylcellulose, polyacrylamides, polyvinyloxoazolidone, and polyvinylalcohols.

Further potential additives include solubility enhancing agents, such as substances that form inclusion compounds with active components. Such agents may be useful in improving the properties of very insoluble and/or unstable actives. In general, these substances are doughnut-shaped molecules with hydrophobic internal cavities and hydrophilic exteriors. Insoluble and/or instable actives may fit within the hydrophobic cavity, thereby producing an inclusion complex, which is soluble in water. Accordingly, the formation of the inclusion complex permits very insoluble and/or instable actives to be dissolved in water. A particularly desirable example of such agents are cyclodextrins, which are cyclic carbohydrates derived from starch. Other similar substances, however, are considered well within the scope of the present invention.

Forming the Film

The films of the present invention must be formed into a sheet prior to drying. After the desired components are combined to form a multi-component matrix, including the polymer, water, and an active or other components as desired, the combination is formed into a sheet or film, by any method known in the art such as extrusion, coating, spreading, casting or drawing the multi-component matrix. If a multi-layered film is desired, this may be accomplished by co-extruding more than one combination of components which may be of the same or different composition. A multi-layered film may also be achieved by coating, spreading, or casting a combination onto an already formed film layer.

Although a variety of different film-forming techniques may be used, it is desirable to select a method that will provide a flexible film, such as reverse roll coating. The flexibility of the film allows for the sheets of film to be rolled and transported for storage or prior to being cut into individual dosage forms. Desirably, the films will also be self-supporting or in other words able to maintain their integrity and structure in the absence of a separate support. Furthermore, the films of the present invention may be selected of materials that are edible or ingestible.

Coating or casting methods are particularly useful for the purpose of forming the films of the present invention. Specific examples include reverse roll coating, gravure coating, immersion or dip coating, metering rod or meyer bar coating, slot die or extrusion coating, gap or knife over roll coating, air knife coating, curtain coating, or combinations thereof, especially when a multi-layered film is desired.

Roll coating, or more specifically reverse roll coating, is particularly desired when forming films in accordance with the present invention. This procedure provides excellent control and uniformity of the resulting films, which is desired in the present invention. In this procedure, the coating material is measured onto the applicator roller by the precision setting of the gap between the upper metering roller and the application roller below it. The coating is transferred from the application roller to the substrate as it passes around the support roller adjacent to the application roller. Both three roll and four roll processes are common.

The gravure coating process relies on an engraved roller running in a coating bath, which fills the engraved dots or lines of the roller with the coating material. The excess coating on the roller is wiped off by a doctor blade and the coating is then deposited onto the substrate as it passes between the engraved roller and a pressure roller.

Offset Gravure is common, where the coating is deposited on an intermediate roller before transfer to the substrate.

In the simple process of immersion or dip coating, the substrate is dipped into a bath of the coating, which is normally of a low viscosity to enable the coating to run back into the bath as the substrate emerges.

In the metering rod coating process, an excess of the coating is deposited onto the substrate as it passes over the bath roller. The wire-wound metering rod, sometimes known as a Meyer Bar, allows the desired quantity of the coating to remain on the substrate. The quantity is determined by the diameter of the wire used on the rod.

In the slot die process, the coating is squeezed out by gravity or under pressure through a slot and onto the substrate. If the coating is 100% solids, the process is termed "Extrusion" and in this case, the line speed is frequently much faster than the speed of the extrusion. This enables coatings to be considerably thinner than the width of the slot.

It may be particularly desirable to employ extrusion methods for forming film compositions containing PEO polymer components. These compositions contain PEO or PEO blends in the polymer component, and may be essentially free of added plasticizers, and/or surfactants, and polyalcohols. The compositions may be extruded as a sheet at processing temperatures of less than about 90° C. Extrusion may proceed by squeezing the film composition through rollers or a die to obtain a uniform matrix. The extruded film composition then is cooled by any mechanism known to those of ordinary skill in the art. For example, chill rollers, air cooling beds, or water cooling beds may be employed. The cooling step is particularly desirable for these film compositions because PEO tends to hold heat.

The gap or knife over roll process relies on a coating being applied to the substrate which then passes through a "gap"

between a "knife" and a support roller. As the coating and substrate pass through, the excess is scraped off.

Air knife coating is where the coating is applied to the substrate and the excess is "blown off" by a powerful jet from the air knife. This procedure is useful for aqueous coatings.

In the curtain coating process, a bath with a slot in the base allows a continuous curtain of the coating to fall into the gap between two conveyors. The object to be coated is passed along the conveyor at a controlled speed and so receives the coating on its upper face.

Drying the Film

The drying step is also a contributing factor with regard to maintaining the uniformity of the film composition. A controlled drying process is particularly important when, in the absence of a viscosity increasing composition or a composition in which the viscosity is controlled, for example by the selection of the polymer, the components within the film may have an increased tendency to aggregate or conglomerate. An alternative method of forming a film with an accurate dosage, that would not necessitate the controlled drying process, would be to cast the films on a predetermined well. With this method, although the components may aggregate, this will not result in the migration of the active to an adjacent dosage form, since each well may define the dosage unit per se.

When a controlled or rapid drying process is desired, this may be through a variety of methods. A variety of methods may be used including those that require the application of heat. The liquid carriers are removed from the film in a manner such that the uniformity, or more specifically, the non-self-aggregating uniform heterogeneity, that is obtained in the wet film is maintained.

Desirably, the film is dried from the bottom of the film to the top of the film. Desirably, substantially no air flow is present across the top of the film during its initial setting period, during which a solid, visco-elastic structure is formed. This can take place within the first few minutes, e.g. about the first 0.5 to about 4.0 minutes of the drying process. Controlling the drying in this manner, prevents the destruction and reformation of the film's top surface, which results from conventional drying methods. This is accomplished by forming the film and placing it on the top side of a surface having top and bottom sides. Then, heat is initially applied to the bottom side of the film to provide the necessary energy to evaporate or otherwise remove the liquid carrier. The films dried in this manner dry more quickly and evenly as compared to air-dried films, or those dried by conventional drying means. In contrast to an air-dried film that dries first at the top and edges, the films dried by applying heat to the bottom dry simultaneously at the center as well as at the edges. This also prevents settling of ingredients that occurs with films dried by conventional means.

The temperature at which the films are dried is about 100° C. or less, desirably about 90° C. or less, and most desirably about 80° C. or less.

Another method of controlling the drying process, which may be used alone or in combination with other controlled methods as disclosed above includes controlling and modifying the humidity within the drying apparatus where the film is being dried. In this manner, the premature drying of the top surface of the film is avoided.

Additionally, it has also been discovered that the length of drying time can be properly controlled, i.e. balanced with the heat sensitivity and volatility of the components, and particularly the flavor oils and drugs. The amount of energy, temperature and length and speed of the conveyor can be balanced to accommodate such actives and to minimize loss, degradation or ineffectiveness in the final film.

A specific example of an appropriate drying method is that disclosed by Magoon. Magoon is specifically directed toward a method of drying fruit pulp. However, the present inventors have adapted this process toward the preparation of thin films.

The method and apparatus of Magoon are based on an interesting property of water. Although water transmits energy by conduction and convection both within and to its surroundings, water only radiates energy within and to water. Therefore, the apparatus of Magoon includes a surface onto which the fruit pulp is placed that is transparent to infrared radiation. The underside of the surface is in contact with a temperature controlled water bath. The water bath temperature is desirably controlled at a temperature slightly below the boiling temperature of water. When the wet fruit pulp is placed on the surface of the apparatus, this creates a "refractance window." This means that infrared energy is permitted to radiate through the surface only to the area on the surface occupied by the fruit pulp, and only until the fruit pulp is dry. The apparatus of Magoon provides the films of the present invention with an efficient drying time reducing the instance of aggregation of the components of the film.

Another method of controlling the drying process involves a zone drying procedure. A zone drying apparatus may include a continuous belt drying tunnel having one or more drying zones located within. The conditions of each drying zone may vary, for example, temperature and humidity may be selectively chosen. It may be desirable to sequentially order the zones to provide a stepped up drying effect.

The speed of the zone drying conveyor desirably is continuous. Alternatively, the speed may be altered at a particular stage of the drying procedure to increase or decrease exposure of the film to the conditions of the desired zone. Whether continuous or modified, the zone drying dries the film without surface skinning.

According to an embodiment of the zone drying apparatus **100**, shown in FIG. **35**, the film **110** may be fed onto the continuous belt **120**, which carries the film through the different drying zones. The first drying zone that the film travels through **101** may be a warm and humid zone. The second zone **102** may be hotter and drier, and the third zone **103** may also be hot and dry. These different zones may be continuous, or alternatively, they may be separated, as depicted by the zone drying apparatus **200** in FIG. **36**. The zone drying apparatus, in accordance with the present invention, is not limited to three drying zones. The film may travel through lesser or additional drying zones of varying heat and humidity levels, if desired, to produce the controlled drying effect of the present invention.

To further control temperature and humidity, the drying zones may include additional atmospheric conditions, such as inert gases. The zone drying apparatus further may be adapted to include additional processes during the zone drying procedure, such as, for example, spraying and laminating processes, so long as controlled drying is maintained in accordance with the invention.

The films may initially have a thickness of about 500 μm to about 1,500 μm, or about 20 mils to about 60 mils, and when dried have a thickness from about 3 μm to about 250 μm, or about 0.1 mils to about 10 mils. Desirably, the dried films will have a thickness of about 2 mils to about 8 mils, and more desirably, from about 3 mils to about 6 mils.

Testing Films for Uniformity

It may be desirable to test the films of the present invention for chemical and physical uniformity during the film manu-

facturing process. In particular, samples of the film may be removed and tested for uniformity in film components between various samples. Film thickness and over all appearance may also be checked for uniformity. Uniform films are desired, particularly for films containing pharmaceutical active components for safety and efficacy reasons.

A method for testing uniformity in accordance with the present invention includes conveying a film through a manufacturing process. This process may include subjecting the film to drying processes, dividing the film into individual dosage units, and/or packaging the dosages, among others. As the film is conveyed through the manufacturing process, for example on a conveyor belt apparatus, it is cut widthwise into at least one portion. The at least one portion has opposing ends that are separate from any other film portion. For instance, if the film is a roll, it may be cut into separate sub-rolls. Cutting the film may be accomplished by a variety of methods, such as with a knife, razor, laser, or any other suitable means for cutting a film.

The cut film then may be sampled by removing small pieces from each of the opposed ends of the portion(s), without disrupting the middle of the portion(s). Leaving the middle section intact permits the predominant portion of the film to proceed through the manufacturing process without interrupting the conformity of the film and creating sample-inducted gaps in the film. Accordingly, the concern of missing doses is alleviated as the film is further processed, e.g., packaged. Moreover, maintaining the completeness of cut portions or sub-rolls throughout the process will help to alleviate the possibility of interruptions in further film processing or packaging due to guilty control issues, for example, alarm stoppage due to notice of missing pieces.

After the end pieces, or sampling sections, are removed from the film portion(s), they may be tested for uniformity in the content of components between samples. Any conventional means for examining and testing the film pieces may be employed, such as, for example, visual inspection, use of analytical equipment, and any other suitable means known to those skilled in the art. If the testing results show non-uniformity between film samples, the manufacturing process may be altered. This can save time and expense because the process may be altered prior to completing an entire manufacturing run. For example, the drying conditions, mixing conditions, compositional components and/or film viscosity may be changed. Altering the drying conditions may involve changing the temperature, drying time, moisture level, and dryer positioning, among others.

Moreover, it may be desirable to repeat the steps of sampling and testing throughout the manufacturing process. Testing at multiple intervals may ensure that uniform film dosages are continuously produced. Alterations to the process can be implemented at any stage to minimize non-uniformity between samples.

Uses of Thin Films

The thin films of the present invention are well suited for many uses. The high degree of uniformity of the components of the film makes them particularly well suited for incorporating pharmaceuticals. Furthermore, the polymers used in construction of the films may be chosen to allow for a range of disintegration times for the films. A variation or extension in the time over which a film will disintegrate may achieve control over the rate that the active is released, which may allow for a sustained release delivery system. In addition, the films may be used for the administration of an active to any of several body surfaces, especially those including mucous membranes, such as oral, anal, vaginal, opthalmological, the surface of a wound, either on a skin surface or within a body such as during surgery, and similar surfaces.

The films may be used to orally administer an active. This is accomplished by preparing the films as described above and introducing them to the oral cavity of a mammal. This film may be prepared and adhered to a second or support layer from which it is removed prior to use, i.e. introduction to the oral cavity. An adhesive may be used to attach the film to the support or backing material which may be any of those known in the art, and is preferably not water soluble. If an adhesive is used, it will desirably be a food grade adhesive that is ingestible and does not alter the properties of the active. Mucoadhesive compositions are particularly useful. The film compositions in many cases serve as mucoadhesives themselves.

The films may be applied under or to the tongue of the mammal. When this is desired, a specific film shape, corresponding to the shape of the tongue may be preferred. Therefore the film may be cut to a shape where the side of the film corresponding to the back of the tongue will be longer than the side corresponding to the front of the tongue. Specifically, the desired shape may be that of a triangle or trapezoid. Desirably, the film will adhere to the oral cavity preventing it from being ejected from the oral cavity and permitting more of the active to be introduced to the oral cavity as the film dissolves.

Another use for the films of the present invention takes advantage of the films' tendency to dissolve quickly when introduce to a liquid. An active may be introduced to a liquid by preparing a film in accordance with the present invention, introducing it to a liquid, and allowing it to dissolve. This may be used either to prepare a liquid dosage form of an active, or to flavor a beverage.

The films of the present invention are desirably packaged in sealed, air and moisture resistant packages to protect the active from exposure oxidation, hydrolysis, volatilization and interaction with the environment. Referring to FIG. **1**, a packaged pharmaceutical dosage unit **10**, includes each film **12** individually wrapped in a pouch or between foil and/or plastic laminate sheets **14**. As depicted in FIG. **2**, the pouches **10**, **10'** can be linked together with tearable or perforated joints **16**. The pouches **10**, **10'** may be packaged in a roll as depicted in FIG. **5** or stacked as shown in FIG. **3** and sold in a dispenser **18** as shown in FIG. **4**. The dispenser may contain a full supply of the medication typically prescribed for the intended therapy, but due to the thinness of the film and package, is smaller and more convenient than traditional bottles used for tablets, capsules and liquids. Moreover, the films of the present invention dissolve instantly upon contact with saliva or mucosal membrane areas, eliminating the need to wash the dose down with water.

Desirably, a series of such unit doses are packaged together in accordance with the prescribed regimen or treatment, e.g., a 10-90 day supply, depending on the particular therapy. The individual films can be packaged on a backing and peeled off for use.

The features and advantages of the present invention are more fully shown by the following examples which are provided for purposes of illustration, and are not to be construed as limiting the invention in any way.

EXAMPLES

Examples A-I

Water soluble thin film compositions of the present invention are prepared using the amounts described in Table 1.

TABLE 1

Component	Weight (g) A	B	C	D	E	F	G	H	I
Hydroxypropylmethyl cellulose		1.76		1.63	32.00		3.67		32.00
Peppermint oil		0.90	1.0	1.05		8.0	2.67		
Sweetener	0.15	0.15	0.22	0.10		4.6	1.53	0.15	
Polyvinylpyrrolidone		0.94		1.05		7.0	2.33		
Tween 80[1]	0.5	0.5	2.0	0.65	11.80		1.35	0.5	11.80
Simethicone[2]	0.2	0.2	0.15	0.30	1.80		0.21	0.2	1.80
Listerine[3]	83.35							83.35	
Methylcellulose	6.0								
Cornstarch[4]			1.75						
Agar			1.25						
Water		42.24	93.63	39.22	768.0	280.0	88.24		768.0
Loratadine[5]					19.2				19.2
Pullulan[6]								6.0	
Ibuprofen									38.4

[1]Available from ICI Americas

[2]Available from OSI

[3]Available from Pfizer, Inc. including thymol (0.064%), eucalyptol (0.092%), methyl salicylate (0.060%), menthol (0.042%), water (up to 72.8%), alcohol (26.9%), benzoic acid, poloxamer 407, sodium benzoate, and caramel color

[4]Available from Grain Processing Corporation as Pure Cote B792

[5]Available from Schering Corporation as Claritin

[6]Available from Hayashibara Biochemical Laboratories, Inc., Japan

The ingredients of inventive compositions A-I were combined by mixing until a uniform mixture was achieved. The compositions were then formed into a film by reverse roll coating. These films were then dried on the top side of an infrared transparent surface, the bottom side of which was in contact with a heated water bath at approximately 99° C. No external thermal air currents were present above the film. The films were dried to less than about 6% by weight water in about 4 to 6 minutes. The films were flexible, self-supporting and provided a uniform distribution of the components within the film.

The uniform distribution of the components within the film was apparent by examination by either the naked eye or under slight magnification. By viewing the films it was apparent that they were substantially free of aggregation, i.e. the carrier and the actives remained substantially in place and did not move substantially from one portion of the film to another. Therefore, there was substantially no disparity among the amount of active found in any portion of the film.

Uniformity was also measured by first cutting the film into individual dosage forms. Twenty-five dosage forms of substantially identical size were cut from the film of inventive composition (E) above from random locations throughout the film. Then eight of these dosage forms were randomly selected and additively weighed. The additive weights of eight randomly selected dosage forms, are as shown in Table 2 below:

TABLE 2

Sample	Additive Weight (g) Trial 1	Trial 2
1	0.04	0.04
2	0.08	0.08
3	0.12	0.12
4	0.16	0.16
5	0.20	0.20
6	0.24	0.24
7	0.28	0.28
8	0.32	0.32

The individual dosages were consistently 0.04 gm, which shows that the distribution of the components within the film was consistent and uniform. This is based on the simple principal that each component has a unique density. Therefore, when the components of different densities are combined in a uniform manner in a film, as in the present invention, individual dosages forms from the same film of substantially equal dimensions, will contain the same mass.

An alternative method of determining the uniformity of the active is to cut the film into individual doses. The individual doses may then be dissolved and tested for the amount of active in films of particular size. This demonstrates that films of substantially similar size cut from different locations on the same film contain substantially the same amount of active.

When the films formed from inventive compositions A-H are placed on the tongue, they rapidly dissolve, releasing the active ingredient. Similarly, when they are placed in water, the films rapidly dissolve which provides a flavored drink when the active is chosen to be a flavoring.

Examples J-L

Thin films that have a controlled degradation time and include combinations of water soluble and water insoluble polymers and water soluble films that allow controlled release of an active are prepared using approximately the amounts described in Table 3.

TABLE 3

Component	Weight (g) J	K	L
Hydroxypropylmethyl cellulose		1.0	1.0
Tween 80[1]	0.7	0.7	0.7
Water			5.0
Aquacoat ECD[2]	17.0	17.0	17.5
Peppermint oil	1.0	0.4	1.1

[1]Available from ICI Americas

[2]A 30% by weight aqueous dispersion of ethyl cellulose available from FMC

The components of inventive compositions J-L were combined and formed into films using the methods for preparing

inventive compositions A-I above. These films were also flexible, self-supporting and provided a uniform distribution of active which permits accuracy in dosing.

The uniformity of the films prepared from inventive compositions J-L may also be tested by either visual means measuring the weights of individual dosage films, or by dissolving the films and testing for the amount of active as described above.

Examples M-O

An alternative method of preparing films which provides an accurate dosing may be used for any of inventive compositions A-I. The method begins with first combining the ingredients with mixing. The combination of ingredients is then divided among individual wells or molds. In such a method, aggregation of the components during drying is prevented by the individual wells.

TABLE 4

	Weight %		
Component	M	N	O
5% Methylcellulose Solution[1]	73.22	44.22	74.22
Raspberry Flavor	3.28	3.28	3.28
Sweetener Blends	1.07	1.07	1.07
Tween-80[2]	2.47	2.47	2.47
Polyvinylpyrrolidone	3.30	3.30	3.30
Ethanol 95%	8.24	8.24	8.24
Propylene Glycol	1.65	1.65	1.65
Calcium Carbonate	4.12	4.12	4.12
Cornstarch[3]	1.65	1.65	1.65
Red Dye[4]	1.00		
Corn Syrup[5]		30.00	

[1]Available from Dow Chemical Co. as Methocel K35
[2]Available from ICI Americas
[3]Available from Grain Processing Corporation as Pure Cote B792
[4]Available from McCormick
[5]Available from Bestfoods, Inc. as Karo Syrup

The ingredients in the above Table 4 were combined and formed into a film by casting the combination of ingredients onto the glass surface and applying heat to the bottom side of the glass. This provided inventive compositions M-O.

The film of composition M was examined both prior to and after drying for variations in the shading provided by the red dye. The film was examined both under sunlight and by incandescent bulb light. No variations in shade or intensity of color were observed.

Further testing of the films of composition M included testing of absorption which is directly related to concentration. The film was cut into segments each measuring 1.0 in. by 0.75 in., which were consecutively assigned numbers. Approximately 40 mg of the scrap material from which the segments were cut was dissolved in about 10 ml of distilled water and then quantitatively transferred to a 25 ml volumetric flask and brought to volume. The solution was centrifuged and scanned at 3 nm intervals from 203-1200 nm. The frequency of maximum absorption was found to be 530 nm. The solution was then re-centrifuged at a higher RPM (for the same length of time) and re-scanned, which demonstrated no change in the % transmission or frequency.

Each of the segments were weighed to 0.1 mg and then dissolved in 10 ml distilled water and transferred quantitatively to a 25 ml volumetric flask and brought to volume with distilled water. Each segment solution was then centrifuged as above, and then scanned, at first from 203-1200 nm and later from only 500 nm to 550 nm at a 1 nm scanning speed. The value recorded was the % transmission at the lowest wave length, which was most frequently 530 nm.

The absorption values are shown in Table 5 below:

TABLE 5

Segment	mg/% A
1-2	1.717
3-4	1.700
5-6	1.774
7*	1.701
9-10	1.721
11-12	1.729
13-14	1.725
15-16	1.713

*segment 8 was lost

The overall average absorption was 1.724. Of the 15 segments tested, the difference between the highest and lowest values was 0.073 units, or 4% based on the average. This shows excellent control over the uniformity of the dye within the composition because the absorption is directly proportional to the concentration of the dye within each segment.

The film of inventive composition N provided a very flexible film. This film was able to be stretched and exhibited a very high tensile strength.

After forming the film of inventive composition O, the film was removed from the glass by very rapidly stripping the length of the glass with a razor. This provided very tightly wound "toothpick-like" dosage forms. Each dosage form consistently weighed 0.02 g. This demonstrates the uniformity of the dosage forms as well as the superior self-supporting properties of the films.

Examples P-W

Compositions P-W were prepared to demonstrate the interaction among various conditions in production of films as they relate to the present invention. The ingredients in the below Table 6 were combined and formed into a film using the process parameters listed in Table 7 below, prepared in a 6 m drying tunnel designed to incorporate bottom drying of the films. Each of the examples shows the effect of different ingredient formulations and processing techniques on the resultant film products.

TABLE 6

	Weight (g)							
Component	P	Q	R	S	T	U	V	W
Hydroxy propylmethyl cellulose	320	320	320	320	320	320	345	345
Water	1440	1440	1440	1440		1440	999	999
Sweetener						60	60	45
Mint Flavor						80	80	
Propylene Glycol	50	50	50	100	100	100	100	69.3
Xanthan	22		11	11.23	10	10	10	6.9
Water/ Ethanol (60/40)					1440			
Orange Flavor								42

TABLE 7

	Film Thickness (Micron)	Top[1] v (m/sec)	Bot.[1] v (m/sec)	T[1] (° C.)	Top[2] v (m/sec)
P1	100	0	22	75	0
P2	350	0	22	75	0
P3	350	0	40	75	0
P4	350	0	40	75	0
P5	350	10	40	75	10
Q	350	0	40	75	10
R	350	0	40	85	10
S1	250	0	40	100	0
S2	300	0	40	100	0
S3	350	0	40	100	0
T1	250	0	40	100	0
T2	350	0	40	100	0
U1	300	0	40	100	0
U2	250	0	40	100	0
U3	300	0	40	100	0
V1	300	0	40	100	0
V2	300	0	40	100	0
V3	300	0	40	100	0
W1	300	0	40	93	0
W2	250	0	40	90	0
W3	200	0	40	90	0

	Bot.[2] v (m/sec)	T[2] (° C.)	Film Weight (g)	Coater Speed m/min	% Moisture
P1	23	60	109	5	>20
P2	23	60	n/a	5	>20
P3	40	60	161	3	>20
P4	40	75	191	3	>20
P5	40	75	253	3	>20
Q	40	75	n/a	3	>20
R	0	85		2.5	>20
S1	40	90	163	1.5	<5
S2	40	90	193	1.5	<5
S3	40	90	225	1.5	<5
T1	40	90	64	1.5	<5
T2	40	90	83	1.5	<5
U1	40	90	208	1.5	20
U2	40	90	177	1.5	20
U3	40	90	212	1.3	20
V1	40	90	237	1.3	20
V2	40	100	242	1.3	20
V3	40	100	221	1	6
W1	40	90	220	1.3	5
W2	40	90	199	1.3	5
W3	40	90	169	1.3	5

[1]First Heater Section (3 m)
[2]Second Heater Section (3 m)

In Table 7, each of the process parameters contributes to different properties of the films. Film thickness refers to the distance between the blade and the roller in the reverse roll coating apparatus. Bottom velocity and top velocity refer to the speed of air current on the bottom and top sides of the film, respectively. The film weight is a measure of the weight of a circular section of the substrate and the film of 100 cm^2.

Compositions P-R show the effects of visco-elastic properties on the ability to coat the film composition mixture onto the substrate for film formation. Composition P displayed a stringy elastic property. The wet film would not stay level, the coating was uneven, and the film did not dry. In Composition Q, substantially the same formulation as P was used however the xanthan was not included. This product coated the substrate but would not stay level due to the change in the visco-elastic properties of the wet foam. Composition R was prepared using substantially the same formulation, but incorporated one-half of the amount of xanthan of Composition P. This formulation provided a composition that could be evenly coated. Compositions P-Q demonstrate the importance of proper formulation on the ability of the film matrix to conform to a particular coating technique.

The films produced from Composition S contained a large amount of air in the films. This is shown by the dried film thickness which was the same despite that variation in the coated thickness as in Table 7. Microscopic examination of the film revealed a large number of air bubbles in the film. In order to correct for the addition of air in the films, care must be taken in the mixing process to avoid air inclusion.

Composition T included a change in the solvent to 60/40 water ethanol. Composition T was stirred slowly for 45 min. to deaerate the mixture. The dried weight film products T1 and T2 were consistent with the increase in solids from T1 to T2. The films dried much faster with less than 5% moisture. With the particular combination of ingredients in Composition T, the substitution of part ethanol for part water allowed the film to dry more quickly. The elimination of air from the film as a result of the slow stirring also contributed to the uniformity of the final film product and the faster drying time.

Only water was used as a solvent in Composition U. The dried weight of the U1-U3 changed consistently in accordance with the change in coating thickness indicating that no air bubbles were present. However, these films contained 20% moisture upon exit from the oven, unlike the films of Composition T, which included part ethanol and dried completely.

The amount of solids was increased and the amount of water was decreased in Compositions V1 and V2. The dried weight was greater than U1-U3 due to the increase in solids, however the films still contained 20% moisture upon exit from the oven, similar to Composition U.

The coating line speed was reduced for Composition V3, to prevent premature drying of the exposed top film surface. This film product dried to 6% moisture.

While increasing the amount of solids improved the film weight, longer drying times were required. This was due to the surface of the film sealing preventing easy removal of the water. Therefore, for Compositions W1-W3, the temperature in the first 3 m section of the dryer was decreased. This prevented the premature drying of the top surface of the films. Even at greater film thicknesses, the films were dried to 5% moisture even at faster coater line speeds.

Examples X-AA

TABLE 8

	Weight (g)			
Component	X	Y	Z	AA
Loratadine	104.69			
Zomig		52.35		
Paxil			104.69	
Hydroxypropyl methylcellulose	320	320	320	150
Sweetener blend	60	60	60	0.4
Simethicone	1.5	1.5	1.5	1.5
Propylene glycol	100	100	100	
Water	1440	1440	1440	790
Cream essence				0.4
Polyvinyl pyrrolidinone				4
Ethanol				40
Cocoa				55.2
Polyoxyl-40-stearate				7

Compositions X, Y and Z of Table 8 were taste mask coated using a Glatt coater and Eudragit E-100 polymethacrylate

polymer as the coating. The coating was spray coated at a 20% level. Therefore 10 mg of drug 12.5 mg of the final dry product must be weighed.

The base formula which excluded the drug additive was mixed with care to not incorporate air. After initial mixing the formula was slowly mixed to deaerate over 30 min. During this time the drug was weighed and prepared for addition to the base mix.

For Composition X, the Loratadine (80% drug) was added slowly to the mix with stirring. After 5 min. of stirring, the total mix was added to the pan of a three roll coater set (reverse roll coater) at 30 micron coating thickness.

The process bottom temperature was set at 90° C. with no top heat or air, the bottom air velocity was set at 40 m/sec., and the line speed was set at 1.3 m/min. Total drying time for the film was 4.6 min.

The liquid was coated at 30 microns and dried in the oven in less than 5 min. The film was flexible and a 1"×0.75" piece weighed 70 mg and contained 10 mg of Loratadine.

The experiment was repeated for Compositions Y and Z, Zomig and Paxil, respectively. Both produced flexible films with the target weight of 70 mg containing 5 mg of Zomig and 70 mg containing 10 mg of Paxil, respectively.

The products were sweet without any noticeable drug aftertaste.

Examples BA-BI

The incorporation of the anti-foaming/de-foaming agent (i.e., simethicone) provided a film that not only provided a uniform film that substantially reduced or eliminated air bubbles in the film product, but also provided other benefits. The films displayed more desirable organoleptic properties. The films had an improved texture that was less "paper-like" provided a better mouth-feel to the consumer.

The compositions in Table 9 were prepared (including the addition of simethicone in inventive compositions BA-BG) and mixed under vacuum to remove air bubbles.

The resultant uncut films of inventive compositions BA-BG exhibited uniformity in content particularly with respect to the insoluble active, as well as unit doses of ¾" by 1" by 5 mils cut therefrom. The inventive compositions also were observed to have a smooth surface, absent of air bubbles. The significantly higher amounts of simethicone present in inventive compositions BF-BG also provided a very uniform film, but not significantly improved from that of inventive compositions BA-BE.

By contrast, comparative examples BH-BI were observed to have a rougher surface, exhibiting the inclusion of air bubbles in the resultant film which provided a less uniform texture and distribution of the ingredients.

TABLE 9

Component	BA	BB	BC	BD	BE	BF	BG	BH	BI
Hydroxypropylmethyl cellulose	0	3.77	3.70	3.84	0	3.67	0	0	3.84
Peppermint oil	2.94	1.93	2.39	0	0	2.67	2.94	2.67	0
Sweetener	2.20	0.32	0.23	0	0.17	1.53	2.20	1.54	0
Polyvinylpyrrolidone	2.68	2.01	2.39	0	0	2.33	2.68	2.34	0
Tween 80[1]	2.24	1.07	1.48	1.42	0.55	1.35	2.24	0	1.42
Simethicone[2]	0.66	0.42	0.68	0.22	0.22	5.00	2.00	0	0
Listerine[3]	0	0	0	0	92.41	0	0	0	0
Methylcellulose	4.03	0	0	0	0	0	4.03	0	0
Cornstarch[4]	2.68	0	0	0	0	0	2.68	0	0
Water	73.53	90.47	89.14	92.22	0	83.45	72.19	93.46	92.44
Loratadine[5]	4.29	0	0	2.31	0	0	4.29	0	2.31
Pullulan[6]	0	0	0	0	6.65	0	0	0	0
Calcium Carbonate	1.43	0	0	0	0	0	1.43	0	0
Xanthan Gum	0.30	0	0	0	0	0	0.30	0	0
Propylene Glycol	3.02	0	0	0	0	0	3.02	0	0

[1]Available from ICI Americas

[2]Available from OSI

[3]Available from Pfizer, Inc. including thymol (0.064%), eucalyptol (0.092%), methyl salicylate (0.060%), menthol (0.042%), water (up to 72.8%), alcohol (26.9%), benzoic acid, poloxamer 407, sodium benzoate, and caramel color

[4]Available from Grain Processing Corporation as Pure Cote B792

[5]Available from Schering Corporation as Claritin

[6]Available from Hayashibara Biochemical Laboratories, Inc., Japan

The ingredients of Composition AA were mixed in order to reduce air captured in the fluid matrix. After mixing 45 g of loratadine coated at a 80% active level and 20% coating using Eudragit E-100, this mixture was added slowing with mixing until the drug was evenly dispersed, approximately 5 min. The liquid was then deposited into the 3 roll coater (reverse roll coater) and coated at 30 microns at a line speed of 1.3 m/min. The oven temperature was set at 90° C. to apply air and heat to the bottom only, with an air velocity set at 40 m/sec. The dried film was 0.005 inch. thick (5 mil) and was cut into 1 in.×0.75 in. pieces weighing 70 mg+/−0.7 mg, demonstrating the uniformity of the composition of the film. The film was flexible with 5% moisture, free of air bubbles, and had uniform drug distribution as seen under the light microscope, as well as shown by the substantially identical weight measurements of the film pieces.

Examples CA-CC

The following examples of the present invention describe films and film-forming compositions that use an ethoxylated caster oil as a surfactant, or alternatively are free of surfactants, plasticizers and/or polyalcohols. Desirably, the films or film-forming compositions of the present invention are essentially free of surfactants. Moreover, the films or film-forming compositions of the present invention are desirably formulated to be essentially free of surfactants. Furthermore, the films or film-forming compositions of the present invention are desirably formulated to be essentially free of plasticizers. Still furthermore, the films or film-forming compositions of the present invention are desirably formulated to be essentially free of polyalcohols. Moreover, the films or film-form-

ing compositions of the present invention are desirably formulated to be essentially free of surfactants and plasticizers. Furthermore, the films or film-forming compositions of the present invention are desirably formulated to be essentially free of surfactants, plasticizers and polyalcohols.

TABLE 10

Component	(parts by wt.) CA
POLYMERS:	
Hydroxypropylmethyl cellulose	15.6
Cornstarch[1]	10.41
Polyvinylpyrrolidone	10.41
Xanthan Gum	1.14
SURFACTANT[2]:	2.0
PLASTICIZER[3]:	11.67
ANTI-FOAM AGENT[4]	2.44
OTHER	
Spearmint Flavor	10.43
Loratadine (drug)	16.62
Calcium Carbonate	5.54
Sweetener	9.36

[1]Available from Grain Processing Corporation as Pure Cote B792
[2]Ethoxylated caster oil, Cremophor ® EL available from BASF
[3]Propylene Glycol
[4]Silicone Emulsion

The above ingredients were added at 30% to 70% water and stirred until polymers were fully hydrated which took 45 min. The mix was then put under vacuum to eliminate entrapped air. Vacuum was added in a steady manner starting at 500 mm and progressing up to 760 mm over 45 min.

After release of the vacuum, 6 grams of the liquid was added to a coating paper using a 200 micron spiral wound rod and a K Control Coater Model 101 (RK Print Coat Inst. Ltd.). The paper substrate onto which the coating was added was a silicone coated paper. The coated paper was then dried at 90° C. until about 5% moisture remained. The formula coated and dried to a film thickness of approx. 60 microns and quickly dissolved in the mouth.

TABLE 11

Component	(parts by wt.) CB
POLYMERS:	
Hydroxypropylmethyl cellulose	15.6
Cornstarch[1]	10.41
Polyvinylpyrrolidone	10.41
PLASTICIZER/SOLVENT[2]:	22.1
ANTI-FOAM AGENT[3]	2.44
OTHER	
Raspberry Flavor	0.3
Calcium Carbonate[4]	30.38
Sweetener	8.36

[1]Available from Grain Processing Corporation as Pure Cote B792
[2]Propylene Glycol
[3]Polydimethyl Siloxane Emulsion
[4]Functioned to mimic drug loading

The above ingredients were added to water at 40% until a homogeneous suspension was made. Vacuum was added over 20 min. starting at 500 mm Hg. and ending at 660 mm Hg. until all air was removed from suspension. Film was made as described in prior experiments. The liquid coated the silicone release substrate and dried to a uniform flexible film. The film passed the 180° bend test without cracking and dissolved in the mouth.

TABLE 12

Component	(parts by wt.) CC
POLYMERS:	
Hydroxypropylmethyl cellulose	7.8
Hydroxypropyl cellulose	7.8
ANTI-FOAM AGENT[1]	0.75
OTHER	
Peppermint & Bittermint Flavor	2.25
Tastemasking Flavor[2]	0.3
Calcium Carbonate[3]	15.2
Sweeteners	0.9

[1]Polydimethyl Siloxane Emulsion
[2]Prosweet from Virginia Dare
[3]Functioned to mimic drug loading

The above ingredients were added at 30% to 70% water and stirred until polymers were fully hydrated which took 20 min. The mix was then put under vacuum to eliminate entrapped air. Vacuum was added in a steady manner up to 760 mm over 35 min.

After release of the vacuum, the liquid was added to a coating paper using a 350 micron smooth bar and a K Control Coater Model 101 (RK Print Coat Inst. Ltd.). The paper substrate onto which the coating was added was a silicone coated paper. The coated paper was then dried at 90° C. until about 4% moisture remained. The formula coated and dried to a film. The film had an acceptable taste and quickly dissolved in the mouth. The taste-masking flavor is an ingredient that affects the taste receptors to mask the receptors from registering a different, typical undesirable, taste. The film passed the 180° bend test without cracking and dissolved in the mouth.

Example CD

The following example of the present invention describes films and film-forming compositions that use a taste-masked, pharmaceutically active agent which also contains flavors and taste-masking aids. A taste-masking flavor is an ingredient that effects taste receptors to mask the receptors from registering a different, typically undesirable, taste.

TABLE 13

Component	(grams) CD
Hydroxypropylmethyl cellulose	4.26
Hydroxypropyl cellulose	1.42
Precipitated calcium Carbonate	1.22
Sweetner[1]	0.6
Taste-Masking flavor[2]	0.08
Taste-masked Acetaminophen[3]	5.86
Cinnamon Flavor	0.9
Spearmint Flavor	0.43
Polydimethylsiloxane emulsion	0.23

[1]Sucralose, available from McNeil Nutritionals
[2]Magna Sweet, available from Mafco Worldwide Corp.
[3]Gutte Enteric, coated acetaminophen, Gatte, LLC

The above ingredients, except for the pharmaceutically active agent and flavors, were added at 35 grams water and stirred until polymers were fully hydrated which took about 20 min. Food coloring (7 drops of red food coloring and 1

drop of yellow fool coloring) was also added. The mix was then put under vacuum to eliminate entrapped air. Vacuum was added in a steady manner starting at 500 mm and progressing up to 760 mm over about 10 to 20 minutes. The taste-masked Acetaminophen was added to the mix in about 4 minutes was stirring under vacuum. The flavors were then added to the mix in about 4 minutes was stirring under vacuum.

After release of the vacuum, the liquid solution was added to a coating paper using a 350 micron smooth bar. The paper substrate onto which the coating was added was a silicone coated paper. The coated paper was then dried at 90° C. for about 11 minutes until about 3% moisture remained.

The formula coated and dried to a film. The film had an acceptable taste and moderately quickly dissolved in the mouth. The film did not curl on standing. The film passed the 180° bend test without cracking and dissolved in the mouth.

Examples CE-CF

Thin film compositions of the present invention were prepared using the amounts described in Table 14.

TABLE 14

Component	Weight (g)
Hydroxypropylmethyl cellulose	3.92
Pullulan	3.92
Trehalose[1]	3.5
Precipitated Calcium Carbonate	3.85
Propylene Glycol	1.96
Simethicone[2]	0.35
Bovine Extract[3]	32.5
Water	q.s.

[1]Available from Cargill Inc.
[2]Available from Sentry
[3]Available from Amarillo Biosciences Inc.

The above ingredients were combined by mixing until a uniform mixture was achieved. A sufficient amount of water was present in the film compositions prior to drying, i.e., q.s., which may range between about 200 g to about 1000 g. The bovine extract protein contained in the compositions is a heat sensitive protein. After mixing, the compositions were cast into films on release paper using a K-Control Coater with a 250 micron smooth bar.

In Example CE, the films subsequently were dried in an oven at approximately 80° C. for about 6 minutes. The films were dried to about 4.3 percent moisture. In Example CF, the films were dried in an oven at approximately 60° C. for about 10 minutes. The films were dried to about 5.06 percent moisture. After drying, the protein derived from bovine extract, which was contained in the films, was tested to determine whether or not it remained substantially active. To test the activity, a film dosage unit of this example was administered to a human. After ingesting the dosage, a microarray on the human's blood was conducted. The results, listed in Appendix A which is incorporated by reference herein, and graphically represented in FIG. **32**, demonstrate that the protein was approximately 100 percent active in the final, dried film products of both Examples CE and CF. Therefore, the heat sensitive active did not substantially degrade or denaturize during the drying process.

Example CG

Thin film compositions of the present invention were prepared using the amounts described in Table 15.

TABLE 15

Component	Weight (g unless otherwise indicated) CG	CH
Hydroxypropylmethyl cellulose	4.59	9.18
Hydroxypropyl cellulose	1.53	3.06
Sucralose[1]	0.7	1.4
Magna Sweet[2]	0.09	0.18
Precipitated calcium carbonate	2.0	4
Fat-coated dextromethorphan hydrobromide	5.96	11.93
Orange concentrate flavor	1.05	2.1
Prosweet MM24[3]	0.18	0.35
Propylene glycol	1.22	2.45
Simethicone[4]	0.18	0.35
Water	32.5	65
Red food color		4 drops
Yellow food color		6 drops

[1]Available from McNeil Nutritional
[2]Taste-masking flavor, available from Mafco Worldwide Corp.
[3]Taste-masking flavor, available from Virginia Dare
[4]Available from Sentry

The above ingredients in the amounts listed for CG were combined by mixing, and then cast into two films on release paper using a K-Control Coater with a 350 micron smooth bar. The films were subsequently dried according to conventional drying techniques, rather than via the uniform drying process of the present invention. One film was dried in an oven at 80° C. for 9 minutes on a wire rack. The second film was dried in an oven at 80° C. for 9 minutes on a wire screen. Both films were dried to about 2.4 percent moisture.

The resulting dried films showed imprints of the wire rack and screen after drying. These configurations comprise imprints of wire supports typically used in the drying process. Without uniform heat diffusion, the wire supports conducted heat more intensely at the points of contact with the substrate, leading to increased evaporation at these points. This caused more vigorous mixing, thereby pulling more particles to the contact points. The result is increased particle density seen as aggregations at the contact points.

The solution was cast into two more films on release paper using the K-Control Coater with a 350 micron smooth bar. These films were dried by the process of the present invention, under the same time and temperature conditions as above. In particular, the films were dried in an 80° C. air oven for 9 minutes on trays lined with furnace filters, which uniformly disperse heat. The films were dried to about 1.89 percent moisture. The resulting films had no streaks, and were homogenous. Due to uniform heat diffusion throughout the film, no particle aggregations developed.

Example CH

The ingredients in Table 15, in the amounts listed for CH, were combined by mixing, and then cast into three films on release paper using a K-Control Coater with a 350 micron smooth bar. The films were dried for 9 minutes in an 80° C. air oven on trays lined with furnace filters, which uniformly distribute heat. The films were dried to about 2.20 percent moisture. As depicted in FIG. **17**, the dried films **200** had no streaks, and were homogenous, i.e., no particle aggregations developed. The active particles appeared intact in the dried films. The films exhibited adequate strength and passed the 180° bend test without cracking, in which the films are bent in half with pressure.

The mixed solution was cast into three more films on release paper using a K-Control Coater with a 350 micron smooth bar. These films similarly were dried for 9 minutes in

an 80° C. air oven, but by conventional top and bottom drying means. Two of the films were dried on wire racks, while the third was dried on a wire screen. All three films were dried to about 2.65 percent moisture. The dried films showed the imprints of the wire racks and screen, for the reasons described above in Example CG.

More particularly, the dried films **100** exhibited aggregations **110** of particles in both line and diamond configurations, as shown in FIGS. **9-16**. These configurations comprise imprints of wire supports used in the drying process to display the disuniformity in heat transfer which occurs in conventional top and bottom drying. As discussed above, the wire supports conducted heat more intensely at the points of contact with the substrate, leading to increased evaporation at these points. This caused more vigorous mixing, thereby pulling more particles to the contact points. The resulting increased particle density at the contact points is depicted in FIGS. **9-16**.

Moreover, the fat-coated dextromethorphan particles contained within the films of this example were not destroyed by the drying processes. FIGS. **28-31** depict fat-coated dextromethorphan particles **500** prior to any processing, and particularly, their substantially spherical shape. After exposure to drying conditions of 80° C. for 9 minutes, the fat-coated drug particles **500** were found to have remained intact within the films, i.e., maintained their spherical shape, as shown in FIGS. **18-25**. Although the active particles were exposed to potentially deleterious temperatures, they did not degrade. In contrast, fat-coated dextromethorphan particles placed in an evaporating dish and heated in an air oven at 80° C. for 9 minutes substantially degrade. As seen in FIGS. **26** and **27**, the fat-coated dextromethorphan particles appear completely melted after the exposure.

Example CI

Thin film compositions of the present invention were prepared using the amounts described in Table 16.

TABLE 16

Component	Weight (g unless otherwise indicated)
Hydroxypropylcellulose	6.00
Polyethylene oxide	2.00
Sucralose[1]	0.84
Magna sweet[2]	0.09
Mixture of microcrystalline cellulose and sodium carboxymethylcellulose[3]	0.18
Precipitated calcium carbonate	1.55
Sildenafil[4]	2.91
Peppermint & bittermint flavor	1.75
Prosweet[5]	0.44
Masking flavor[6]	1.31
N,2,3-trimethyl-2-isopropylbutanamide[7]	0.075
Simethicone[8]	0.035
Water	32.5
Blue food coloring	3 drops

[1]Available from McNeil Nutritional
[2]Taste-masking flavor, available from Mafco Worldwide Corp.
[3]Avicel CL-611, available from FMC Biopolymer
[4]Available from Pfizer, Inc. as Viagra ®
[5]Taste-masking flavor, available from Virginia Dare
[6]Available from Ungerer and Co.
[7]Cooling agent
[8]Available from Sentry

The above ingredients were combined by mixing until a uniform mixture was achieved, and then cast into two films on release paper using a K-Control Coater with a 350 micron smooth bar. One film was dried for 10 minutes in an 80° C. air oven to a moisture level of 3.52%, while the second film was dried for 10 minutes in an 80° C. air oven to a moisture level of 3.95%. The dried films had adequate strength and tear resistance. The films passed the 180° bend test without breaking. The films also dissolved at a moderately fast rate in the mouth and exhibited an acceptable flavor.

As mentioned above, the controlled drying process of the present invention allows for uniform drying to occur, whereby evaporative cooling and thermal mixing contribute to the rapid formation of viscoelastic film and the "locking-in" of uniformity of content throughout the film. One of the additional advantages of the present invention is that the film composition reaches its viscoelastic state, and even the fully dried state, without exposing the components of the composition to temperatures which will cause them to be altered or unusable for their intended purpose. For example, heat sensitive drugs, proteins, flavors, sweeteners, volatile components, antigens, antibodies and the like, readily decompose at certain temperatures become inactive or denature, making them ineffective for their intended use. In the present invention, due to the combination of a short heat history required to dry, and the controlled non-top-skinning drying process, the film composition never need to attain the oven temperature (or other heat source) to reach the dried state. To demonstrate this, films were made in accordance with the present invention and dried as discussed below. A first thermocouple was placed within the film and a second thermocouple was suspended in the oven in order to measure the temperature differential between the oven environment and the film composition during the drying process.

To measure the temperature differentials, a thermocouple, which was connected to a Microtherma 1 thermometer, was placed within the films, and another thermocouple was suspended in the drying oven. Temperature readings in the films and oven were recorded every 30 seconds during the drying of the films.

The thermocouple results for the first film are listed in Table 17 below, and graphically represented in FIG. **33**. The results for the second film are listed in Table 18 below, and graphically represented in FIG. **34**. The results show that even after 10 minutes of drying, the temperatures of the film were substantially below (at least about 5° C.) the oven environment. Films dried for less than 10 minutes may experience significantly greater temperature differentials. For example, drying for 4 to 6 minutes, which is a particularly desirable time frame for many films of the present invention, produces differentials of about 25° C. to about 30° C. Accordingly, films may be dried at high, potentially deleterious temperatures without harming heat sensitive actives contained within the films.

TABLE 17

Time (Min.)	Probe Temp (° C.)	Oven Temp (° C.)
0	42.7	78
1	48.1	80
2	48.8	81
3	50	80
4	51.6	80
5	53.6	80
6	56.8	80
7	61.4	80
8	66.8	80
9	72.7	80
10	76.1	80

TABLE 18

Time (Min.)	Probe Temp (° C.)	Oven Temp (° C.)
0	44.4	77
1	49.8	81
2	49.2	81
3	49.4	80
4	51	80
5	52	80
6	55	80
7	58.9	80
8	64.5	80
9	69.8	80
10	74.4	80

Examples CJ-DB

The following examples describe film compositions of the present invention, which contain water-soluble polymers including polyethylene oxide (PEO) alone or in combination with hydroxypropyl cellulose (HPC) or hydroxypropylmethyl cellulose (HPMC). Thin film compositions were prepared using the polymer amounts listed in Table 19.

TABLE 19

Composition	PEO (g)	HPC (g)	HPMC (g)
CJ		32	8
CK		24	16
CL		16	24
CM		8	32
CN			40
CO	8		32
CP	16		24
CQ	24		16
CR	32		8
CS	40		
CT	4		36
CV	6		34
CV	32	8	
CW	24	16	
CX	16	24	
CY	8	32	
CZ		40	
DA	4	36	
DB	6	34	

The above polymer components were combined with equal amounts of precipitated calcium carbonate (mimics drug loading), simethicone emulsion, and water to form the film compositions. The components were combined by mixing until a uniform mixture was achieved, and then cast into films on release paper using a K-Control Coater with a 350 micron smooth bar. The films then were dried for about 9 minutes at 80° C. in accordance with the present invention. The film compositions were tested for various properties, the results of which are described in Table 20 below.

TABLE 20

Composition	Composition of Polymer in Film	Solution Coating Rating	Solution Leveling Rating	% Moisture in Film	180° Bend Test	Dissolution Test (seconds)	Curl Test
CJ	20% HPMC/ 80% HPC	well	well	2.9	Failed at crease	12, 15	Curl
CK	40% HPMC/ 60% HPC	well	well	1.70	Failed at crease	21, 22	Curl
CL	60% HPMC/ 40% HPC	well	well	2.40	Failed at crease	24, 27	Curl
CM	80% HPMC/ 20% HPC	well	well	2.76	Failed at crease	31, 31	Curl
CN	100% HPMC	reasonably well	well	2.66	Failed at crease	35, 38	Curl
CO	10% PEO/ 90% HPMC	some streaking	well	2.27	Failed at crease	31, 32	Curl
CP	15% PEO/ 85% HPMC	well	well	3.31	Failed	24, 27	Curl
CQ	20% PEO/ 80% HPMC	well	well	2.06	Passed	22, 31	Slight curl
CR	40% PEO/ 60% HPMC	well	well	2.01	Passed	13, 12	Slight curl
CS	60% PEO/ 40% HPMC	well	well	1.40	Passed	5, 6	Very slight curl
CT	80% PEO/ 20% HPMC	well	well	1.35	Passed	5, 6	Very slight curl
CU	100% PEO	well	well	0.98	Passed	5, 5	No curl
CV	20% HPC/ 80% PEO	well	well	1.01	Passed	5, 5	No curl
CW	40% HPC/ 60% PEO	well	well	2.00	Passed	6, 6	No curl
CX	60% HPC/ 40% PEO	well	well	0.97	Passed	7, 7	Slight curl
CY	80% HPC/ 20% PEO	well	well	1.41	Passed	12, 12	Very slight curl
CZ	85% HPC/ 15% PEO	well	well	1.86	Failed at crease	13, 14	Curl
DA	90% HPC/ 10% PEO	well	well	1.62	Failed at crease	14, 13	Curl

TABLE 20-continued

Composition	Composition of Polymer in Film	Solution Coating Rating	Solution Leveling Rating	% Moisture in Film	180° Bend Test	Dissolution Test (seconds)	Curl Test
DB	100% HPC	well	well	2.01	Failed at crease	16, 17	Curl

The solution coating rating and solution leveling rating were both based upon panel observations made during casting of the film compositions.

For the 180° bend test, the dried films were placed in a moisture analyzer (HR73 Moisture Analyzer from Mettler Toledo) to obtain percent moisture and to remove any solvent (e.g. water) remaining in the films after drying at 80° C. in accordance with the present invention. The films then were creased to about 180° and observed for break. Films that broke during creasing were considered a failure. If the film did not break during creasing, a 200 g weight was dropped onto the creased film from a height of about 8.5 mm. Films that broke were considered a failure, and those that did not break were considered a pass. It should be noted, however, that this flexibility test is an extreme test. Films that failed this test are still considered operable within the scope of the present invention. More specifically, there may be certain applications that do not require such extreme flexibility properties.

The films also were tested for dissolution rate. An approximately 20 mm by 100 mm piece of film, having a 2.85 g weight attached, was lowered into a 32.5° C. water bath to a depth of about 50 mm. The time required for the film to dissolve and separate into two pieces was determined (in seconds).

For the curl test, samples of film (about 35 mm by 35 mm) were placed on a glass plate in a laboratory window ledge. The film samples were allowed to stand in the window ledge at room conditions for two to three days and then were observed for curling.

In accordance with the present invention, desirable film compositions are flexible, fast dissolving, and not likely to substantially curl. As indicated by the results in Table 20, Compositions CQ-CY performed best, exhibiting good flexibility, dissolution, and curling properties. In particular, Compositions CQ-CY passed the 180° bend test and dissolved at moderate to fast rates. These compositions also exhibited no or only slight curl. Accordingly, it may be desirable to employ polymer components as in Compositions CQ-CY, particularly about 20% to 100% PEO in the polymer component optionally combined with about 0% to 80% HPC or HPMC.

Examples DC-DG

The following examples of the present invention describe films that include PEO or PEO-polymeric blends and an active component. Thin film compositions with these components were prepared using the amounts described in Table 21.

TABLE 21

Component	Weight (g unless otherwise indicated) DC	DD	DE	DF	DG
PEO[1]	8.75	7	1.75	7	1.75
Sucralose	0.7	0.7	0.7	0.7	0.7
Precipitated calcium carbonate	3.65	3.65	3.65	3.65	3.65
Orange concentrate flavor	1.05	1.05	1.05	1.05	1.05
Vanilla	0.5	0.5	0.5	0.5	0.5
HPMC		1.75	7.0		
HPC				1.75	7.0
Simethicone[2]	0.35	0.35	0.35	0.35	0.35
Water	32.5	32.5	32.5	32.5	32.5
Loratadine[3]	2.5	2.5	2.5	2.5	2.5
Yellow food coloring	3 drops	3 drops	3 drops	3 drops	3 drops
Red food coloring	2 drops	2 drops	2 drops	2 drops	2 drops

[1]Available from the Dow Chemical Company
[2]Available from Sentry
[3]Available from Schering Corporation as Claritin

The above components for each of Compositions DC through DG were combined by mixing until a uniform mixture was achieved, and then cast into films on release paper using a K-Control Coater with a 350 micron smooth bar. The films were dried for about 9 minutes at 80° C. in accordance with the method of the present invention to varying moisture levels.

After drying, the films were tested for various properties, including the 180° bend test, dissolution test, and curl test, as described above in Examples CJ-DB. The films also were tested for resistance to tearing. Tear resistance was measured by a panel test in which members tried to tear the film apart by pulling on opposing ends of the film. Films that tore cleanly received a low grade. Films that stretched a little and began to break received a moderate grade, and films that stretched and were difficult to tear received a high grade.

Composition DC, which included a 100% PEO film base, was dried in accordance with the method of the present invention to about 1.30 percent moisture. The dried film had good strength, and passed the 180° bend test. The film also exhibited good resistance to tearing (high grade). The film dissolved at a fast rate on the tongue, and had a dissolution testing rate of about 3.5 to 4 seconds. The film exhibited no curling.

Composition DD, which included an 80%/20% PEO/HPMC film base, was dried in accordance with the method of the present invention to about 2.30 percent moisture. The dried film exhibited adequate strength, and passed the 180° bend test. The film also exhibited good resistance to tearing. It dissolved at a moderate to fast rate on the tongue, and had a dissolution testing rate of about 5 seconds. The film exhibited slight curling.

Composition DE, which included a 20%/80% PEO/HPMC film base, was dried in accordance with the method of the present invention to about 3.0 percent moisture. The film had good strength, and passed the 180° bend test. The film exhib-

ited moderate tear resistance, dissolved on the tongue at a slow rate, and had a dissolution testing rate of 16 seconds. The film exhibited some curling.

Composition DF, which included an 80%/20% PEO/HPC film base, was dried in accordance with the method of the present invention to about 2.52 percent moisture. The film exhibited good strength, passed the 180° bend test, and exhibited high tear resistance. The film also dissolved at a fast rate on the tongue, and had a dissolution rating of 4 seconds. The film exhibited very slight curling.

Composition DG, which included a 20%/80% PEO/HPC film base, was dried in accordance with the method of the present invention to about 2.81 percent moisture. The film had adequate strength, passed the 180° bend test, and exhibited moderate tear resistance. The film dissolved on the tongue at a fast rate, and had a 10 second dissolution testing rate. The film exhibited no curling.

As indicated above, each of Compositions DC-DG contained about 20% to 100% PEO in the polymer component, optionally in combination with varying levels of HPC or HPMC. The results indicate that varying the polymer component achieved different film properties.

Examples DH-DZ

The following examples of the present invention describe films that include PEO or PEO-HPC polymer blends. The film compositions include PEO of varying molecular weights. Thin film compositions with these components were prepared using the amounts described in Table 22 (listed by weight percent of the polymer component).

TABLE 22

Composition	100,000 PEO (wt. %)	200,000 PEO (wt. %)	300,000 PEO (wt. %)	900,000 PEO (wt. %)	HPC (wt. %)
DH			20		80
DI			50		50
DJ			80		20
DK		50			50
DL		67.5			32.5
DM		70			30
DN		75			25
DO		100			
DP	50				50
DQ	100				
DR				10	90
DS				20	80
DT		40		10	50
DU	25			15	60
DV	20	80			
DW		80		20	
DX		80	20		
DY		50	50		
DZ		20	80		

The above polymer components were combined with sucralose, precipitated calcium carbonate (mimics drug loading), orange concentrate flavor, Tween 80 (available from ICI Americas), vanilla flavor, simethicone emulsion, water, and yellow and red food coloring to form the film compositions. The components were combined by mixing until a uniform mixture was achieved, and then cast into films on release paper using a K-Control Coater with a 350 micron smooth bar. The solution coating and leveling properties were observed. The films then were dried for about 9 minutes at 80° C. in accordance with the method of the present invention. The film compositions were tested for various properties to determine the effect of varying the PEO molecular weight and level in the polymer component, the results of which are described in Table 23 below.

TABLE 23

Composition	Film thickness (mils)	% Moisture	Roof of Mouth Tendency	180° Bend Test	Dissolution Test (seconds)	Tear Resistance
DH	3.5	2.5	low	passed	8	poor
DI	3.8	2.01	low	passed	7	moderate
DJ	2.6	2.63	high	passed	3	excellent
DK	3.4	2.35	low	passed	4	poor
DL	3.5	1.74	low	passed	4	good to excellent
DM	3.5	1.68	low	passed	4	good to excellent
DN	3.3	2.33	moderate	passed	3	good to excellent
DO	3.1	2.14	high	passed	4	excellent
DP	4.1	1.33	high	passed	3.5	poor
DQ	3.2	2.07	high	passed	4	good
DR	3.4	1.90	low	passed	10	poor
DS	3.5	2.04	low	passed	10	poor
DT	3.3	2.25	moderate	passed	5	good
DU	3.6	2.84	low to moderate	passed	6	moderate
DV	2.5	3.45	high	passed	2	excellent
DW	2.5	2.83/1.68	high	passed	3-4	excellent
DX	3.5	2.08	high	passed	5	excellent
DY	2.8	1.67	high	passed	3	excellent
DZ	2.5	1.89/0.93	high	passed	3	excellent

The films were tested for various properties, including the 180° bend test, dissolution test, and tear resistance, as described above. The films also were tested for adhesion, i.e., tendency to go to the roof of the mouth. Adhesion was rated by a panel test in which films that did not stick to the roof of the mouth received a low grade, films that stuck somewhat received a moderate grade, and films that stuck completely received a high grade.

As indicated above, the level and molecular weight of PEO in the polymer component were varied to achieve different film properties. In general, the higher the level of PEO in the polymer component, the greater the adhesiveness and tear resistance exhibited by the film. Film compositions containing about 50% or greater levels of PEO attained higher tear resistance ratings than those with less than 50% PEO. The tear resistance of lower levels of PEO, however, was shown to be improved by combining small amounts of higher molecular weight PEOs with the lower molecular weight PEOs (e.g. Compositions DT and DU).

Compositions containing about 20% to 75% PEO performed best with respect to adhesion prevention (lower tendencies to go to the roof of the mouth). Compositions containing higher levels of PEO performed well when adhesion was desired.

As regards dissolution rate, polymer components containing about 50% or higher levels of PEO performed best, providing faster dissolving film compositions. In those films containing combinations of varying molecular weight PEOs, those with about 60% or higher of the lower molecular weight PEOs (100,000 to 300,000) in the PEO combination dissolved faster.

Example EA

The following example of the present invention describes films that include PEO and polyvinyl pyrrolidone (PVP) polymeric blends. Thin film compositions with these components were prepared using the amounts described in Table 24. In particular, the polymer component of the films contained about 80% PEO and 20% PVP, or a ratio of 4:1 PEO to PVP.

TABLE 24

Component	Weight (g unless otherwise noted)
PVP	3.75
PEO	15
Sucralose[1]	1.5
Precipitated calcium carbonate	14.57
Orange concentrate flavor	2.25
Tween 80[2]	0.056
Simethicone[3]	0.38
Water	62.5
Yellow food color	6 drops
Red food color	4 drops

[1]Available from McNeil Nutritionals
[2]Available from Fisher
[3]Available from Sentry

The above components were combined by mixing until a uniform mixture was achieved, and then cast into films on release paper using a K-Control Coater with a 350 micron smooth bar. The films were dried for about 9 minutes at 80° C. in accordance with the method of the present invention to a moisture level of about 2.19%. The films exhibited good strength, dissolved in the mouth at a moderate to fast rate, had high tear resistance, a thickness of about 4 mils, good flavor, low tendency to adhere to the roof of the mouth, and passed the 180° bend test. The film had a dissolution rate of 4 seconds, according to the test described above. In addition, the film easily released from the release paper.

Example EB-ED

The following examples of the present invention describe extruded films that include PEO-based polymer components. Film compositions were prepared using the amounts described in Table 25 for Example EC and Table 26 for Example ED.

TABLE 25

COMPONENT	WEIGHT (g unless otherwise noted)
HPC	73.78
Polyethylene oxide	153.22
Sucralose	18.16
Precipitated calcium carbonate	176.38
Orange concentrated flavor	27.24
Tween 80	0.68
Simethicone	4.54
Yellow food coloring	27 drops
Red food coloring	18 drops

TABLE 26

COMPONENT	WEIGHT (g unless otherwise noted)
Polyethylene oxide	227
Sucralose	18.16
Precipitated calcium carbonate	176.38
Orange concentrated flavor	27.24
Tween 80	0.68
Simethicone	4.54
Yellow food coloring	27 drops
Red food coloring	18 drops

The films of Examples EB-ED were extruded using a single screw extruder in accordance with the specifications provided in Table 27 below (temperatures are in ° F.).

TABLE 27

		Temp. Barrel	Temp. Barrel	Temp. Barrel	Temp.	Temp.	Temp.	PSI Pressure		
Composition	RPM	Zn. 1	Zn. 2	Zn. 3	Zn. 4	Die	Melt	P1	P2	Amps
EB	73	175	181	185	190	190	194	600	1250	12
EB	153	177	181	199	211	210	217	175	1070	7.8
ED	253	175	181	200	211	210	222	0	761	6.3

TABLE 27-continued

Composition	RPM	Temp. Barrel Zn. 1	Temp. Barrel Zn. 2	Temp. Barrel Zn. 3	Temp. Zn. 4	Temp. Die	Temp. Melt	PSI Pressure P1	PSI Pressure P2	Amps
ED	109	175	181	200	211	210	207	0	1000	6.0
EC	109	175	181	200	211	210	217	0	875	12.1
EC	149	175	200	226	248	239	258	0	583	7.3

More specifically, for Example EB, two pounds of PEO having a molecular weight of about 200,000 were weighed and placed in a polyethylene plastic bag. This PEO flush was then extruded according to the specifications in Table 27.

For Example EC, a blend of the components listed in Table 25 was prepared. The HPC, PEO, sucralose, and precipitated calcium carbonate were placed in a large electric blender and allowed to mix. A solution of orange concentrate flavor and Tween 80 was added to the blender while mixing, after which a solution of simethicone and the food colors was added to the blender while mixing. The blended composition was extruded in accordance with the specifications in Table 27.

For Example ED, a blend of the components listed in Table 26 was prepared. The PEO, sucralose, and precipitated calcium carbonate were placed in a large electric blender and allowed to mix. A solution of orange concentrate flavor and Tween 80 was added to the blender while mixing, after which a solution of simethicone and the food colors was added to the blender while mixing. The blended composition was extruded in accordance with the specifications in Table 27.

The extruded films did not exhibit stickiness to each other during processing. As such, the resulting film could be rolled or wound onto itself without the need for a backing material.

Examples EE-EH

The following examples of the present invention describe films that include a densifying agent. A thin film composition including PEO-polymeric blends and a densifying agent (simethicone) were prepared using the amounts described in Table 28.

TABLE 28

Component	Weight (g unless otherwise indicated) EE	EF	EG	EH
Hydroxypropylcellulose	3.05	3.05	3.05	3.05
Polyethylene oxide	6.33	6.33	6.33	6.33
Sucralose	0.75	0.75	0.75	0.75
Precipitated calcium carbonate	7.47	7.47	7.09	7.09
Orange concentrate flavor	1.12	1.12	1.12	1.12
Tween 80	0.028	0.028	0.028	0.028
Simethicone	0	0	0.38	0.38
Water	31.25	31.25	31.25	31.25
Yellow food coloring	3 drops	3 drops	3 drops	3 drops
Red food coloring	2 drops	2 drops	2 drops	2 drops

The densities of these thin film compositions were measured, the results of which are shown in Table 29.

TABLE 29

Composition	Average Weight of Film/Density
EE	146.5 mg/1.123
EF	126.5 mg/0.969
EG	137 mg/1.057
EH	146 mg/1.119

Vacuum conditions were added to two of the film compositions (EE and EH). Composition EE contained 0% simethicone and vacuum was applied. Composition EF contained 0% simethicone and no vacuum applied. As shown in Table 29 above, the density increased with the addition of vacuum conditions from 0.969 (EF) to 1.123 (EE). Composition EG contained 2% simethicone and no vacuum applied. Composition EH contained 2% simethicone and vacuum was applied. Again, density increased from 1.057 (EG) to 1.119 (EH). Overall, the density of the films increased from 0.969 (EF: no simethicone and no vacuum) to 1.057 (EG: simethicone but no vacuum) to 1.119 (EH: simethicone and vacuum).

Examples EI-EW

The following examples of the present invention describe films that include PEO or PEO-polymeric blends. In particular, PEO was combined with polyvinylpyrrolidone (PVP), starch (pregelatinized modified corn starch), sodium carboxymethyl cellulose (CMC), hydroxypropylcellulose (HPC), hydroxypropylmethyl cellulose (HPMC) or polyvinyl alcohol (PVA) to form the polymer components of the films. Thin film compositions with these components were prepared in accordance with the method of the present invention using the amounts described in FIG. **38**.

In addition to the polymer components listed in FIG. **38**, each of these film compositions included: about 4% sucralose, about 38.85% calcium carbonate, about 6% orange flavor, about 0.15% Tween 80, about 1% simethicone, and food coloring. The PEO included in the polymer component of these examples had a molecular weight of about 200,000.

FIG. **38** also displays certain properties of these films, including: percent solids of solution; viscosity; percent moisture; film thickness; film strength; tear resistance of the film; tendency of the film to go to the roof of the mouth; the 180° bend test; whether molding, or aggregations, are present in the film; dissolution times of the film; rating of dissolution in the mouth; and time in drying oven. Each of these film property tests is described in detail above. The results of these various tests are indicated in FIG. **38**.

Examples EX-FK

The following examples of the present invention describe films that include PEO or PEO-polymeric blends (with HPC)

and different active components. Thin film compositions with these components were prepared in accordance with the method of the present invention using the amounts described in Tables 30 and 31.

TABLE 30

	Weight (in g, unless otherwise indicated)						
Component	EX	EY	EZ	FA	FB	FC	FD
HPC	5.68	5.64	6	6.73	6.22	6.22	
PEO	1.89	1.88	2	2.25	1.78	1.78	9.04
Sucralose	0.84	0.84	0.44	0.66	0.84	0.84	0.44
Magna Sweet	0.08	0.08	0.09	0.10	0.09	0.09	
Avicel CL 611[1]	0.18	0.18	0.18	0.20	0.18	0.18	
Precipitated calcium carbonate	0.67		2.2		0.71	3.07	
Dextromethorphan	5.83	6.94					
Caffeine			3.28				
Tadalafil[2]				4.92			
Sildenafil[3]					4.38		
Loperamide[4]						2.8	
Prosweet	0.18	0.18		0.20	0.61	0.18	
Taste Masking Flavor			0.87		1.31	0.89	
Peppermint			0.87				
Peppermint Bittermask flavor			1.07				
Vanilla flavor				0.56			
Watermelon artificial flavor	1.23	1.23			1.22		
Orange flavor				1.18			
Hawaiian punch flavor						1.22	
Strawberry & cream flavor							1.11
WS-23[5]	0.075	0.075	0.075	0.084	0.075	0.075	
WS-3[6]							0.025
Simethicone	0.08	0.08	0.18	0.39	0.09	0.18	46.43
Propylene glycol	0.76	0.38	0.25	0.22			
Water	32.5	32.5	32.5	32.5	32.5	32.5	
Green color	5 drop	5 drop			5 drop		
Red color				2 drop		5 drop	7 drop
Blue color			3 drop				
Yellow color				3 drop			

[1]Mixture of microcrystalline cellulose and sodium carboxymethylcellulose, available from FMC Biopolymer
[2]Available from Lilly ICOS, LLC, as Cialis ®
[3]Available from Pfizer, Inc. as Viagra ®
[4]Available as Imodium
[5]N-2,3-trimethyl-2-isopropyl butanamide
[6]N-Ethyl-p-menthane-3-carboxamide

TABLE 31

	Weight (in g, unless otherwise indicated)						
Component	FE	FF	FG	FH	FI	FJ	FK
HPC	1.28	3.05	4.5	3.29	2.6	2.92	3.29
PEO	2.66	6.33	3	6.83	5.4	6.08	6.83
Sucralose	0.31	0.9	0.6		0.64		
Magna Sweet		0.09					
Avicel CL 611[1]		0.56	0.45				
Precipitated calcium carbonate	1.07	2.02	0.99	6.05	0.90	2.67	1.39
Meloxicam[2]	1.97						
Risperidone[3]		0.62					
Zyrtec ®[4]			3.75				
Five Grass Powder[5]				2.207			
Tea Tree Oil[6]					4		
Antibacterial concentrate[7]						6.12	
Mite extract[8]							6.87
Prosweet		0.66					
Taste Masking Flavor		1.41					
Peppermint Bittermask flavor		2.81			2.24		
Orange flavor	0.47						
Strawberry & cream flavor			1.5				

TABLE 31-continued

Component	Weight (in g, unless otherwise indicated)						
	FE	FF	FG	FH	FI	FJ	FK
WS-3[9]	0.020	0.081	0.038		0.04		
Tween 80	0.012	0.028	0.022		0.024	0.027	
Simethicone	0.08	0.19	0.15	0.37	0.16	0.18	0.37
Water	14.63	31.25	25	31.25	24	22	31.25
Red color	2 drop		5 drop				
Blue color		3 drop			3 drop		
Yellow color	3 drop						

[1]Mixture of microcrystalline cellulose and sodium carboxymethylcellulose, available from FMC Biopolymer
[2]Available as Mobic ®
[3]Available as Risperdal ®
[4]Available from Pfizer, Inc.
[5]Allergy treatment
[6]Antibiotic
[7]MegaBac ™, available from Nicrosol Technologies
[8]Allergy treatment
[9]N-Ethyl-p-menthane-3-carboxamide

The above components were combined by mixing until a uniform mixture was achieved, and then cast into films on release paper using a K-Control Coater with a 250 or 350 micron smooth bar. The films were dried for about 9 to 10 minutes at 80° C. in accordance with the method of the present invention resulting in dried films having adequate to good strength.

While there have been described what are presently believed to be the preferred embodiments of the invention, those skilled in the art will realize that changes and modifications may be made thereto without departing from the spirit of the invention, and it is intended to include all such changes and modifications as fall within the true scope of the invention.

What is claimed is:

1. A process for making a film having a substantially uniform distribution of components, comprising the steps of:

(a) forming a masterbatch pre-mix comprising a solvent and a polymer selected from the group consisting of water-soluble polymers, water-swellable polymers and combinations thereof;

(b) adding an active to a pre-determined amount of said masterbatch pre-mix to form a flowable polymer matrix, said matrix having a substantially uniform distribution of said active;

(c) casting said flowable polymer matrix;

(d) evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film within about 10 minutes or fewer to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film; and

(e) forming a resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained.

2. The process of claim **1**, wherein said pre-determined amount of master batch pre-mix is controllably fed via a first metering pump and a control valve to a first mixer and a second mixer.

3. The process of claim **2**, wherein said first mixer and said second mixer are arranged in parallel, series or a combination thereof.

4. The process of claim **1**, wherein said water-soluble polymer comprises polyethylene oxide.

5. The process of claim **1**, wherein said polymer comprises a polymer selected from the group consisting of cellulose, a cellulose derivative, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyvinyl copolymers, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof, alone or in combination with polyethylene oxide.

6. The process of claim **5**, wherein said polymer further comprises a water insoluble polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone and combinations thereof.

7. The process of claim **5**, wherein said polymer further comprises a polymer selected from the group consisting of methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(α-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof.

8. The process of claim **5**, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

9. The process of claim **5**, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate,

polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(d-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

10. The process of claim **1**, wherein said solvent is selected from the group consisting of water, polar organic solvent, and combinations thereof.

11. The process of claim **10**, wherein said solvent is selected from the group consisting of ethanol, isopropanol, acetone, and combinations thereof.

12. The process of claim **1**, wherein said active is selected from the group consisting of bioactive active, pharmaceutical actives, drugs, medicaments and combinations thereof.

13. The process of claim **1**, wherein said active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, anti-tumor drugs, anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, anti-convulsants, neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, anti-asthmatics, cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

14. The process of claim **1**, wherein said active is selected from the group consisting of cosmetic actives, antigens, allergens, spores, microorganisms, seeds, mouthwash components, flavors, fragrances, enzymes, preservatives, sweetening agents, colorants, spices, vitamins and combinations thereof.

15. The process of claim **1**, wherein said active is a bioactive active.

16. The process of claim **1**, wherein said active is a biological response modifier.

17. The process of claim **1**, wherein said active is an opiate or opiate-derivative.

18. The process of claim **1**, wherein said active is an anti-emetic.

19. The process of claim **1**, wherein said active is an amino acid preparation.

20. The process of claim **1**, wherein said active is selected from the group consisting of sildenafils, tadalafils, vardenafils, apomorphines, yohimbine hydrochlorides, alprostadils and combinations thereof.

21. The process of claim **1**, wherein said active is a protein.

22. The process of claim **1**, wherein said active is insulin.

23. The process of claim **1**, wherein said active is an anti-diabetic.

24. The process of claim **1**, wherein said active is an anti-histamine.

25. The process of claim **1**, wherein said active is an anti-tussive.

26. The process of claim **1**, wherein said active is a non-steroidal anti-inflammatory.

27. The process of claim **1**, wherein said active is an anti-asthmatics.

28. The process of claim **1**, wherein said active is an anti-diarrhea.

29. The process of claim **1**, wherein said active is an alkaloid.

30. The process of claim **1**, wherein said active is an anti-psychotic.

31. The process of claim **1**, wherein said active is an anti-spasmodic.

32. The process of claim **1**, wherein said active is a biological response modifier.

33. The process of claim **1**, wherein said active is an anti-obesity drug.

34. The process of claim **1**, wherein said active is an H_2-antagonist.

35. The process of claim **34**, wherein said H_2-antagonist is selected from the group consisting of cimetidine, ranitidine hydrochloride, famotidine, nizatidine, ebrotidine, mifentidine, roxatidine, pisatidine, aceroxatidine and combinations thereof.

36. The process of claim **1**, wherein said active is a smoking cessation aid.

37. The process of claim **1**, wherein said active is an anti-parkinsonian agent.

38. The process of claim **1**, wherein said active is an anti-depressant.

39. The process of claim **1**, wherein said active is an anti-migraine.

40. The process of claim **1**, wherein said active is an anti-Alzheimer's agents.

41. The process of claim **1**, wherein said active is a dopamine receptor agonist.

42. The process of claim **1**, wherein said active is a cerebral dilator.

43. The process of claim **1**, wherein said active is a psychotherapeutic agent.

44. The process of claim **1**, wherein said active is an antibiotic.

45. The process of claim 1, wherein said active is an anesthetic.

46. The process of claim 1, wherein said active is a contraceptive.

47. The process of claim 1, wherein said active is an antithrombotic drug.

48. The process of claim 1, wherein said active is diphenhydramine.

49. The process of claim 1, wherein said active is nabilone.

50. The process of claim 1, wherein said active is albuterol sulfate.

51. The process of claim 1, wherein said active is an antitumor drug.

52. The process of claim 1, wherein said active is a glycoprotein.

53. The process of claim 1, wherein said active is an analgesic.

54. The process of claim 1, wherein said active is a hormone.

55. The process of claim 1, wherein said active is a decongestant.

56. The process of claim 1, wherein said active is a loratadine.

57. The process of claim 1, wherein said active is dextromethorphan.

58. The process of claim 1, wherein said active is chlorpheniramine maleate.

59. The process of claim 1, wherein said active is selected from the group consisting of an analgesic, an anti-inflammatory, an antihistamine, a decongestant, a cough suppressant and combinations thereof.

60. The process of claim 1, wherein said active is an appetite stimulant.

61. The process of claim 1, wherein said active is a gastrointestinal agent.

62. The process of claim 1, wherein said active is a hypnotic.

63. The process of claim 1, wherein said active is taste-masked.

64. The process of claim 1, wherein said active is taste-masked using a flavor.

65. The process of claim 1, wherein said active is coated with a controlled release composition.

66. The process of claim 65, wherein said controlled release composition provides an immediate release.

67. The process of claim 65, wherein said controlled release composition provides a delayed release.

68. The process of claim 65, wherein said controlled release composition provides a sustained release.

69. The process of claim 65, wherein said controlled release composition provides a sequential release.

70. The process of claim 1, wherein said active is a particulate.

71. The process of claim 1, further comprising adding a degassing agent to said masterbatch premix.

72. The process of claim 1, further comprising a step of providing a second film layer.

73. The process of claim 72, wherein said second film layer is coated onto said resulting film.

74. The process of claim 72, wherein said second film layer is spread onto said resulting film.

75. The process of claim 72, wherein said second film layer is cast onto said resulting film.

76. The process of claim 72, wherein said second film layer is extruded onto said resulting film.

77. The process of claim 72, wherein said second film layer is sprayed onto said resulting film.

78. The process of claim 72, wherein said second film layer is laminated onto said resulting film.

79. The process of claim 72, further comprising laminating said resulting film to another film.

80. The process of claim 72, wherein said second film comprises an active.

81. The process of claim 72, wherein said active in said second film is different than said active in said resulting film.

82. A process for making a film having a substantially uniform distribution of components, comprising the steps of:

(a) forming a flowable polymer matrix comprising a polymer selected from the group consisting of a water-soluble polymer, a water swellable polymer and combinations thereof, a solvent and an active selected from the group consisting of bioactive actives, pharmaceutical actives, drugs, medicaments and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix;

(c) evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film within about 10 minutes or fewer to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film; and

(d) forming a resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained.

83. The process of claim 82, wherein said water-soluble polymer comprises polyethylene oxide.

84. The process of claim 82, wherein said polymer comprises a polymer selected from the group consisting of cellulose, a cellulose derivative, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyvinyl copolymers, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof, alone or in combination with polyethylene oxide.

85. The process of claim 84, wherein said polymer further comprises a water insoluble polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone and combinations thereof.

86. The process of claim 84, wherein said polymer further comprises a polymer selected from the group consisting of methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(α-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof.

87. The process of claim 84, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

88. The process of claim 84, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(α-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

89. The process of claim 82, wherein said solvent is selected from the group consisting of water, polar organic solvent, and combinations thereof.

90. The process of claim 89, wherein said solvent is selected from the group consisting of ethanol, isopropanol, acetone, and combinations thereof.

91. The process of claim 82, wherein said active is selected from the group consisting of bioactive active, pharmaceutical actives, drugs, medicaments and combinations thereof.

92. The process of claim 82, wherein the active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, anti-tumor drugs, anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, anti-convulsants, neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, anti-asthmatics, cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

93. The process of claim 82, wherein said active is selected from the group consisting of cosmetic actives, antigens, allergens, spores, microorganisms, seeds, mouthwash components, flavors, fragrances, enzymes, preservatives, sweetening agents, colorants, spices, vitamins and combinations thereof.

94. The process of claim 82, wherein said active is a bioactive active.

95. The process of claim 82, wherein said active is a biological response modifier.

96. The process of claim 82, wherein said active is an opiate or opiate-derivative.

97. The process of claim 82, wherein said active is an anti-emetic.

98. The process of claim 82, wherein said active is an amino acid preparation.

99. The process of claim 82, wherein said active is selected from the group consisting of sildenafils, tadalafils, vardenafils, apomorphines, yohimbine hydrochlorides, alprostadils and combinations thereof.

100. The process of claim 82, wherein said active is a protein.

101. The process of claim 82, wherein said active is insulin.

102. The process of claim 82, wherein said active is an anti-diabetic.

103. The process of claim 82, wherein said active is an antihistamine.

104. The process of claim 82, wherein said active is an anti-tussive.

105. The process of claim 82, wherein said active is a non-steroidal anti-inflammatory.

106. The process of claim 82, wherein said active is an anti-asthmatics.

107. The process of claim 82, wherein said active is an anti-diarrhea.

108. The process of claim 82, wherein said active is an alkaloid.

109. The process of claim 82, wherein said active is an anti-psychotic.

110. The process of claim 82, wherein said active is an anti-spasmodic.

111. The process of claim 82, wherein said active is a biological response modifier.

112. The process of claim 82, wherein said active is an anti-obesity drug.

113. The process of claim 82, wherein said active is an H_2-antagonist.

114. The process of claim 82, wherein said H_2-antagonist is selected from the group consisting of cimetidine, ranitidine hydrochloride, famotidine, nizatidine, ebrotidine, mifentidine, roxatidine, pisatidine, aceroxatidine and combinations thereof.

115. The process of claim 82, wherein said active is a smoking cessation aid.

116. The process of claim 82, wherein said active is an anti-parkinsonian agent.

117. The process of claim 82, wherein said active is an anti-depressant.

118. The process of claim 82, wherein said active is an anti-migraine.

119. The process of claim 82, wherein said active is an anti-Alzheimer's agents.

120. The process of claim 82, wherein said active is a dopamine receptor agonist.

121. The process of claim 82, wherein said active is a cerebral dilator.

122. The process of claim 82, wherein said active is a psychotherapeutic agent.

123. The process of claim 82, wherein said active is an antibiotic.

124. The process of claim 82, wherein said active is an anesthetic.

125. The process of claim 82, wherein said active is a contraceptive.

126. The process of claim, 82, wherein said active is an anti-thrombotic drug.

127. The process of claim 82, wherein said active is diphenhydramine.

128. The process of claim 82, wherein said active is nabilone.

129. The process of claim 82, wherein said active is albuterol sulfate.

130. The process of claim 82, wherein said active is an anti-tumor drug.

131. The process of claim 82, wherein said active is a glycoprotein.

132. The process of claim 82, wherein said active is an analgesic.

133. The process of claim 82, wherein said active is a hormone.

134. The process of claim 82, wherein said active is a decongestant.

135. The process of claim 82, wherein said active is a loratadine.

136. The process of claim 82, wherein said active is dextromethorphan.

137. The process of claim 82, wherein said active is chlorpheniramine maleate.

138. The process of claim 82, wherein said active is selected from the group consisting of an analgesic, an anti-inflammatory, an antihistamine, a decongestant, a cough suppressant and combinations thereof.

139. The process of claim 82, wherein said active is an appetite stimulant.

140. The process of claim 82, wherein said active is a gastrointestinal agent.

141. The process of claim 82, wherein said active is a hypnotic.

142. The process of claim 82, wherein said active is taste-masked.

143. The process of claim 82, wherein said active is taste-masked using a flavor.

144. The process of claim 82, wherein said active is coated with a controlled release composition.

145. The process of claim 144, wherein said controlled release composition provides an immediate release.

146. The process of claim 144, wherein said controlled release composition provides a delayed release.

147. The process of claim 144, wherein said controlled release composition provides a sustained release.

148. The process of claim 144, wherein said controlled release composition provides a sequential release.

149. The process of claim 82, wherein said active is a particulate.

150. The process of claim 82, further comprising adding a degassing agent to said flowable polymer matrix.

151. The process of claim 82, further comprising a step of providing a second film layer.

152. The process of claim 151, wherein said second film layer is coated onto said resulting film.

153. The process of claim 151, wherein said second film layer is spread onto said resulting film.

154. The process of claim 151, wherein said second film layer is cast onto said resulting film.

155. The process of claim 151, wherein said second film layer is extruded onto said resulting film.

156. The process of claim 151, wherein said second film layer is sprayed onto said resulting film.

157. The process of claim 151, wherein said second film layer is laminated onto said resulting film.

158. The process of claim 151, further comprising laminating said resulting film to another film.

159. The process of claim 151, wherein said second film comprises an active.

160. The process of claim 151, wherein said active in said second film is different than said active in said resulting film.

161. A process for making a film capable of being administered to a body surface having a substantially uniform distribution of components, comprising the steps of:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and an active, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix;

(c) evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film within about 10 minutes or fewer to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film;

(d) forming a resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained; and

(e) administering said resulting film to a body surface.

162. The process of claim 161, wherein said body surface is a mucous membrane.

163. The process of claim 162, wherein said mucous membrane is oral, anal, vaginal or ophthalmological.

164. The process of claim 161, wherein said body surface is the surface of a wound.

165. The process of claim 161, wherein said water-soluble polymer comprises polyethylene oxide.

166. The process of claim 161, wherein said polymer comprises a polymer selected from the group consisting of cellulose, a cellulose derivative, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyvinyl copolymers, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof, alone or in combination with polyethylene oxide.

167. The process of claim 166, wherein said polymer further comprises a water insoluble polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone and combinations thereof.

168. The process of claim 166, wherein said polymer further comprises a polymer selected from the group consisting of methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(α-esters), polyanhy-

drides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof.

169. The process of claim **166**, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

170. The process of claim **166**, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(α-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

171. The process of claim **161**, wherein said solvent is selected from the group consisting of water, polar organic solvent, and combinations thereof.

172. The process of claim **161**, wherein said solvent is selected from the group consisting of ethanol, isopropanol, acetone, and combinations thereof.

173. The process of claim **161**, wherein said active is selected from the group consisting of bioactive active, pharmaceutical actives, drugs, medicaments and combinations thereof.

174. The process of claim **161**, wherein said active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, anti-tumor drugs, anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, anti-convulsants, neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, anti-asthmatics, cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

175. The process of claim **161**, wherein said active is selected from the group consisting of cosmetic actives, antigens, allergens, spores, microorganisms, seeds, mouthwash components, flavors, fragrances, enzymes, preservatives, sweetening agents, colorants, spices, vitamins and combinations thereof.

176. The process of claim **161**, wherein said active is a bioactive active.

177. The process of claim **161**, wherein said active is a biological response modifier.

178. The process of claim **161**, wherein said active is an opiate or opiate-derivative.

179. The process of claim **161**, wherein said active is an anti-emetic.

180. The process of claim **161** wherein said active is an amino acid preparation.

181. The process of claim **161**, wherein said active is selected from the group consisting of sildenafils, tadalafils, vardenafils, apomorphines, yohimbine hydrochlorides, alprostadils and combinations thereof.

182. The process of claim **161**, wherein said active is a protein.

183. The process of claim **161**, wherein said active is insulin.

184. The process of claim **161**, wherein said active is an anti-diabetic.

185. The process of claim **161**, wherein said active is an antihistamine.

186. The process of claim **161**, wherein said active is an anti-tussive.

187. The process of claim **161**, wherein said active is a non-steroidal anti-inflammatory.

188. The process of claim **161**, wherein said active is an anti-asthmatics.

189. The process of claim **161**, wherein said active is an anti-diarrhea.

190. The process of claim **161**, wherein said active is an alkaloid.

191. The process of claim **161**, wherein said active is an anti-psychotic.

192. The process of claim **161**, wherein said active is an anti-spasmodic.

193. The process of claim **161**, wherein said active is a biological response modifier.

194. The process of claim **161**, wherein said active is an anti-obesity drug.

195. The process of claim **161**, wherein said active is an H_2-antagonist.

196. The process of claim **195**, wherein said H_2-antagonist is selected from the group consisting of cimetidine, ranitidine hydrochloride, famotidine, nizatidine, ebrotidine, mifentidine, roxatidine, pisatidine, aceroxatidine and combinations thereof.

197. The process of claim **161**, wherein said active is a smoking cessation aid.

198. The process of claim **161**, wherein said active is an anti-parkinsonian agent.

199. The process of claim 161, wherein said active is an anti-depressant.

200. The process of claim 161, wherein said active is an anti-migraine.

201. The process of claim 161, wherein said active is an anti-Alzheimer's agents.

202. The process of claim 161, wherein said active is a dopamine receptor agonist.

203. The process of claim 161, wherein said active is a cerebral dilator.

204. The process of claim 161, wherein said active is a psychotherapeutic agent.

205. The process of claim 161, wherein said active is an antibiotic.

206. The process of claim 161, wherein said active is an anesthetic.

207. The process of claim 161, wherein said active is a contraceptive.

208. The process of claim 161, wherein said active is an anti-thrombotic drug.

209. The process of claim 161, wherein said active is diphenhydramine.

210. The process of claim 161, wherein said active is nabilone.

211. The process of claim 161, wherein said active is albuterol sulfate.

212. The process of claim 161, wherein said active is an anti-tumor drug.

213. The process of claim 161, wherein said active is a glycoprotein.

214. The process of claim 161, wherein said active is an analgesic.

215. The process of claim 161, wherein said active is a hormone.

216. The process of claim 161, wherein said active is a decongestant.

217. The process of claim 161, wherein said active is a loratadine.

218. The process of claim 161, wherein said active is dextromethorphan.

219. The process of claim 161, wherein said active is chlorpheniramine maleate.

220. The process of claim 161, wherein said active is selected from the group consisting of an analgesic, an anti-inflammatory, an antihistamine, a decongestant, a cough suppressant and combinations thereof.

221. The process of claim 161, wherein said active is an appetite stimulant.

222. The process of claim 161, wherein said active is a gastrointestinal agent.

223. The process of claim 161, wherein said active is a hypnotic.

224. The process of claim 161, wherein said active is taste-masked.

225. The process of claim 161, wherein said active is taste-masked using a flavor.

226. The process of claim 161, wherein said active is coated with a controlled release composition.

227. The process of claim 226, wherein said controlled release composition provides an immediate release.

228. The process of 226, wherein said controlled release composition provides a delayed release.

229. The process of claim 226, wherein said controlled release composition provides a sustained release.

230. The process of claim 226, wherein said controlled release composition provides a sequential release.

231. The process of claim 161, wherein said active is a particulate.

232. The process of claim 161, further comprising adding a degassing agent to said flowable polymer matrix.

233. The process of claim 161, further comprising a step of providing a second film layer.

234. The process of claim 233, wherein said second film layer is coated onto said resulting film.

235. The process of claim 233, wherein said second film layer is spread onto said resulting film.

236. The process of claim 233, wherein said second film layer is cast onto said resulting film.

237. The process of claim 233, wherein said second film layer is extruded onto said resulting film.

238. The process of claim 233, wherein said second film layer is sprayed onto said resulting film.

239. The process of claim 233, wherein said second film layer is laminated onto said resulting film.

240. The process of claim 233, further comprising laminating said resulting film to another film.

241. The process of claim 233, wherein said second film comprises an active.

242. The process of claim 233, wherein said active in said second film is different than said active in said resulting film.

243. The process of claim 1, said active is an anti-nauseant.

244. The process of claim 1, said active is an erectile dysfunction.

245. The process of claim 1, said active is a vasoconstrictor.

246. The process of claim 1, said active is a stimulant.

247. The process of claim 1, said active is a migraine treatment.

248. The process of claim 1, said active is granisetron hydrochloride.

249. The process of claim 1, wherein said resulting film provides administration of said active to an individual through the buccal cavity of said individual.

250. The process of claim 1, wherein said resulting film provides administration of said active through gingival application of said individual.

251. The process of claim 1, wherein said resulting film provides administration of said active through sublingual application of said individual.

252. The process of claim 1, wherein said resulting film provides administration of said active to an individual through a mucosal membrane of said individual.

253. The process of claim 1, wherein said resulting film provides administration of said active to an individual by administration within the body of the individual during surgery.

254. The process of claim 1, wherein said resulting film has a variation of active content of less than 10% per film unit.

255. The process of claim 1, further comprising the step of forming a plurality of individual dosage units of substantially the same size, wherein the active content of individual dosage units has a variance of no more than 10%.

256. The method of claim 1, wherein said resulting film contains less than about 6% by weight solvent.

257. The method of claim 1, wherein said at least one edible polymer, said active, and said at least one polar solvent are each ingestible materials.

258. The method of claim 1, wherein said resulting film is orally administrable.

259. The method of claim 1, wherein said active is in the form of a particle.

260. The method of claim 1, wherein said matrix comprises a dispersion.

261. The process of claim **82**, said active is an anti-nauseant.

262. The process of claim **82**, said active is an erectile dysfunction.

263. The process of claim **82**, said active is a vasoconstrictor.

264. The process of claim **82**, said active is a stimulant.

265. The process of claim **82**, said active is a migraine treatment.

266. The process of claim **82**, said active is granisetron hydrochloride.

267. The process of claim **82**, wherein said resulting film provides administration of said active to an individual through the buccal cavity of said individual.

268. The process of claim **82**, wherein said resulting film provides administration of said active through gingival application of said individual.

269. The process of claim **82**, wherein said resulting film provides administration of said active through sublingual application of said individual.

270. The process of claim **82**, wherein said resulting film provides administration of said active to an individual through a mucosal membrane of said individual.

271. The process of claim **82**, wherein said resulting film provides administration of said active to an individual by administration within the body of the individual during surgery.

272. The process of claim **82**, wherein said resulting film has a variation of active content of less than 10% per film unit.

273. The process of claim **82**, further comprising the step of forming a plurality of individual dosage units of substantially the same size, wherein the active content of individual dosage units has a variance of no more than 10%.

274. The method of claim **82**, wherein said resulting film contains less than about 6% by weight solvent.

275. The method of claim **82**, wherein said at least one edible polymer, said active, and said at least one polar solvent are each ingestible materials.

276. The method of claim **82**, wherein said resulting film is orally administrable.

277. The method of claim **82**, wherein said active is in the form of a particle.

278. The method of claim **82**, wherein said matrix comprises a dispersion.

279. The process of claim **161**, said active is an anti-nauseant.

280. The process of claim **161**, said active is an erectile dysfunction.

281. The process of claim **161**, said active is a vasoconstrictor.

282. The process of claim **161**, said active is a stimulant.

283. The process of claim **161**, said active is a migraine treatment.

284. The process of claim **161**, said active is granisetron hydrochloride.

285. The process of claim **161**, wherein said resulting film provides administration of said active to an individual through the buccal cavity of said individual.

286. The process of claim **161**, wherein said resulting film provides administration of said active through gingival application of said individual.

287. The process of claim **161**, wherein said resulting film provides administration of said active through sublingual application of said individual.

288. The process of claim **161**, wherein said resulting film provides administration of said active to an individual through a mucosal membrane of said individual.

289. The process of claim **161**, wherein said resulting film provides administration of said active to an individual by administration within the body of the individual during surgery.

290. The process of claim **161**, wherein said resulting film has a variation of active content of less than 10% per film unit.

291. The process of claim **161**, further comprising the step of forming a plurality of individual dosage units of substantially the same size, wherein the active content of individual dosage units has a variance of no more than 10%.

292. The method of claim **161**, wherein said resulting film contains less than about 6% by weight solvent.

293. The method of claim **161**, wherein said at least one edible polymer, said active, and said at least one polar solvent are each ingestible materials.

294. The method of claim **161**, wherein said resulting film is orally administrable.

295. The method of claim **161**, wherein said active is in the form of a particle.

296. The method of claim **161**, wherein said matrix comprises a dispersion.

297. The method of claim **1**, wherein said matrix comprises an emulsion, a colloid or a suspension.

298. The method of claim **82**, wherein said matrix comprises an emulsion, a colloid or a suspension.

299. The method of claim **161**, wherein said matrix comprises an emulsion, a colloid or a suspension.

* * * * *

EXHIBIT B

TABLE 31-continued

Component	Weight (in g, unless otherwise indicated)						
	FE	FF	FG	FH	FI	FJ	FK
WS-3[9]	0.020	0.081	0.038		0.04		
Tween 80	0.012	0.028	0.022		0.024	0.027	
Simethicone	0.08	0.19	0.15	0.37	0.16	0.18	0.37
Water	14.63	31.25	25	31.25	24	22	31.25
Red color	2 drop		5 drop				
Blue color		3 drop			3 drop		
Yellow color	3 drop						

[1]Mixture of microcrystalline cellulose and sodium carboxymethylcellulose, available from FMC Biopolymer
[2]Available as Mobic ®
[3]Available as Risperdal ®
[4]Available from Pfizer, Inc.
[5]Allergy treatment
[6]Antibiotic
[7]MegaBac ™, available from Nicrosol Technologies
[8]Allergy treatment
[9]N-Ethyl-p-menthane-3-carboxamide

The above components were combined by mixing until a uniform mixture was achieved, and then cast into films on release paper using a K-Control Coater with a 250 or 350 micron smooth bar. The films were dried for about 9 to 10 minutes at 80° C. in accordance with the method of the present invention resulting in dried films having adequate to good strength.

While there have been described what are presently believed to be the preferred embodiments of the invention, those skilled in the art will realize that changes and modifications may be made thereto without departing from the spirit of the invention, and it is intended to include all such changes and modifications as fall within the true scope of the invention.

What is claimed is:

1. A process for making a film having a substantially uniform distribution of components, comprising the steps of:

(a) forming a masterbatch pre-mix comprising a solvent and a polymer selected from the group consisting of water-soluble polymers, water-swellable polymers and combinations thereof;

(b) adding an active to a pre-determined amount of said masterbatch pre-mix to form a flowable polymer matrix, said matrix having a substantially uniform distribution of said active;

(c) casting said flowable polymer matrix;

(d) evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film within about 10 minutes or fewer to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film; and

(e) forming a resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained.

2. The process of claim **1**, wherein said pre-determined amount of master batch pre-mix is controllably fed via a first metering pump and a control valve to a first mixer and a second mixer.

3. The process of claim **2**, wherein said first mixer and said second mixer are arranged in parallel, series or a combination thereof.

4. The process of claim **1**, wherein said water-soluble polymer comprises polyethylene oxide.

5. The process of claim **1**, wherein said polymer comprises a polymer selected from the group consisting of cellulose, a cellulose derivative, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyvinyl copolymers, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof, alone or in combination with polyethylene oxide.

6. The process of claim **5**, wherein said polymer further comprises a water insoluble polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone and combinations thereof.

7. The process of claim **5**, wherein said polymer further comprises a polymer selected from the group consisting of methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(α-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof.

8. The process of claim **5**, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

9. The process of claim **5**, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate,

polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(d-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

10. The process of claim **1**, wherein said solvent is selected from the group consisting of water, polar organic solvent, and combinations thereof.

11. The process of claim **10**, wherein said solvent is selected from the group consisting of ethanol, isopropanol, acetone, and combinations thereof.

12. The process of claim **1**, wherein said active is selected from the group consisting of bioactive active, pharmaceutical actives, drugs, medicaments and combinations thereof.

13. The process of claim **1**, wherein said active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, anti-tumor drugs, anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, anti-convulsants, neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, anti-asthmatics, cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

14. The process of claim **1**, wherein said active is selected from the group consisting of cosmetic actives, antigens, allergens, spores, microorganisms, seeds, mouthwash components, flavors, fragrances, enzymes, preservatives, sweetening agents, colorants, spices, vitamins and combinations thereof.

15. The process of claim **1**, wherein said active is a bioactive active.

16. The process of claim **1**, wherein said active is a biological response modifier.

17. The process of claim **1**, wherein said active is an opiate or opiate-derivative.

18. The process of claim **1**, wherein said active is an anti-emetic.

19. The process of claim **1**, wherein said active is an amino acid preparation.

20. The process of claim **1**, wherein said active is selected from the group consisting of sildenafils, tadalafils, vardenafils, apomorphines, yohimbine hydrochlorides, alprostadils and combinations thereof.

21. The process of claim **1**, wherein said active is a protein.

22. The process of claim **1**, wherein said active is insulin.

23. The process of claim **1**, wherein said active is an anti-diabetic.

24. The process of claim **1**, wherein said active is an anti-histamine.

25. The process of claim **1**, wherein said active is an anti-tussive.

26. The process of claim **1**, wherein said active is a non-steroidal anti-inflammatory.

27. The process of claim **1**, wherein said active is an anti-asthmatics.

28. The process of claim **1**, wherein said active is an anti-diarrhea.

29. The process of claim **1**, wherein said active is an alkaloid.

30. The process of claim **1**, wherein said active is an anti-psychotic.

31. The process of claim **1**, wherein said active is an anti-spasmodic.

32. The process of claim **1**, wherein said active is a biological response modifier.

33. The process of claim **1**, wherein said active is an anti-obesity drug.

34. The process of claim **1**, wherein said active is an H_2-antagonist.

35. The process of claim **34**, wherein said H_2-antagonist is selected from the group consisting of cimetidine, ranitidine hydrochloride, famotidine, nizatidine, ebrotidine, mifentidine, roxatidine, pisatidine, aceroxatidine and combinations thereof.

36. The process of claim **1**, wherein said active is a smoking cessation aid.

37. The process of claim **1**, wherein said active is an anti-parkinsonian agent.

38. The process of claim **1**, wherein said active is an anti-depressant.

39. The process of claim **1**, wherein said active is an anti-migraine.

40. The process of claim **1**, wherein said active is an anti-Alzheimer's agents.

41. The process of claim **1**, wherein said active is a dopamine receptor agonist.

42. The process of claim **1**, wherein said active is a cerebral dilator.

43. The process of claim **1**, wherein said active is a psychotherapeutic agent.

44. The process of claim **1**, wherein said active is an antibiotic.

45. The process of claim 1, wherein said active is an anesthetic.

46. The process of claim 1, wherein said active is a contraceptive.

47. The process of claim 1, wherein said active is an antithrombotic drug.

48. The process of claim 1, wherein said active is diphenhydramine.

49. The process of claim 1, wherein said active is nabilone.

50. The process of claim 1, wherein said active is albuterol sulfate.

51. The process of claim 1, wherein said active is an antitumor drug.

52. The process of claim 1, wherein said active is a glycoprotein.

53. The process of claim 1, wherein said active is an analgesic.

54. The process of claim 1, wherein said active is a hormone.

55. The process of claim 1, wherein said active is a decongestant.

56. The process of claim 1, wherein said active is a loratadine.

57. The process of claim 1, wherein said active is dextromethorphan.

58. The process of claim 1, wherein said active is chlorpheniramine maleate.

59. The process of claim 1, wherein said active is selected from the group consisting of an analgesic, an anti-inflammatory, an antihistamine, a decongestant, a cough suppressant and combinations thereof.

60. The process of claim 1, wherein said active is an appetite stimulant.

61. The process of claim 1, wherein said active is a gastrointestinal agent.

62. The process of claim 1, wherein said active is a hypnotic.

63. The process of claim 1, wherein said active is taste-masked.

64. The process of claim 1, wherein said active is taste-masked using a flavor.

65. The process of claim 1, wherein said active is coated with a controlled release composition.

66. The process of claim 65, wherein said controlled release composition provides an immediate release.

67. The process of claim 65, wherein said controlled release composition provides a delayed release.

68. The process of claim 65, wherein said controlled release composition provides a sustained release.

69. The process of claim 65, wherein said controlled release composition provides a sequential release.

70. The process of claim 1, wherein said active is a particulate.

71. The process of claim 1, further comprising adding a degassing agent to said masterbatch premix.

72. The process of claim 1, further comprising a step of providing a second film layer.

73. The process of claim 72, wherein said second film layer is coated onto said resulting film.

74. The process of claim 72, wherein said second film layer is spread onto said resulting film.

75. The process of claim 72, wherein said second film layer is cast onto said resulting film.

76. The process of claim 72, wherein said second film layer is extruded onto said resulting film.

77. The process of claim 72, wherein said second film layer is sprayed onto said resulting film.

78. The process of claim 72, wherein said second film layer is laminated onto said resulting film.

79. The process of claim 72, further comprising laminating said resulting film to another film.

80. The process of claim 72, wherein said second film comprises an active.

81. The process of claim 72, wherein said active in said second film is different than said active in said resulting film.

82. A process for making a film having a substantially uniform distribution of components, comprising the steps of:

(a) forming a flowable polymer matrix comprising a polymer selected from the group consisting of a water-soluble polymer, a water swellable polymer and combinations thereof, a solvent and an active selected from the group consisting of bioactive actives, pharmaceutical actives, drugs, medicaments and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix;

(c) evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film within about 10 minutes or fewer to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film; and

(d) forming a resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained.

83. The process of claim 82, wherein said water-soluble polymer comprises polyethylene oxide.

84. The process of claim 82, wherein said polymer comprises a polymer selected from the group consisting of cellulose, a cellulose derivative, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyvinyl copolymers, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof, alone or in combination with polyethylene oxide.

85. The process of claim 84, wherein said polymer further comprises a water insoluble polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone and combinations thereof.

86. The process of claim 84, wherein said polymer further comprises a polymer selected from the group consisting of methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(α-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof.

87. The process of claim 84, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

88. The process of claim 84, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(α-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

89. The process of claim 82, wherein said solvent is selected from the group consisting of water, polar organic solvent, and combinations thereof.

90. The process of claim 89, wherein said solvent is selected from the group consisting of ethanol, isopropanol, acetone, and combinations thereof.

91. The process of claim 82, wherein said active is selected from the group consisting of bioactive active, pharmaceutical actives, drugs, medicaments and combinations thereof.

92. The process of claim 82, wherein the active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, anti-tumor drugs, anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, anti-convulsants, neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, anti-asthmatics, cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

93. The process of claim 82, wherein said active is selected from the group consisting of cosmetic actives, antigens, allergens, spores, microorganisms, seeds, mouthwash components, flavors, fragrances, enzymes, preservatives, sweetening agents, colorants, spices, vitamins and combinations thereof.

94. The process of claim 82, wherein said active is a bioactive active.

95. The process of claim 82, wherein said active is a biological response modifier.

96. The process of claim 82, wherein said active is an opiate or opiate-derivative.

97. The process of claim 82, wherein said active is an anti-emetic.

98. The process of claim 82, wherein said active is an amino acid preparation.

99. The process of claim 82, wherein said active is selected from the group consisting of sildenafils, tadalafils, vardenafils, apomorphines, yohimbine hydrochlorides, alprostadils and combinations thereof.

100. The process of claim 82, wherein said active is a protein.

101. The process of claim 82, wherein said active is insulin.

102. The process of claim 82, wherein said active is an anti-diabetic.

103. The process of claim 82, wherein said active is an antihistamine.

104. The process of claim 82, wherein said active is an anti-tussive.

105. The process of claim 82, wherein said active is a non-steroidal anti-inflammatory.

106. The process of claim 82, wherein said active is an anti-asthmatics.

107. The process of claim 82, wherein said active is an anti-diarrhea.

108. The process of claim 82, wherein said active is an alkaloid.

109. The process of claim 82, wherein said active is an anti-psychotic.

110. The process of claim 82, wherein said active is an anti-spasmodic.

111. The process of claim 82, wherein said active is a biological response modifier.

112. The process of claim 82, wherein said active is an anti-obesity drug.

113. The process of claim 82, wherein said active is an H_2-antagonist.

114. The process of claim 82, wherein said H_2-antagonist is selected from the group consisting of cimetidine, ranitidine hydrochloride, famotidine, nizatidine, ebrotidine, mifentidine, roxatidine, pisatidine, aceroxatidine and combinations thereof.

115. The process of claim 82, wherein said active is a smoking cessation aid.

116. The process of claim 82, wherein said active is an anti-parkinsonian agent.

117. The process of claim 82, wherein said active is an anti-depressant.

118. The process of claim 82, wherein said active is an anti-migraine.

119. The process of claim 82, wherein said active is an anti-Alzheimer's agents.

120. The process of claim 82, wherein said active is a dopamine receptor agonist.

121. The process of claim 82, wherein said active is a cerebral dilator.

122. The process of claim 82, wherein said active is a psychotherapeutic agent.

123. The process of claim 82, wherein said active is an antibiotic.

124. The process of claim 82, wherein said active is an anesthetic.

125. The process of claim 82, wherein said active is a contraceptive.

126. The process of claim, 82, wherein said active is an anti-thrombotic drug.

127. The process of claim 82, wherein said active is diphenhydramine.

128. The process of claim 82, wherein said active is nabilone.

129. The process of claim 82, wherein said active is albuterol sulfate.

130. The process of claim 82, wherein said active is an anti-tumor drug.

131. The process of claim 82, wherein said active is a glycoprotein.

132. The process of claim 82, wherein said active is an analgesic.

133. The process of claim 82, wherein said active is a hormone.

134. The process of claim 82, wherein said active is a decongestant.

135. The process of claim 82, wherein said active is a loratadine.

136. The process of claim 82, wherein said active is dextromethorphan.

137. The process of claim 82, wherein said active is chlorpheniramine maleate.

138. The process of claim 82, wherein said active is selected from the group consisting of an analgesic, an anti-inflammatory, an antihistamine, a decongestant, a cough suppressant and combinations thereof.

139. The process of claim 82, wherein said active is an appetite stimulant.

140. The process of claim 82, wherein said active is a gastrointestinal agent.

141. The process of claim 82, wherein said active is a hypnotic.

142. The process of claim 82, wherein said active is taste-masked.

143. The process of claim 82, wherein said active is taste-masked using a flavor.

144. The process of claim 82, wherein said active is coated with a controlled release composition.

145. The process of claim 144, wherein said controlled release composition provides an immediate release.

146. The process of claim 144, wherein said controlled release composition provides a delayed release.

147. The process of claim 144, wherein said controlled release composition provides a sustained release.

148. The process of claim 144, wherein said controlled release composition provides a sequential release.

149. The process of claim 82, wherein said active is a particulate.

150. The process of claim 82, further comprising adding a degassing agent to said flowable polymer matrix.

151. The process of claim 82, further comprising a step of providing a second film layer.

152. The process of claim 151, wherein said second film layer is coated onto said resulting film.

153. The process of claim 151, wherein said second film layer is spread onto said resulting film.

154. The process of claim 151, wherein said second film layer is cast onto said resulting film.

155. The process of claim 151, wherein said second film layer is extruded onto said resulting film.

156. The process of claim 151, wherein said second film layer is sprayed onto said resulting film.

157. The process of claim 151, wherein said second film layer is laminated onto said resulting film.

158. The process of claim 151, further comprising laminating said resulting film to another film.

159. The process of claim 151, wherein said second film comprises an active.

160. The process of claim 151, wherein said active in said second film is different than said active in said resulting film.

161. A process for making a film capable of being administered to a body surface having a substantially uniform distribution of components, comprising the steps of:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and an active, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix;

(c) evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film within about 10 minutes or fewer to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film;

(d) forming a resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained; and

(e) administering said resulting film to a body surface.

162. The process of claim 161, wherein said body surface is a mucous membrane.

163. The process of claim 162, wherein said mucous membrane is oral, anal, vaginal or ophthalmological.

164. The process of claim 161, wherein said body surface is the surface of a wound.

165. The process of claim 161, wherein said water-soluble polymer comprises polyethylene oxide.

166. The process of claim 161, wherein said polymer comprises a polymer selected from the group consisting of cellulose, a cellulose derivative, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyvinyl copolymers, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof, alone or in combination with polyethylene oxide.

167. The process of claim 166, wherein said polymer further comprises a water insoluble polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone and combinations thereof.

168. The process of claim 166, wherein said polymer further comprises a polymer selected from the group consisting of methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(α-esters), polyanhy-

drides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof.

169. The process of claim **166**, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

170. The process of claim **166**, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(α-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

171. The process of claim **161**, wherein said solvent is selected from the group consisting of water, polar organic solvent, and combinations thereof.

172. The process of claim **161**, wherein said solvent is selected from the group consisting of ethanol, isopropanol, acetone, and combinations thereof.

173. The process of claim **161**, wherein said active is selected from the group consisting of bioactive active, pharmaceutical actives, drugs, medicaments and combinations thereof.

174. The process of claim **161**, wherein said active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, anti-tumor drugs, anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, anti-convulsants, neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, anti-asthmatics, cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

175. The process of claim **161**, wherein said active is selected from the group consisting of cosmetic actives, antigens, allergens, spores, microorganisms, seeds, mouthwash components, flavors, fragrances, enzymes, preservatives, sweetening agents, colorants, spices, vitamins and combinations thereof.

176. The process of claim **161**, wherein said active is a bioactive active.

177. The process of claim **161**, wherein said active is a biological response modifier.

178. The process of claim **161**, wherein said active is an opiate or opiate-derivative.

179. The process of claim **161**, wherein said active is an anti-emetic.

180. The process of claim **161** wherein said active is an amino acid preparation.

181. The process of claim **161**, wherein said active is selected from the group consisting of sildenafils, tadalafils, vardenafils, apomorphines, yohimbine hydrochlorides, alprostadils and combinations thereof.

182. The process of claim **161**, wherein said active is a protein.

183. The process of claim **161**, wherein said active is insulin.

184. The process of claim **161**, wherein said active is an anti-diabetic.

185. The process of claim **161**, wherein said active is an antihistamine.

186. The process of claim **161**, wherein said active is an anti-tussive.

187. The process of claim **161**, wherein said active is a non-steroidal anti-inflammatory.

188. The process of claim **161**, wherein said active is an anti-asthmatics.

189. The process of claim **161**, wherein said active is an anti-diarrhea.

190. The process of claim **161**, wherein said active is an alkaloid.

191. The process of claim **161**, wherein said active is an anti-psychotic.

192. The process of claim **161**, wherein said active is an anti-spasmodic.

193. The process of claim **161**, wherein said active is a biological response modifier.

194. The process of claim **161**, wherein said active is an anti-obesity drug.

195. The process of claim **161**, wherein said active is an H_2-antagonist.

196. The process of claim **195**, wherein said H_2-antagonist is selected from the group consisting of cimetidine, ranitidine hydrochloride, famotidine, nizatidine, ebrotidine, mifentidine, roxatidine, pisatidine, aceroxatidine and combinations thereof.

197. The process of claim **161**, wherein said active is a smoking cessation aid.

198. The process of claim **161**, wherein said active is an anti-parkinsonian agent.

199. The process of claim 161, wherein said active is an anti-depressant.

200. The process of claim 161, wherein said active is an anti-migraine.

201. The process of claim 161, wherein said active is an anti-Alzheimer's agents.

202. The process of claim 161, wherein said active is a dopamine receptor agonist.

203. The process of claim 161, wherein said active is a cerebral dilator.

204. The process of claim 161, wherein said active is a psychotherapeutic agent.

205. The process of claim 161, wherein said active is an antibiotic.

206. The process of claim 161, wherein said active is an anesthetic.

207. The process of claim 161, wherein said active is a contraceptive.

208. The process of claim 161, wherein said active is an anti-thrombotic drug.

209. The process of claim 161, wherein said active is diphenhydramine.

210. The process of claim 161, wherein said active is nabilone.

211. The process of claim 161, wherein said active is albuterol sulfate.

212. The process of claim 161, wherein said active is an anti-tumor drug.

213. The process of claim 161, wherein said active is a glycoprotein.

214. The process of claim 161, wherein said active is an analgesic.

215. The process of claim 161, wherein said active is a hormone.

216. The process of claim 161, wherein said active is a decongestant.

217. The process of claim 161, wherein said active is a loratadine.

218. The process of claim 161, wherein said active is dextromethorphan.

219. The process of claim 161, wherein said active is chlorpheniramine maleate.

220. The process of claim 161, wherein said active is selected from the group consisting of an analgesic, an anti-inflammatory, an antihistamine, a decongestant, a cough suppressant and combinations thereof.

221. The process of claim 161, wherein said active is an appetite stimulant.

222. The process of claim 161, wherein said active is a gastrointestinal agent.

223. The process of claim 161, wherein said active is a hypnotic.

224. The process of claim 161, wherein said active is taste-masked.

225. The process of claim 161, wherein said active is taste-masked using a flavor.

226. The process of claim 161, wherein said active is coated with a controlled release composition.

227. The process of claim 226, wherein said controlled release composition provides an immediate release.

228. The process of 226, wherein said controlled release composition provides a delayed release.

229. The process of claim 226, wherein said controlled release composition provides a sustained release.

230. The process of claim 226, wherein said controlled release composition provides a sequential release.

231. The process of claim 161, wherein said active is a particulate.

232. The process of claim 161, further comprising adding a degassing agent to said flowable polymer matrix.

233. The process of claim 161, further comprising a step of providing a second film layer.

234. The process of claim 233, wherein said second film layer is coated onto said resulting film.

235. The process of claim 233, wherein said second film layer is spread onto said resulting film.

236. The process of claim 233, wherein said second film layer is cast onto said resulting film.

237. The process of claim 233, wherein said second film layer is extruded onto said resulting film.

238. The process of claim 233, wherein said second film layer is sprayed onto said resulting film.

239. The process of claim 233, wherein said second film layer is laminated onto said resulting film.

240. The process of claim 233, further comprising laminating said resulting film to another film.

241. The process of claim 233, wherein said second film comprises an active.

242. The process of claim 233, wherein said active in said second film is different than said active in said resulting film.

243. The process of claim 1, said active is an anti-nauseant.

244. The process of claim 1, said active is an erectile dysfunction.

245. The process of claim 1, said active is a vasoconstrictor.

246. The process of claim 1, said active is a stimulant.

247. The process of claim 1, said active is a migraine treatment.

248. The process of claim 1, said active is granisetron hydrochloride.

249. The process of claim 1, wherein said resulting film provides administration of said active to an individual through the buccal cavity of said individual.

250. The process of claim 1, wherein said resulting film provides administration of said active through gingival application of said individual.

251. The process of claim 1, wherein said resulting film provides administration of said active through sublingual application of said individual.

252. The process of claim 1, wherein said resulting film provides administration of said active to an individual through a mucosal membrane of said individual.

253. The process of claim 1, wherein said resulting film provides administration of said active to an individual by administration within the body of the individual during surgery.

254. The process of claim 1, wherein said resulting film has a variation of active content of less than 10% per film unit.

255. The process of claim 1, further comprising the step of forming a plurality of individual dosage units of substantially the same size, wherein the active content of individual dosage units has a variance of no more than 10%.

256. The method of claim 1, wherein said resulting film contains less than about 6% by weight solvent.

257. The method of claim 1, wherein said at least one edible polymer, said active, and said at least one polar solvent are each ingestible materials.

258. The method of claim 1, wherein said resulting film is orally administrable.

259. The method of claim 1, wherein said active is in the form of a particle.

260. The method of claim 1, wherein said matrix comprises a dispersion.

261. The process of claim **82**, said active is an anti-nauseant.

262. The process of claim **82**, said active is an erectile dysfunction.

263. The process of claim **82**, said active is a vasoconstrictor.

264. The process of claim **82**, said active is a stimulant.

265. The process of claim **82**, said active is a migraine treatment.

266. The process of claim **82**, said active is granisetron hydrochloride.

267. The process of claim **82**, wherein said resulting film provides administration of said active to an individual through the buccal cavity of said individual.

268. The process of claim **82**, wherein said resulting film provides administration of said active through gingival application of said individual.

269. The process of claim **82**, wherein said resulting film provides administration of said active through sublingual application of said individual.

270. The process of claim **82**, wherein said resulting film provides administration of said active to an individual through a mucosal membrane of said individual.

271. The process of claim **82**, wherein said resulting film provides administration of said active to an individual by administration within the body of the individual during surgery.

272. The process of claim **82**, wherein said resulting film has a variation of active content of less than 10% per film unit.

273. The process of claim **82**, further comprising the step of forming a plurality of individual dosage units of substantially the same size, wherein the active content of individual dosage units has a variance of no more than 10%.

274. The method of claim **82**, wherein said resulting film contains less than about 6% by weight solvent.

275. The method of claim **82**, wherein said at least one edible polymer, said active, and said at least one polar solvent are each ingestible materials.

276. The method of claim **82**, wherein said resulting film is orally administrable.

277. The method of claim **82**, wherein said active is in the form of a particle.

278. The method of claim **82**, wherein said matrix comprises a dispersion.

279. The process of claim **161**, said active is an anti-nauseant.

280. The process of claim **161**, said active is an erectile dysfunction.

281. The process of claim **161**, said active is a vasoconstrictor.

282. The process of claim **161**, said active is a stimulant.

283. The process of claim **161**, said active is a migraine treatment.

284. The process of claim **161**, said active is granisetron hydrochloride.

285. The process of claim **161**, wherein said resulting film provides administration of said active to an individual through the buccal cavity of said individual.

286. The process of claim **161**, wherein said resulting film provides administration of said active through gingival application of said individual.

287. The process of claim **161**, wherein said resulting film provides administration of said active through sublingual application of said individual.

288. The process of claim **161**, wherein said resulting film provides administration of said active to an individual through a mucosal membrane of said individual.

289. The process of claim **161**, wherein said resulting film provides administration of said active to an individual by administration within the body of the individual during surgery.

290. The process of claim **161**, wherein said resulting film has a variation of active content of less than 10% per film unit.

291. The process of claim **161**, further comprising the step of forming a plurality of individual dosage units of substantially the same size, wherein the active content of individual dosage units has a variance of no more than 10%.

292. The method of claim **161**, wherein said resulting film contains less than about 6% by weight solvent.

293. The method of claim **161**, wherein said at least one edible polymer, said active, and said at least one polar solvent are each ingestible materials.

294. The method of claim **161**, wherein said resulting film is orally administrable.

295. The method of claim **161**, wherein said active is in the form of a particle.

296. The method of claim **161**, wherein said matrix comprises a dispersion.

297. The method of claim **1**, wherein said matrix comprises an emulsion, a colloid or a suspension.

298. The method of claim **82**, wherein said matrix comprises an emulsion, a colloid or a suspension.

299. The method of claim **161**, wherein said matrix comprises an emulsion, a colloid or a suspension.

* * * * *

EXHIBIT G

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	Yang et al.	Examiner:	Lee, Edmund H.
Application No.:	12/614,928	Group Art Unit:	1791
Confirmation No:	9528	Docket:	1199-26 RCE/CON
Filed:	November 9, 2010	Dated:	November 16, 2010
For:	POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM		

Commissioner for Patents
P.O. Box 1450,
Alexandria, VA 22313

TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER "PRIOR" PATENT(S) AND OVER A PENDING "REFERENCE" APPLICATION

The owner*, MonoSol Rx, LLC., of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term **prior patent** No(s). 7357891, 7425292 and 7666337 as the term of said prior patent is defined in 35 U.S.C. 154 and 173, and as the term of said prior patent is presently shortened by any terminal disclaimer. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the **prior patent** are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer with respect to the granted patents, the owner does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. 154 and 173 of the prior patent, "as the term of said **prior patent** is presently shortened by any terminal disclaimer," in the event that said **prior patent** later:

expires for failure to pay a maintenance fee;
is held unenforceable;

is found invalid by a court of competent jurisdiction;
is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321;
has all claims canceled by a reexamination certificate;
is reissued; or
is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

The owner*, MonoSol Rx, LLC., of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of any patent granted on pending **reference** Application Number(s) 12/411505, filed on March 26, 2009 and 12/171692, filed on July 11, 2008, as such term is defined in 35 U.S.C. 154 and 173, and as the term of any patent granted on said on **reference** applications may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending **reference** applications. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent granted on the **reference** applications are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer with respect to the pending patent application, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. 154 and 173 of any patent granted on said **reference** applications, "as the term of any patent granted on said **reference** applications may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending **reference** applications," in the event that: any such patent: granted on the pending **reference** applications: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321, has all claims canceled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as shortened by any terminal disclaimer filed prior to its grant.

Check either box 1 or 2 below, if appropriate.

1. ☐ For submissions on behalf of a business/organization (e.g., corporation, partnership, university, government agency, etc.), the undersigned is empowered to act on behalf of the business/organization.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States

Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

2. ☒ The undersigned is an attorney or agent of record. Reg. No. 55,832

Nichole E. Martiak — November 16, 2010
Signature — Date

Nichole E. Martiak
Typed or printed name

(973) 331-1700
Telephone Number

☒ Terminal disclaimer fee under 37 CFR 1.20(d) included.

☒ PTO suggested wording for terminal disclaimer was unchanged.

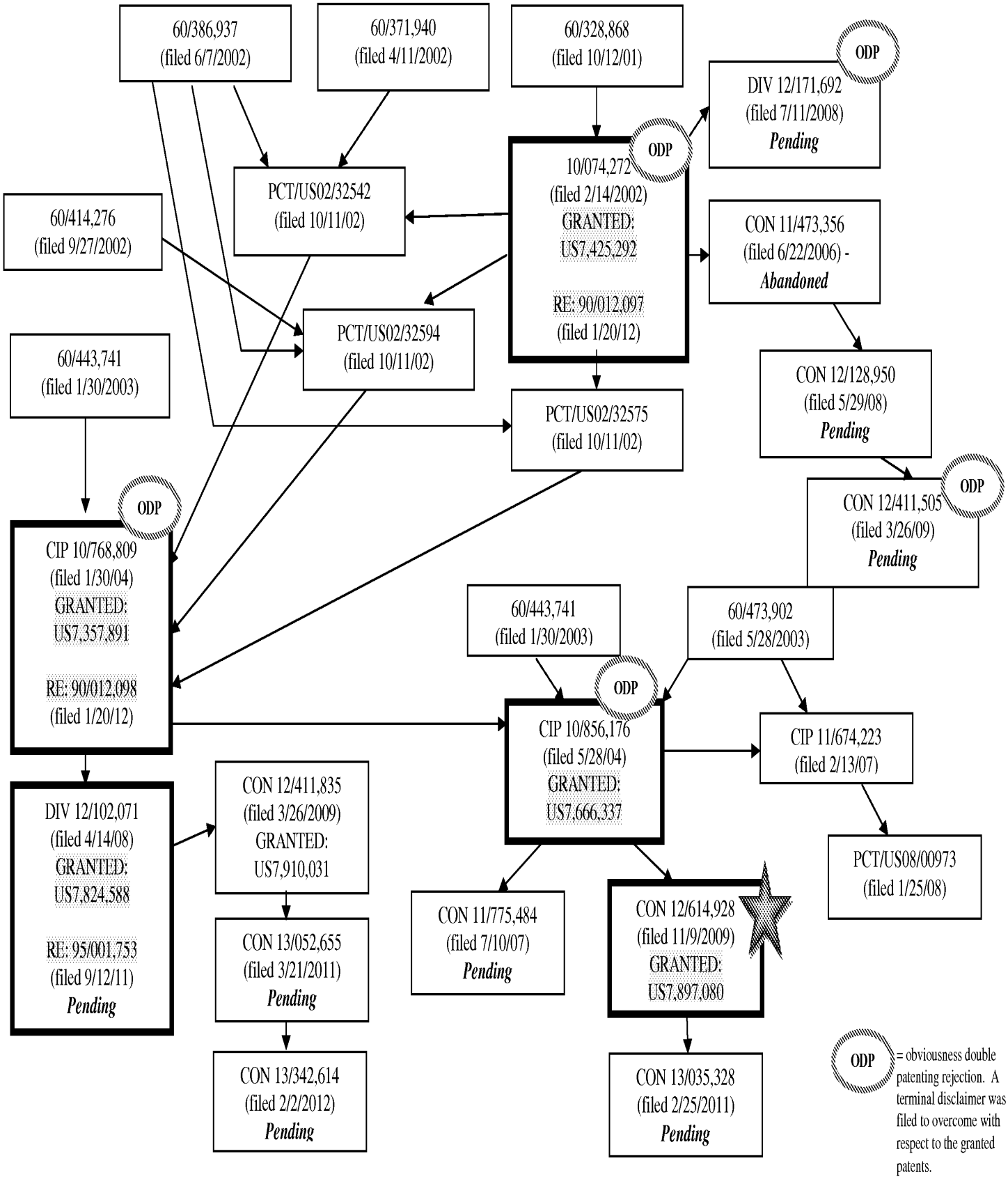
WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

* Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner). Form PTO/SB/96 may be used for making this certification. See MPEP § 324.

EXHIBIT H

Partial Patent Family Tree

117744-00023



ME1 14091285v.1

DRL - EXHIBIT 1007
DRL3190

EXHIBIT I

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/614,928	11/09/2009	Robert K. Yang	1199-26 RCE/CON	9528

23869 7590 09/29/2010
HOFFMANN & BARON, LLP
6900 JERICHO TURNPIKE
SYOSSET, NY 11791

EXAMINER	
LEE, EDMUND H	

ART UNIT	PAPER NUMBER
1791	

MAIL DATE	DELIVERY MODE
09/29/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	12/614,928	YANG ET AL.	
	Examiner	Art Unit	
	EDMUND H. LEE	1791	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 December 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-242* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-242* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

2. Claims 1-161 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-30 of U.S. Patent No. 7666337. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of USPN 7666337 encompass the instant claimed limitations.

3. Claims 1-161are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9 of U.S. Patent No. 7357891 (hereinafter '891) in view of USPN 7666337 (hereinafter '337). USPN '891 teaches the claimed invention expect forming a resulting film having the claimed water content. USPN '337 teach a film wherein the resulting film has the claimed water content. Since USPNs '891 and '337 are analogous with respect to forming a film, it would have been obvious to one of ordinary skill in the art at the time the invention was made to set the water content of the film of USPN '891 to 10% or less as taught by USPN '337 in order to ensure uniformity.

4. Claims 1-161 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 62-66 of copending Application No. 12/411505 in view of USPN 7666337 (hereinafter '337). Application '505 teaches the claimed invention expect forming a resulting film having the claimed water content. USPN '337 teach a film wherein the resulting film has the claimed water content. Since application '505 and '337 are analogous with respect to forming a film, it would have been obvious to one of ordinary skill in the art at the time

the invention was made to set the water content of the film of application ‘505 to 10% or less as taught by USPN '337 in order to ensure uniformity.

This is a provisional obviousness-type double patenting rejection.

5. Claims 1-161 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 32-46 and 62-74 of copending Application No. 12/171692 in view of USPN 7666337 (hereinafter ‘337). Application ‘’692 teaches the claimed invention expect forming a resulting film having the claimed water content. USPN ‘337 teach a film wherein the resulting film has the claimed water content. Since application ‘692 and '337 are analogous with respect to forming a film, it would have been obvious to one of ordinary skill in the art at the time the invention was made to set the water content of the film of application ‘692 to 10% or less as taught by USPN '337 in order to ensure uniformity.

This is a provisional obviousness-type double patenting rejection.

6. Claims 1-161 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-22 of U.S. Patent No. 7425292 (hereinafter ‘292) in view of USPN 7666337 (hereinafter ‘337). USPN ‘292 teaches the claimed invention expect forming a resulting film having the claimed water content. USPN ‘337 teach a film wherein the resulting film has the claimed water content. Since USPNs '292 and '337 are analogous with respect to forming a film, it would have been obvious to one of ordinary skill in the art at the time the invention was made to set the

water content of the film of USPN '292 to 10% or less as taught by USPN '337 in order to ensure uniformity.

7. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. The following USPNs teach the state of the art: 5629003;4049848;5766525 and 4872270.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to EDMUND H. LEE whose telephone number is 571.272.1204. The examiner can normally be reached on MONDAY-THURSDAY FROM 9AM-4PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yogendra Gupta can be reached on 571.272.1316. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

EDMUND H. LEE
Primary Examiner
Art Unit 1791

EHL
/EDMUND H. LEE/
Primary Examiner, Art Unit 1791

EXHIBIT J

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	Yang et al.	Examiner:	Lee, Edmund H.
Application No.:	12/614,928	Group Art Unit:	1791
Confirmation No:	9528	Docket:	1199-26 RCE/CON
Filed:	November 9, 2010	Dated:	November 16, 2010
For:	POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM		

Commissioner for Patents
P.O. Box 1450,
Alexandria, VA 22313

AMENDMENT AND RESPONSE

Sir:

This submission is in response to the non-final Office Action mailed on September 29, 2010, a response for which is due December 29, 2010. Please amend the above-identified application as follows:

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks begin on page 37 of this paper.

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of claims:

1. (Currently amended) A process for making a film having a substantially uniform distribution of components, comprising the steps of:

(a) forming a masterbatch pre-mix comprising a solvent and a polymer selected from the group consisting of water-soluble polymers, water-swellable polymers and combinations thereof;

(b) adding an active to a pre-determined amount of said masterbatch pre-mix to form a flowable polymer matrix, said matrix having a substantially uniform distribution of said active;

(c) casting said flowable polymer matrix;

(d) evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film within about 10 minutes or fewer to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film; and

(e) forming a resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained.

2. (Original) The process of claim 1, wherein said pre-determined amount of master batch pre-mix is controllably fed via a first metering pump and a control valve to a first mixer and a second mixer.

3. (Original) The process of claim 2, wherein said first mixer and said second mixer are arranged in parallel, series or a combination thereof.

4. (Original) The process of claim 1, wherein said water-soluble polymer comprises polyethylene oxide.

5. (Original) The process of claim 1, wherein said polymer comprises a polymer selected from the group consisting of cellulose, a cellulose derivative, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyvinyl copolymers, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragancanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof, alone or in combination with polyethylene oxide.

6. (Original) The process of claim 5, wherein said polymer further comprises a water insoluble polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone and combinations thereof.

7. (Original) The process of claim 5, wherein said polymer further comprises a polymer selected from the group consisting of methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanoes, polyoxalates, poly (ά-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acides, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof.

8. (Original) The process of claim 5, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragancanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

9. (Original) The process of claim 5, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanoes, polyoxalates, poly (ά-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acides, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragancanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

10. (Original) The process of claim 1, wherein said solvent is selected from the group consisting of water, polar organic solvent, and combinations thereof.

11. (Currently amended) The process of claim 10, wherein said solvent is selected from the group consisting of ethanol, isopropanol, acetone, ~~methylene chloride,~~ and or ~~any~~ combinations thereof.

12. (Original) The process of claim 1, wherein said active is selected from the group consisting of bioactive active, pharmaceutical actives, drugs, medicaments and combinations thereof.

13. (Original) The process of claim 1, wherein said active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, anti-tumor drugs, anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, anti-convulsants, neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, anti-asthmatics, cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof

14. (Original) The process of claim 1, wherein said active is selected from the group consisting of cosmetic actives, antigens, allergens, spores, microorganisms, seeds, mouthwash components, flavors, fragrances, enzymes, preservatives, sweetening agents, colorants, spices, vitamins and combinations thereof.

15. (Original) The process of claim 1, wherein said active is a bioactive active.

16. (Original) The process of claim 1, wherein said active is a biological response modifier.

17. (Original) The process of claim 1, wherein said active is an opiate or opiate-derivative.

18. (Original) The process of claim 1, wherein said active is an anti-emetic.

19. (Original) The process of claim 1, wherein said active is an amino acid preparation.

20. (Original) The process of claim 1, wherein said active is selected from the group consisting of sildenafils, tadalafils, vardenafils, apomorphines, yohimbine hydrochlorides, alprostadils and combinations thereof.

21. (Original) The process of claim 1, wherein said active is a protein.

22. (Original) The process of claim 1, wherein said active is insulin.

23. (Original) The process of claim 1, wherein said active is an anti-diabetic.

24. (Original) The process of claim 1, wherein said active is an antihistamine.

25. (Original) The process of claim 1, wherein said active is an anti-tussive.

26. (Original) The process of claim 1, wherein said active is a non-steroidal anti-inflammatory.

27. (Original) The process of claim 1, wherein said active is an anti-asthmatics.

28. (Original) The process of claim 1, wherein said active is an anti-diarrhea.

29. (Original) The process of claim 1, wherein said active is an alkaloid.

30. (Original) The process of claim 1, wherein said active is an anti-psychotic.

31. (Original) The process of claim 1, wherein said active is an anti-spasmodic.

32. (Original) The process of claim 1, wherein said active is a biological response modifier.

33. (Original) The process of claim 1, wherein said active is an anti-obesity drug

.

34. (Original) The process of claim 1, wherein said active is an H_2-antagonist.

35. (Currently amended) The process of claim 34, wherein said H_2-antagonist is selected from the group consisting of cimetidine, ranitidine hydrochloride, famotidine, ~~nizatidien,~~ nizatidine, ebrotidine, mifentidine, roxatidine, pisatidine, aceroxatidine and combinations thereof.

36. (Original) The process of claim 1, wherein said active is a smoking cessation aid.

37. (Original) The process of claim 1, wherein said active is an anti-parkinsonian agent.

38. (Original) The process of claim 1, wherein said active is an anti-depressant.

39. (Original) The process of claim 1, wherein said active is an anti-migraine.

40. (Original) The process of claim 1, wherein said active is an anti-Alzheimer's agents.

41. (Original) The process of claim 1, wherein said active is a dopamine receptor agonist.

42. (Original) The process of claim 1, wherein said active is a cerebral dilator.

43. (Original) The process of claim 1, wherein said active is a psychotherapeutic agent.

44. (Original) The process of claim 1, wherein said active is an antibiotic.

45. (Original) The process of claim 1, wherein said active is an anesthetic.

46. (Original) The process of claim 1, wherein said active is a contraceptive.

47. (Original) The process of claim 1, wherein said active is an anti-thrombotic drug.

48. (Original) The process of claim 1, wherein said active is diphenhydramine.

49. (Original) The process of claim 1, wherein said active is nabilone.

50. (Original) The process of claim 1, wherein said active is albuterol sulfate.

51. (Original) The process of claim 1, wherein said active is an anti-tumor drug.

52 (Original) The process of claim 1, wherein said active is a glycoprotein.

53. (Original) The process of claim 1, wherein said active is an analgesic.

54. (Original) The process of claim 1, wherein said active is a hormone.

55. (Original) The process of claim 1, wherein said active is a decongestant.

56. (Original) The process of claim 1, wherein said active is a loratadine.

57. (Original) The process of claim 1, wherein said active is dextromethorphan.

58. (Original) The process of claim 1, wherein said active is chlorpheniramine maleate.

59. (Original) The process of claim 1, wherein said active is selected from the group consisting of an analgesic, an anti-inflammatory, an antihistamine, a decongestant, a cough suppressant and combinations thereof.

60. (Original) The process of claim 1, wherein said active is an appetite stimulant.

61. (Original) The process of claim 1, wherein said active is a gastrointestinal agent.

62. (Original) The process of claim 1, wherein said active is a hypnotic.

63. (Original) The process of claim 1, wherein said active is taste-masked.

64. (Original) The process of claim 1, wherein said active is taste-masked using a flavor.

65. (Original) The process of claim 1, wherein said active is coated with a controlled release composition.

66. (Original) The process of claim 65, wherein said controlled release composition provides an immediate release.

67. (Original) The process of claim 65, wherein said controlled release composition provides a delayed release.

68. (Original) The process of claim 65, wherein said controlled release composition provides a sustained release.

69. (Original) The process of claim 65, wherein said controlled release composition provides a sequential release.

70. (Currently amended) The process of claim 1 ~~2~~, wherein said active is a particulate.

71. (Original) The process of claim 1, further comprising adding a degassing agent to said masterbatch premix.

72. (Original) The process of claim 1, further comprising a step of providing a second film layer.

73. (Original) The process of claim 72, wherein said second film layer is coated onto said resulting film.

74. (Original) The process of claim 72, wherein said second film layer is spread onto said resulting film.

75. (Original) The process of claim 72, wherein said second film layer is cast onto said resulting film.

76. (Original) The process of claim 72, wherein said second film layer is extruded onto said resulting film.

77. (Original) The process of claim 72, wherein said second film layer is sprayed onto said resulting film.

78. (Original) The process of claim 72, wherein said second film layer is laminated onto said resulting film.

79. (Original) The process of claim 72, further comprising laminating said resulting film to another film.

80. (Original) The process of claim 72, wherein said second film comprises an active.

81. (Original) The process of claim 72, wherein said active in said second film is different than said active in said resulting film.

82. (Currently amended) A process for making a film having a substantially uniform distribution of components, comprising the steps of:

(a) forming a flowable polymer matrix comprising a polymer selected from the group consisting of a water-soluble polymer, a water swellable polymer and combinations thereof, a solvent and an active selected from the group

consisting of bioactive actives, pharmaceutical actives, drugs, medicaments and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix;

(c) evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film within about 10 minutes or fewer to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film; and

(d) forming a resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained.

83. (Original) The process of claim 82, wherein said water-soluble polymer comprises polyethylene oxide.

84. (Original) The process of claim 82, wherein said polymer comprises a polymer selected from the group consisting of cellulose, a cellulose derivative, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyvinyl copolymers, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragancanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof, alone or in combination with polyethylene oxide.

85. (Original) The process of claim 84, wherein said polymer further comprises a water insoluble polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin,

poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone and combinations thereof.

86. (Original) The process of claim 84, wherein said polymer further comprises a polymer selected from the group consisting of methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanoes, polyoxalates, poly (ά-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acides, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof.

87. (Original) The process of claim 84, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragancanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

88. (Original) The process of claim 84, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanoes, polyoxalates, poly (ά-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acides, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragancanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

89. (Original) The process of claim 82, wherein said solvent is selected from the group consisting of water, polar organic solvent, and combinations thereof.

90. (Currently amended) The process of claim 89, wherein said solvent is selected from the group consisting of ethanol, isopropanol, acetone, ~~methylene chloride, or any~~ and combinations thereof.

91. (Original) The process of claim 82, wherein said active is selected from the group consisting of bioactive active, pharmaceutical actives, drugs, medicaments and combinations thereof.

92. (Original) The process of claim 82, wherein the active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins,

anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, anti-tumor drugs, anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, anti-convulsants, neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, anti-asthmatics, cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof

93. (Original) The process of claim 82, wherein said active is selected from the group consisting of cosmetic actives, antigens, allergens, spores, microorganisms, seeds, mouthwash components, flavors, fragrances, enzymes, preservatives, sweetening agents, colorants, spices, vitamins and combinations thereof.

94. (Original) The process of claim 82, wherein said active is a bioactive active.

95. (Original) The process of claim 82, wherein said active is a biological response modifier.

96. (Original) The process of claim 82, wherein said active is an opiate or opiate-derivative.

97. (Original) The process of claim 82, wherein said active is an anti-emetic.

98. (Original) The process of claim 82, wherein said active is an amino acid preparation.

99. (Original) The process of claim 82, wherein said active is selected from the group consisting of sildenafils, tadalafils, vardenafils, apomorphines, yohimbine hydrochlorides, alprostadils and combinations thereof.

100. (Original) The process of claim 82, wherein said active is a protein.

101. (Original) The process of claim 82, wherein said active is insulin.

102. (Original) The process of claim 82, wherein said active is an anti-diabetic.

103. (Original) The process of claim 82, wherein said active is an antihistamine.

104. (Original) The process of claim 82, wherein said active is an anti-tussive.

105. (Original) The process of claim 82, wherein said active is a non-steroidal anti-inflammatory.

106. (Original) The process of claim 82, wherein said active is an anti-asthmatics.

107. (Original) The process of claim 82, wherein said active is an anti-diarrhea.

108. (Original) The process of claim 82, wherein said active is an alkaloid.

109. (Original) The process of claim 82, wherein said active is an anti-psychotic.

110. (Original) The process of claim 82, wherein said active is an anti-spasmodic.

111. (Original) The process of claim 82, wherein said active is a biological response modifier.

112. (Original) The process of claim 82, wherein said active is an anti-obesity drug.

113. (Original) The process of claim 82, wherein said active is an H_2-antagonist.

114. (Currently amended) The process of claim 82, wherein said H_2-antagonist is selected from the group consisting of cimetidine, ranitidine hydrochloride, famotidine, ~~nizatidien~~, nizatidine, ebrotidine, mifentidine, roxatidine, pisatidine, aceroxatidine and combinations thereof.

115. (Original) The process of claim 82, wherein said active is a smoking cessation aid.

116. (Original) The process of claim 82, wherein said active is an anti-parkinsonian agent.

117. (Original) The process of claim 82, wherein said active is an anti-depressant.

118. (Original) The process of claim 82, wherein said active is an anti-migraine.

119. (Original) The process of claim 82, wherein said active is an anti-Alzheimer's agents.

120. (Original) The process of claim 82, wherein said active is a dopamine receptor agonist.

121. (Original) The process of claim 82, wherein said active is a cerebral dilator.

122. (Original) The process of claim 82, wherein said active is a psychotherapeutic agent.

123. (Original) The process of claim 82, wherein said active is an antibiotic.

124. (Original) The process of claim 82, wherein said active is an anesthetic.

125. (Original) The process of claim 82, wherein said active is a contraceptive.

126. (Original) The process of claim, 82, wherein said active is an anti-thrombotic drug.

127. (Original) The process of claim 82, wherein said active is diphenhydramine.

128. (Original) The process of claim 82, wherein said active is nabilone.

129. (Original) The process of claim 82, wherein said active is albuterol sulfate.

130. (Original) The process of claim 82, wherein said active is an anti-tumor drug.

131. (Original) The process of claim 82, wherein said active is a glycoprotein.

132. (Original) The process of claim 82, wherein said active is an analgesic.

133. (Original) The process of claim 82, wherein said active is a hormone.

134. (Original) The process of claim 82, wherein said active is a decongestant.

135. (Original) The process of claim 82, wherein said active is a loratadine.

136. (Original) The process of claim 82, wherein said active is dextromethorphan.

137. (Original) The process of claim 82, wherein said active is chlorpheniramine maleate.

138. (Original) The process of claim 82, wherein said active is selected from the group consisting of an analgesic, an anti-inflammatory, an antihistamine, a decongestant, a cough suppressant and combinations thereof.

139. (Original) The process of claim 82, wherein said active is an appetite stimulant.

140. (Original) The process of claim 82, wherein said active is a gastrointestinal agent.

141. (Original) The process of claim 82, wherein said active is a hypnotic.

142. (Original) The process of claim 82, wherein said active is taste-masked.

143. (Original) The process of claim 82, wherein said active is taste-masked using a flavor.

144. (Original) The process of claim 82, wherein said active is coated with a controlled release composition.

145. (Original) The process of claim 144, wherein said controlled release composition provides an immediate release.

146. (Original) The process of claim 144, wherein said controlled release composition provides a delayed release.

147. (Original) The process of claim 144, wherein said controlled release composition provides a sustained release.

148. (Original) The process of claim 144, wherein said controlled release composition provides a sequential release.

149. (Original) The process of claim 82, wherein said active is a particulate.

150. (Currently amended) The process of claim 82, further comprising adding a degassing agent to said flowable polymer matrix~~masterbatch premix~~.

151. (Currently amended) The process of claim 82 ~~81~~, further comprising a step of providing a second film layer.

152. (Original) The process of claim 151, wherein said second film layer is coated onto said resulting film.

153. (Original) The process of claim 151, wherein said second film layer is spread onto said resulting film.

154. (Original) The process of claim 151, wherein said second film layer is cast onto said resulting film.

155. (Original) The process of claim 151, wherein said second film layer is extruded onto said resulting film.

156. (Original) The process of claim 151, wherein said second film layer is sprayed onto said resulting film.

157. (Original) The process of claim 151, wherein said second film layer is laminated onto said resulting film.

158. (Original) The process of claim 151, further comprising laminating said resulting film to another film.

159. (Original) The process of claim 151, wherein said second film comprises an active.

160. (Original) The process of claim 151, wherein said active in said second film is different than said active in said resulting film.

161. (Currently amended) A process for making a film capable of being administered to a body surface having a substantially uniform distribution of components, comprising the steps of:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and an active, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix;

(c) evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film within about 10 minutes or fewer to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film;

(d) forming a resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained; and

(e) administering said resulting film to a body surface.

162. (Currently amended) The process of claim 161, wherein said body surface is a mucous ~~mucus~~ membrane.

163. (Currently amended) The process of claim 162, wherein said mucous ~~mucus~~ membrane is oral, anal, vaginal or ophthalmological.

164. (Original) The process of claim 161, wherein said body surface is the surface of a wound.

165. (Original) The process of claim 161, wherein said water-soluble polymer comprises polyethylene oxide.

166. (Original) The process of claim 161, wherein said polymer comprises a polymer selected from the group consisting of cellulose, a cellulose derivative, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyvinyl copolymers, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragancanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof, alone or in combination with polyethylene oxide.

167. (Original) The process of claim 166, wherein said polymer further comprises a water insoluble polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone and combinations thereof.

168. (Original) The process of claim 166, wherein said polymer further comprises a polymer selected from the group consisting of methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanoes, polyoxalates, poly (ά-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters),

polyamino acides, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof.

169. (Original) The process of claim 166, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragancanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

170. (Original) The process of claim 166, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanoes, polyoxalates, poly (ά-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acides, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragancanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

171. (Original) The process of claim 161, wherein said solvent is selected from the group consisting of water, polar organic solvent, and combinations thereof.

172. (Currently amended) The process of claim 161, wherein said solvent is selected from the group consisting of ethanol, isopropanol, acetone, ~~methylene chloride, or any~~ and combinations thereof.

173. (Original) The process of claim 161, wherein said active is selected from the group consisting of bioactive active, pharmaceutical actives, drugs, medicaments and combinations thereof.

174. (Original) The process of claim 161, wherein said active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, anti-tumor drugs, anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, anti-convulsants, neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, anti-obesity drugs,

erythropoietic drugs, anti-asthmatics, cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof

175. (Original) The process of claim 161, wherein said active is selected from the group consisting of cosmetic actives, antigens, allergens, spores, microorganisms, seeds, mouthwash components, flavors, fragrances, enzymes, preservatives, sweetening agents, colorants, spices, vitamins and combinations thereof.

176. (Original) The process of claim 161, wherein said active is a bioactive active.

177. (Original) The process of claim 161, wherein said active is a biological response modifier.

178. (Original) The process of claim 161, wherein said active is an opiate or opiate-derivative.

179. (Original) The process of claim 161, wherein said active is an anti-emetic.

180. (Original) The process of claim 161 wherein said active is an amino acid preparation.

181. (Original) The process of claim 161, wherein said active is selected from the group consisting of sildenafils, tadalafils, vardenafils, apomorphines, yohimbine hydrochlorides, alprostadils and combinations thereof.

182. (Original) The process of claim 161, wherein said active is a protein.

183. (Original) The process of claim 161, wherein said active is insulin.

184. (Original) The process of claim 161, wherein said active is an anti-diabetic.

185. (Original) The process of claim 161, wherein said active is an antihistamine.

186. (Original) The process of claim 161, wherein said active is an anti-tussive.

187. (Original) The process of claim 161, wherein said active is a non-steroidal anti-inflammatory.

188. (Original) The process of claim 161, wherein said active is an anti-asthmatics.

189. (Original) The process of claim 161, wherein said active is an anti-diarrhea.

190. (Original) The process of claim 161, wherein said active is an alkaloid.

191. (Original) The process of claim 161, wherein said active is an anti-psychotic.

192. (Original) The process of claim 161, wherein said active is an anti-spasmodic.

193. (Original) The process of claim 161, wherein said active is a biological response modifier.

194. (Original) The process of claim 161, wherein said active is an anti-obesity drug.

195. (Original) The process of claim 161, wherein said active is an H_2-antagonist.

196. (Currently amended) The process of claim 195, wherein said H_2-antagonist is selected from the group consisting of cimetidine, ranitidine hydrochloride, famotidine, ~~nizatidien,~~ nizatidine, ebrotidine, mifentidine, roxatidine, pisatidine, aceroxatidine and combinations thereof.

197. (Original) The process of claim 161, wherein said active is a smoking cessation aid.

198. (Original) The process of claim 161, wherein said active is an anti-parkinsonian agent.

199. (Original) The process of claim 161, wherein said active is an anti-depressant.

200. (Original) The process of claim 161, wherein said active is an anti-migraine.

201. (Original) The process of claim 161, wherein said active is an anti-Alzheimer's agents.

202. (Original) The process of claim 161, wherein said active is a dopamine receptor agonist.

203. (Original) The process of claim 161, wherein said active is a cerebral dilator.

204. (Original) The process of claim 161, wherein said active is a psychotherapeutic agent.

205. (Original) The process of claim 161, wherein said active is an antibiotic.

206. (Original) The process of claim 161, wherein said active is an anesthetic.

207. (Original) The process of claim 161, wherein said active is a contraceptive.

208. (Original) The process of claim 161, wherein said active is an anti-thrombotic drug.

209. (Original) The process of claim 161, wherein said active is diphenhydramine.

210. (Original) The process of claim 161, wherein said active is nabilone.

211. (Original) The process of claim 161, wherein said active is albuterol sulfate.

212. (Original) The process of claim 161, wherein said active is an anti-tumor drug.

213. (Original) The process of claim 161, wherein said active is a glycoprotein.

214. (Original) The process of claim 161, wherein said active is an analgesic.

215. (Original) The process of claim 161, wherein said active is a hormone.

216. (Original) The process of claim 161, wherein said active is a decongestant.

217. (Original) The process of claim 161, wherein said active is a loratadine.

218. (Original) The process of clam 161, wherein said active is dextromethorphan.

219. (Original) The process of claim 161, wherein said active is chlorpheniramine maleate.

220. (Original) The process of claim 161, wherein said active is selected from the group consisting of an analgesic, an anti-inflammatory, an antihistamine, a decongestant, a cough suppressant and combinations thereof.

221. (Original) The process of claim 161, wherein said active is an appetite stimulant.

222. (Original) The process of claim 161, wherein said active is a gastrointestinal agent.

223. (Original) The process of claim 161, wherein said active is a hypnotic.

224. (Original) The process of claim 161, wherein said active is taste-masked.

225. (Original) The process of claim 161, wherein said active is taste-masked using a flavor.

226. (Original) The process of claim 161, wherein said active is coated with a controlled release composition.

227. (Original) The process of claim 226, wherein said controlled release composition provides an immediate release.

228. (Original) The process of 226, wherein said controlled release composition provides a delayed release.

229. (Original) The process of claim 226, wherein said controlled release composition provides a sustained release.

230. (Original) The process of claim 226, wherein said controlled release composition provides a sequential release.

231. (Original) The process of claim 161, wherein said active is a particulate.

232. (Currently amended) The process of claim 161, further comprising adding a degassing agent to said flowable polymer matrix .

233. (Original) The process of claim 161, further comprising a step of providing a second film layer.

234. (Original) The process of claim 233, wherein said second film layer is coated onto said resulting film.

235. (Original) The process of claim 233, wherein said second film layer is spread onto said resulting film.

236. (Original) The process of claim 233, wherein said second film layer is cast onto said resulting film.

237. (Original) The process of claim 233, wherein said second film layer is extruded onto said resulting film.

238. (Original) The process of claim 233, wherein said second film layer is sprayed onto said resulting film.

239. (Original) The process of claim 233, wherein said second film layer is laminated onto said resulting film.

240. (Original) The process of claim 233, further comprising laminating said resulting film to another film.

241. (Original) The process of claim 233, wherein said second film comprises an active.

242. (Original) The process of claim 233, wherein said active in said second film is different than said active in said resulting film.

243. (New) The process of claim 1, said active is an anti-nauseant.

244. (New) The process of claim 1, said active is an erectile dysfunction.

245. (New) The process of claim 1, said active is a vasoconstrictor.

246. (New) The process of claim 1, said active is a stimulant.

247. (New) The process of claim 1, said active is a migraine treatment.

248. (New) The process of claim 1, said active is granisetron hydrochloride.

249. (New) The process of claim 1, wherein said resulting film is capable of providing administration of said active to an individual through the buccal cavity of said individual.

250. (New) The process of claim 1, wherein said resulting film is capable of providing administration of said active through gingival application of said individual.

251. (New) The process of claim 1, wherein said resulting film is capable of providing administration of said active through sublingual application of said individual.

252. (New) The process of claim 1, wherein said resulting film is capable of providing administration of said active to an individual through a mucosal membrane of said individual.

253. (New) The process of claim 1, wherein said resulting film is capable of providing administration of said active to an individual by administration within the body of the individual during surgery.

254. (New) The process of claim 1, wherein said resulting film has a variation of active content of less than 10% per film unit.

255. (New) The process of claim 1, further comprising the step of forming a plurality of individual dosage units of substantially the same size, wherein the active content of individual dosage units has a variance of no more than 10%.

256. (New) The method of claim 1, wherein said resulting film contains less than about 6% by weight solvent.

257. (New) The method of claim 1, wherein said at least one edible polymer, said active, and said at least one polar solvent are each ingestible materials.

258. (New) The method of claim 1, wherein said resulting film is orally administrable.

259. (New) The method of claim 1, wherein said active is in the form of a particle.

260. (New) The method of claim 1, wherein said matrix comprises a dispersion.

261. (New) The process of claim 82, said active is an anti-nauseant.

262. (New) The process of claim 82, said active is an erectile dysfunction.

263. (New) The process of claim 82, said active is a vasoconstrictor.

264. (New) The process of claim 82, said active is a stimulant.

265. (New) The process of claim 82, said active is a migraine treatment.

266. (New) The process of claim 82, said active is granisetron hydrochloride.

267. (New) The process of claim 82, wherein said resulting film is capable of providing administration of said active to an individual through the buccal cavity of said individual.

268. (New) The process of claim 82, wherein said resulting film is capable of providing administration of said active through gingival application of said individual.

269. (New) The process of claim 82, wherein said resulting film is capable of providing administration of said active through sublingual application of said individual.

270. (New) The process of claim 82, wherein said resulting film is capable of providing administration of said active to an individual through a mucosal membrane of said individual.

271. (New) The process of claim 82, wherein said resulting film is capable of providing administration of said active to an individual by administration within the body of the individual during surgery.

272. (New) The process of claim 82, wherein said resulting film has a variation of active content of less than 10% per film unit.

273. (New) The process of claim 82, further comprising the step of forming a plurality of individual dosage units of substantially the same size, wherein the active content of individual dosage units has a variance of no more than 10%.

274. (New) The method of claim 82, wherein said resulting film contains less than about 6% by weight solvent.

275. (New) The method of claim 82, wherein said at least one edible polymer, said active, and said at least one polar solvent are each ingestible materials.

276. (New) The method of claim 82, wherein said resulting film is orally administrable.

277. (New) The method of claim 82, wherein said active is in the form of a particle.

278. (New) The method of claim 82, wherein said matrix comprises a dispersion.

279. (New) The process of claim 161, said active is an anti-nauseant.

280. (New) The process of claim 161, said active is an erectile dysfunction.

281. (New) The process of claim 161, said active is a vasoconstrictor.

282. (New) The process of claim 161, said active is a stimulant.

283. (New) The process of claim 161, said active is a migraine treatment.

284. (New) The process of claim 161, said active is granisetron hydrochloride.

285. (New) The process of claim 161, wherein said resulting film is capable of providing administration of said active to an individual through the buccal cavity of said individual.

286. (New) The process of claim 161, wherein said resulting film is capable of providing administration of said active through gingival application of said individual.

287. (New) The process of claim 161, wherein said resulting film is capable of providing administration of said active through sublingual application of said individual.

288. (New) The process of claim 161, wherein said resulting film is capable of providing administration of said active to an individual through a mucosal membrane of said individual.

289. (New) The process of claim 161, wherein said resulting film is capable of providing administration of said active to an individual by administration within the body of the individual during surgery.

290. (New) The process of claim 161, wherein said resulting film has a variation of active content of less than 10% per film unit.

291. (New) The process of claim 161, further comprising the step of forming a plurality of individual dosage units of substantially the same size, wherein the active content of individual dosage units has a variance of no more than 10%.

292. (New) The method of claim 161, wherein said resulting film contains less than about 6% by weight solvent.

293. (New) The method of claim 161, wherein said at least one edible polymer, said active, and said at least one polar solvent are each ingestible materials.

294. (New) The method of claim 161, wherein said resulting film is orally administrable.

295. (New) The method of claim 161, wherein said active is in the form of a particle.

296. (New) The method of claim 161, wherein said matrix comprises a dispersion.

297. (New) The method of claim 1, wherein said matrix comprises an emulsion, a colloid or a suspension.

298. (New) The method of claim 82, wherein said matrix comprises an emulsion, a colloid or a suspension.

299. (New) The method of claim 161, wherein said matrix comprises an emulsion, a colloid or a suspension.

REMARKS

Reconsideration of the present application is respectfully requested. Claims 1, 11, 35, 70, 82, 90, 114, 150, 151, 161, 172, 196 and 232 have been amended. New claims 243-299 have been added. Support for the new claims can be found in the application as originally filed. No new matter has been added.

In the Office Action, the Examiner rejected claims 1-161 on the ground of non-statutory obviousness-type double patenting over claims 1-30 of U.S. Patent No. 7,666,337.

In addition, the Examiner rejected claims 1-161 on the ground of non-statutory obviousness-type double patenting over claims 1-9 of U.S. Patent No. 7,357,891 in view of U.S. Patent No. 7,666,337.

The Examiner also rejected claims 1-161 on the ground of non-statutory obviousness-type double patenting over claims 62-66 of U.S. Application No. 12/411,505 in view of U.S. Patent No. 7,666,337.

The Examiner rejected claims 1-161 on the ground of non-statutory obviousness-type double patenting over claims 32-46 and 62-74 of U.S. Application No. 12/171,692 in view of U.S. Patent No. 7,666,337.

In addition, the Examiner rejected claims 1-161 on the ground of non-statutory obviousness-type double patenting over claims 1-22 of U.S. Patent No. 7,425,292 in view of U.S. Patent No. 7,666,337.

In an effort to further prosecution, the Applicant submits herewith a terminal disclaimer to obviate the rejection over U.S. Patent Nos. 7,357,891, 7,425,292 and 7,666,337 and U.S. Application Nos. 12/171692 and 12/411505. It is respectfully submitted that this terminal disclaimer is sufficient to overcome the rejections. Withdrawal of the rejection is therefore respectfully requested.

The Applicant submits herewith a supplemental Information Disclosure Statement. The Applicant is submitting this information for purposes of disclosure, and does not make any representation regarding the references cited therein.

The Applicant asserts that the fees incurred with filing of 57 additional dependent claims and the aforementioned terminal disclaimer is currently due. The Commissioner is authorized to charge payment of these fees to Deposit Account No. 08-2461. No other fees are due, however, if additional fees are due, the Commissioner is hereby authorized to charge payment any fees associated with this communication, or credit any overpayment, to Deposit Account No. 08-2461. Such authorization includes authorization to charge fees for extensions of time, if any, under 37 C.F.R § 1.17 and also should be treated as a constructive petition for an extension of time in this reply or any future reply pursuant to 37 C.F.R. § 1.136.

The foregoing office action has now been responded to in full. In view of the terminal disclaimer submitted herewith, the Applicant respectfully asserts that the claims are now in position for allowance. Favorable action thereon is earnestly solicited. If there are any questions or if additional information is required, the Examiner is respectfully requested to contact Applicant's attorney at the number listed below.

Respectfully submitted,

Nichole E. Martiak

Nichole E. Martiak, Esq.
Registration No.: 55,832
Attorney for Applicant(s)

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6900 Jericho Turnpike
Syosset, New York 11791
(973) 331-1700

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	Yang et al.	Examiner:	Lee, Edmund H.
Application No.:	12/614,928	Group Art Unit:	1791
Confirmation No:	9528	Docket:	1199-26 RCE/CON
Filed:	November 9, 2010	Dated:	November 16, 2010
For:	POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM		

Commissioner for Patents
P.O. Box 1450,
Alexandria, VA 22313

TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER "PRIOR" PATENT(S) AND OVER A PENDING "REFERENCE" APPLICATION

The owner*, MonoSol Rx, LLC., of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term **prior patent** No(s). 7357891, 7425292 and 7666337 as the term of said prior patent is defined in 35 U.S.C. 154 and 173, and as the term of said prior patent is presently shortened by any terminal disclaimer. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the **prior patent** are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer with respect to the granted patents, the owner does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. 154 and 173 of the prior patent, "as the term of said **prior patent** is presently shortened by any terminal disclaimer," in the event that said **prior patent** later:

expires for failure to pay a maintenance fee;
is held unenforceable;

is found invalid by a court of competent jurisdiction;
is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321;
has all claims canceled by a reexamination certificate;
is reissued; or
is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

The owner*, MonoSol Rx, LLC., of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of any patent granted on pending **reference** Application Number(s) 12/411505, filed on March 26, 2009 and 12/171692, filed on July 11, 2008, as such term is defined in 35 U.S.C. 154 and 173, and as the term of any patent granted on said on **reference** applications may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending **reference** applications. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent granted on the **reference** applications are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer with respect to the pending patent application, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. 154 and 173 of any patent granted on said **reference** applications, "as the term of any patent granted on said **reference** applications may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending **reference** applications," in the event that: any such patent: granted on the pending **reference** applications: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321, has all claims canceled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as shortened by any terminal disclaimer filed prior to its grant.

Check either box 1 or 2 below, if appropriate.

1. ☐ For submissions on behalf of a business/organization (e.g., corporation, partnership, university, government agency, etc.), the undersigned is empowered to act on behalf of the business/organization.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States

Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

2. ☒ The undersigned is an attorney or agent of record. Reg. No. 55,832

Nichole E. Martiak
Signature

November 16, 2010
Date

Nichole E. Martiak
Typed or printed name

(973) 331-1700
Telephone Number

☒ Terminal disclaimer fee under 37 CFR 1.20(d) included.

☒ PTO suggested wording for terminal disclaimer was unchanged.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

* Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner). Form PTO/SB/96 may be used for making this certification. See MPEP § 324.

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	Yang et al.	Examiner:	Lee, Edmund H.
Application No.:	12/614,928	Group Art Unit:	1791
Confirmation No:	9528	Docket:	1199-26 RCE/CON
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For:	POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM		

Commissioner for Patents
P.O. Box 1450,
Alexandria, VA 22313

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

Sir:

In fulfillment of the requirements of candor and good faith set forth in 37 C.F.R. §1.56, Applicants submit herewith the following Supplemental Information Disclosure Statement in accordance with the provisions of 37 C.F.R. §1.97 and 1.98. It is understood that the information provided herein is solely for the purpose of fulfilling Applicants' obligations under the law and should not be construed as, nor is it intended to be, an admission of prior art.

Copies of the U.S. Patents and U.S. Patent Application Publications listed on the attached Form PTO-1449 are not provided as the U.S. Patent office has waived the requirement for paper submission of such documents. Copies of foreign patent documents and other documents are provided herewith.

The Commissioner is hereby authorized to charge payment of any additional fees associated with this communication, or credit any overpayment, to Deposit Account No. 08-2461. Such authorization includes authorization to charge fees for extensions of time, if any, under 37 C.F.R § 1.17 and also should be treated as a constructive petition for an extension of time in this reply or any future reply pursuant to 37 C.F.R. § 1.136.

If the examiner has any questions or comments relating to the present application, he is respectfully invited to contact the undersigned at the telephone number set forth below.

Respectfully submitted,

Nichole E. Martiak

Nichole E. Martiak
Registration No.: 55,832

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Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (01-10)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99**)		
	Application Number	12614928
	Filing Date	2009-11-09
	First Named Inventor	Robert K. Yang
	Art Unit	1791
	Examiner Name	Lee, Edmund H.
	Attorney Docket Number	1199-26 RCE/CON

U.S.PATENTS						
Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	3007848		1961-11-07	J.H. Stroop	
	2	4631837		1986-12-30	Magoon	
	3	4880416		1989-11-14	Horiuchi et al.	
	4	5605696		1997-02-25	Eury et al.	
	5	5800832		1998-09-01	Tapolsky et al.	
	6	5806284		1998-09-15	Gifford	
	7	6072100		2000-06-06	Mooney et al.	
	8	6375963	B1	2002-04-23	Repka et al.	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	12614928
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	First Named Inventor	Robert K. Yang
	Art Unit	1791
	Examiner Name	Lee, Edmund H.
	Attorney Docket Number	1199-26 RCE/CON

	9	6800329	B2	2004-10-05	Horstmann et al.	
	10	6824829	B2	2004-11-30	Berry et al.	
	11	7005142	B2	2006-02-28	Leon	
	12	7579019	B2	2009-08-25	Tapolsky et al.	

If you wish to add additional U.S. Patent citation information please click the Add button.

U.S.PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20020127254	A1	2002-09-12	Fotinos et al.	
	2	20030107149	A1	2003-06-12	Yang et al.	
	3	20040096569	A1	2004-05-20	Barkalow et al.	
	4	20040191302	A1	2004-09-30	Davidson	
	5	20050048102	A1	2005-03-03	Tapolsky et al.	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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	First Named Inventor	Robert K. Yang
	Art Unit	1791
	Examiner Name	Lee, Edmund H.
	Attorney Docket Number	1199-26 RCE/CON

	6	20060210610	A1	2006-09-21	Davidson et al.	
	7	20070087036	A1	2007-04-19	Durshlag et al.	
	8	20070148097	A1	2007-06-28	Finn et al.	
	9	20080254105	A1	2008-10-16	Tapolsky et al.	

If you wish to add additional U.S. Published Application citation information please click the Add button.

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	1510999	GB	A	1978-05-17	Schering AG		☐
	2	0598606	EP	B1	1999-06-30	Johnson & Johnson Consumer Products, Inc.		☐
	3	200018365	WO	A	2000-04-06	Warner Lambert Co.		☐
	4	2003030881	WO	A	2003-04-17	Kosmos Pharma		☐
	5	2003030882	WO	A	2003-04-17	Kosmos Pharma		☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	12614928
	Filing Date	2009-11-09
	First Named Inventor	Robert K. Yang
	Art Unit	1791
	Examiner Name	Lee, Edmund H.
	Attorney Docket Number	1199-26 RCE/CON

	6	2003030883	WO	A	2003-04-17	Kosmos Pharma		☐
	7	2008011194	WO	A2	2008-01-24	Biodelivery Sciences International, Inc.		☐

If you wish to add additional Foreign Patent Document citation information please click the Add button

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	Repka et al., "Influence of Vitamin E TPGS on the properties of hydrophilic films produced by hot-melt extrusion," International Journal of Pharmaceuticals 202: 63-70 (2000).	☐
	2	Repka et al., "Bioadhesive properties of hydroxypropylcellulose topical films produced by hot-melt extrusion," Journal of Controlled Release 70: 341-351 (2001).	☐
	3	Lazaridou et al., "Thermophysical properties of chitosan, chitosan-starch and chitosan-pullulan films near the glass transition," Carbohydrate Polymers 48: 179-190 (2002).	☐

If you wish to add additional non-patent literature document citation information please click the Add button

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	12614928
	Filing Date	2009-11-09
	First Named Inventor	Robert K. Yang
	Art Unit	1791
	Examiner Name	Lee, Edmund H.
	Attorney Docket Number	1199-26 RCE/CON

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☒ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Nichole E. Martiak, Reg No. 55,832/	Date (YYYY-MM-DD)	2010-11-16
Name/Print	Nichole E. Martiak	Registration Number	55,832

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

EXHIBIT K

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/102,071	04/14/2008	Robert K. Yang	1199-4B/DIV	9473

23869 7590 02/04/2010
HOFFMANN & BARON, LLP
6900 JERICHO TURNPIKE
SYOSSET, NY 11791

EXAMINER	
LEE, EDMUND H	

ART UNIT	PAPER NUMBER
1791	

MAIL DATE	DELIVERY MODE
02/04/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	12/102,071	YANG ET AL.	
	Examiner	Art Unit	
	EDMUND H. LEE	1791	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 November 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-147* is/are pending in the application.

4a) Of the above claim(s) *1-73* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *74-147* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/1/08,8/1/08,8/1/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-18 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 11/20/09.

2. Applicant's election without traverse of claims 19-147 in the reply filed on 11/20/09 is acknowledged.

3. In regard to the species restriction, Applicant's election with traverse of claims 74-147 in the reply filed on 11/20/09 is acknowledged. The traversal is on the ground(s) that the field of search would be the same. This is not found persuasive because a search of the elected claims would not include a search in the subclasses involving coating a film.

The requirement is still deemed proper and is therefore made FINAL.

4. In regard to the species restriction, claims 19-73 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 11/20/09.

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422

F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claim 123 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 7425292. Although the conflicting claims are not identical, they are not patentably distinct from each other because claim 1 of USPN 7425292 encompasses the claimed limitations of instant claim 123.

7. Claim 123 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim62 of copending Application No. 10/856176. Although the conflicting claims are not identical, they are not patentably distinct from each other because claim 62 encompasses the claimed limitations of instant claim 123.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

8. Claim 123 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 7357891. Although the conflicting claims are not identical, they are not patentably distinct from each other because claim 1 encompasses the claimed limitations of instant claim 123.

9. Claims 74-97 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "said pharmaceutical or biological active component" (cl 74, lns 7-8) lacks antecedent basis in the claim.

Correction is required.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

11. Claims 123,124,127,143,144,145,146, and 147 are rejected under 35 U.S.C. 102(e) as being anticipated by Berry et al (USPN 6824829). Berry et al teach the claimed process as evidenced at col 1, ln 5-col 6, ln 64; figs 1-8. It should be noted that flavorings have therapeutic properties, e.g. reducing stress or changing mood. It should also be noted that the film of Berry et al is uniform, and the water of Berry et al has an inherent boiling point of less than 100C.

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 74-97 are rejected under 35 U.S.C. 103(a) as being unpatentable over Berry et al (USPN 6824829) in view of Strobush et al (USPN 5881476). In regard to claim 74, Berry et al teach all of the claimed limitations (col 1, ln 5-col 6, ln 64; figs 1-8) except heating the matrix to less 100C or less during the step of removal. Strobush et al teach a method of drying a coating on a substrate (col 12, ln 26-col 16, ln 49; fig 5) wherein the coated substrate enters the drying apparatus at a temperature less than the drying gas temperature, and is continuously raised throughout the length of the drying apparatus until it reaches the same temperature of the drying gas, which is less than the solvent temperature (col 13, lns 58-63; col 16, lns 40-48). It should be noted that the Strobush et al teach using a drying gas less than 100C (col 13, lns 58-63). It should also be noted that the drying process of Strobush et al results in a more efficient evaporating process, i.e., less energy is required and less cost is involved (col 16, lns 40-48). Since Berry et al and Strobush et al are analogous with using a drying apparatus having multiple zones, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the drying apparatus of Strobush et al in the process of Berry et al in order to keep the manufacturing costs down without compromising product quality. In regard to claims 79 and 93-97, such are taught, explicitly or inherently, by Berry et al (col 1, ln 5-col 6, ln 64; figs 1-8). In regard to claims 76-77, 80-89 and 91-92, such is a mere obvious matter of choice dependent on the desired final product and of little patentable consequence to the claimed process since it is not a manipulative feature or step of the claimed process. Further, the claimed product limitations are well-known in the ingestible or insertable film art. Thus, it would

have been obvious to one of ordinary skill in the art at the time the invention was made to include those components into the slurry of Berry et al or use the product constraints in the process of Berry et al in order to form a desired therapeutic film. In regard to claim 75, drying time is well-known in the molding art as an important molding parameter and the desired duration would have been obviously and readily determined through routine experimentation by one having ordinary skill in the art at the time the invention was made. Further, the claimed duration is generally well-known in the molding art and it would have been obvious to one of ordinary skill in the art at the time the invention was made to dry the film of Berry et al within 10 minutes in order to reduce manufacturing costs without sacrificing quality. In regard to claim 78, such is well-known in the molding art in order to maintain uniformity. Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to dearate the slurry of Berry et al in order to maintain the homogeneity of the components. in regard to claim 90, such is well-known in the molding art as an effective method of mixing components. Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to mix the flavor of Berry et al into a premix of the solvent and polymer of Berry et al in order to prevent premature activation of the flavor during mixing.

14. Claims 98-122 are rejected under 35 U.S.C. 103(a) as being unpatentable over Berry et al (USPN 6824829) in view of Strobush et al (USPN 5881476). In regard to claim 98, Berry et al teach all of the claimed limitations (col 1, ln 5-col 6, ln 64; figs 1-8)

except heating the matrix to less than the boiling point of the at least one solvent. Strobush et al teach a method of drying a coating on a substrate (col 12, ln 26-col 16, ln 49; fig 5) wherein the coated substrate enters the drying apparatus at a temperature less than the drying gas temperature, and is continuously raised throughout the length of the drying apparatus until it reaches the same temperature of the drying gas, which is less than the solvent temperature (col 13, lns 58-63; col 16, lns 40-48). It should also be noted that the drying process of Strobush et al results in a more efficient evaporating process, i.e., less energy is required and less cost is involved (col 16, lns 40-48). Since Berry et al and Strobush et al are analogous with using a drying apparatus having multiple zones, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the drying apparatus of Strobush et al in the process of Berry et al in order to keep the manufacturing costs down without compromising product quality. In regard to claim 99, Strobush et al teach using a drying gas less than 100C (col 13, lns 58-63), thus the above combination teaches a temperature less than about 100C. In regard to claim 100, drying time is well-known in the molding art as an important molding parameter and the desired duration would have been obviously and readily determined through routine experimentation by one having ordinary skill in the art at the time the invention was made. Further, the claimed duration is generally well-known in the molding art and it would have been obvious to one of ordinary skill in the art at the time the invention was made to dry the film of Berry et al within 10 minutes in order to reduce manufacturing costs without sacrificing quality. In regard to claims 101-102, 104-114, and 116-117, such is a mere obvious matter of choice dependent on the

desired final product and of little patentable consequence to the claimed process since it is not a manipulative feature or step of the claimed process. Further, the claimed product limitations are well-known in the ingestible or insertable film art. Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to include those components into the slurry of Berry et al or use the product constraints in the process of Berry et al in order to form a desired therapeutic film. In regard to claim 103, such is well-known in the molding art in order to maintain uniformity. Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to dearate the slurry of Berry et al in order to maintain the homogeneity of the components. In regard to claim 115, such is well-known in the molding art as an effective method of mixing components. Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to mix the flavor of Berry et al into a premix of the solvent and polymer of Berry et al in order to prevent premature activation of the flavor during mixing. In regard to claims 118-122, such are taught, explicitly or inherently, by Berry et al (col 1, ln 5-col 6, ln 64; figs 1-8).

15. Claim 124 is rejected under 35 U.S.C. 103(a) as being unpatentable over Berry et al (USPN 6824829) as applied to claim 123 above and further in in view of Strobush et al (USPN 5881476). Berry et al teach all of the claimed limitations (col 1, ln 5-col 6, ln 64; figs 1-8) except heating the matrix to less than about 100C. Strobush et al teach a method of drying a coating on a substrate (col 12, ln 26-col 16, ln 49; fig 5) wherein the coated substrate enters the drying apparatus at a temperature less than the drying gas temperature, and is continuously raised throughout the length of the drying

apparatus until it reaches the same temperature of the drying gas, which is less than the solvent temperature (col 13, lns 58-63; col 16, lns 40-48). It should be noted that Strobush et al teach using a drying gas less than 100C (col 13, lns 58-63). It should also be noted that the drying process of Strobush et al results in a more efficient evaporating process, i.e., less energy is required and less cost is involved (col 16, lns 40-48). Since Berry et al and Strobush et al are analogous with using a drying apparatus having multiple zones, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the drying apparatus of Strobush et al in the process of Berry et al in order to keep the manufacturing costs down without compromising product quality.

16. Claims 125-128, 130- 142 are rejected under 35 U.S.C. 103(a) as being unpatentable over Berry et al (USPN 6824829). The above teachings of Berry et al are incorporated hereinafter. In regard to claim 125, drying time is well-known in the molding art as an important molding parameter and the desired duration would have been obviously and readily determined through routine experimentation by one having ordinary skill in the art at the time the invention was made. Further, the claimed duration is generally well-known in the molding art and it would have been obvious to one of ordinary skill in the art at the time the invention was made to dry the film of Berry et al within 10 minutes in order to reduce manufacturing costs without sacrificing quality. In regard to claims 126-127, 130-139, and 141-142, such is a mere obvious matter of choice dependent on the desired final product and of little patentable consequence to

the claimed process since it is not a manipulative feature or step of the claimed process. Further, the claimed product limitations are well-known in the ingestible or insertable film art. Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to include those components into the slurry of Berry et al or use the product constraints in the process of Berry et al in order to form a desired therapeutic film. In regard to claim 128, such is well-known in the molding art in order to maintain uniformity. Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to dearate the slurry of Berry et al in order to maintain the homogeneity of the components. In regard to claim 140, such is well-known in the molding art as an effective method of mixing components. Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to mix the flavor of Berry et al into a premix of the solvent and polymer of Berry et al in order to prevent premature activation of the flavor during mixing.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to EDMUND H. LEE whose telephone number is 571.272.1204. The examiner can normally be reached on MONDAY-THURSDAY FROM 9AM-4PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yogendra Gupta can be reached on 571.272.1316. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

EDMUND H. LEE
Primary Examiner
Art Unit 1791

EHL

/EDMUND H. LEE/
Primary Examiner, Art Unit 1791

EXHIBIT M

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): Yang et al.

Application No.: 10/856,176

Filed: May 28, 2004

For: POLYETHYLENE OXIDE-BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM

Examiner: Lee, Edmund H.

Group Art Unit: 1791

Docket: 1199-26

Dated: September 4, 2009

Confirmation No.: 4017

Certificate of EFS-Web Transmission
I hereby certify that this correspondence is being transmitted to the U.S. Patent and Trademark Office via the Office's electronic filing system.

Dated: September 4, 2009

Signature: Marcy Mancuso/ 

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT AND RESPONSE PURSUANT TO 37 C.F.R. §1.114

Sir:

This is in response to the final Office Action dated March 18, 2009, a reply to which is due September 18, 2009, with a three-month extension of time and in consideration of the concurrently-filed Request for Continued Examination (RCE). In view of the remarks set forth below, reconsideration of the Examiner's rejection is respectfully requested.

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks begin on page 8 of this paper.

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1-27. (Cancelled)

28. (Cancelled)

29. (Currently amended) The process according to Claim 56 ~~28~~, wherein the step of ~~forming a film from said matrix further comprises~~ casting said matrix comprises casting onto a surface having top and bottom sides.

30. (Currently amended) The process according to Claim 29, wherein the step of evaporating ~~drying said film~~ further comprises applying heat to said bottom side of said surface.

31. (Withdrawn) A process for making a film having a substantially uniform distribution of components, comprising the steps of:
(a) combining at least one water-soluble polymer comprising polyethylene oxide alone or in combination with a hydrophilic cellulosic polymer, and an active component to form a matrix with a uniform distribution of said components; and
(b) extruding said matrix to form a film,
wherein said film is free of added plasticizers.

32. (Withdrawn) The process according to Claim 31, further comprising the step of cooling said extruded film.

33-36. (Canceled)

37. (Currently amended) The process according to Claim 56 ~~28~~, wherein said water-soluble polymer comprises at least about 20% by weight polyethylene oxide.

38. (Currently amended) The process according to Claim 56 ~~28~~, wherein said water-soluble polymer comprises about 20% to about 100% by weight polyethylene oxide.

39. (Cancelled)

40. (Currently amended) The process according to Claim 56 ~~28~~, ~~wherein said~~ further comprising a hydrophilic cellulosic polymer ~~is~~ present in the amount of about 0% to about 80% by weight of said water-soluble polymer composition, wherein said hydrophilic cellulosic polymer is selected from the group consisting of hydroxypropylmethyl cellulose, hydroxypropyl cellulose and combinations thereof.

41. (Cancelled)

42. (Currently amended) The process according to Claim 40 ~~28~~, wherein said water-soluble polymer composition comprises said hydrophilic cellulosic polymer in a ratio of up to about 4:1 with polyethylene oxide.

43. (Currently amended) The process according to Claim 56 ~~28~~, wherein said water-soluble polymer composition comprises polyethylene oxide having a molecular weight of about 100,000 to about 900,000.

44. (Currently amended) The process according to Claim 56 ~~28~~, wherein said water-soluble polymer composition comprises polyethylene oxide having a molecular weight of about 100,000 to about 4 million.

45. (Currently amended) The process according to Claim 56 ~~28~~, wherein said water-soluble polymer composition comprises polyethylene oxide having a molecular weight of about 100,000 to about 300,000 in combination with polyethylene oxide having a molecular weight of about 600,000 to about 900,000.

46. (Currently amended) The process according to Claim 56 ~~28~~, wherein said water-soluble polymer composition comprises at least 1mg polyethylene oxide.

47. (Currently amended) The process according to Claim 56 ~~28~~, wherein said water-soluble polymer composition comprises no greater than about 200mg polyethylene oxide.

48. (Currently amended) The process according to Claim 56 ~~28~~, wherein said active component is selected from the group consisting of cosmetic agents, pharmaceutical agents, bioactive agents, and combinations thereof.

49. (Currently amended) The process according to Claim 56 ~~28~~, wherein said matrix of step (a) further comprises a densifying agent.

50. (Previously presented) The process according to Claim 49, wherein said densifying agent is simethicone.

51. (Currently amended) The process according to Claim 56 ~~28~~, wherein said matrix of step (a) further comprises a solubility enhancing agent.

52. (Currently amended) The process according to Claim 56 ~~28~~, wherein said ~~one~~ water-soluble polymer composition consists essentially of polyethylene oxide in the amount of about 20% to about 100% by weight of the polymer composition and a hydrophilic cellulosic polymer selected from the group consisting of hydroxypropylmethyl cellulose, hydroxypropyl cellulose and combinations thereof in the amount of about 0% to about 80% by weight of the polymer composition.

53. (Currently amended) The process according to Claim 56 ~~28~~, wherein said matrix of step (a) further comprises an anti-foaming or surface-tension reducing agent and is free of bubbles.

54. (Currently amended) The process according to Claim56 ~~28~~, wherein the temperature of said matrix is 100°C or less.

55. (Cancelled)

56. (New) A process for making a film having a substantially uniform distribution of components, comprising the steps of:
(a) forming a flowable polymer matrix comprising a water-soluble polymer composition comprising polyethylene oxide, at least 30% solvent and an active component, said matrix having a uniform distribution of said active component;
(b) casting said flowable polymer matrix;
(c) evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film within about 10 minutes or fewer to maintain said uniform distribution of said active component by locking-in or substantially preventing migration of said active component within said visco-elastic film; and

(d) forming a resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said uniform distribution of active by said locking-in or substantially preventing migration of said active component is maintained.

57. (New) The process according to Claim 56, wherein said resulting film has a thickness of about 2 mils to about 10 mils.

58. (New) The process of claim 56, wherein said evaporating is conducted by applying radiant energy selected from the group consisting of air currents, heat, infrared radiation, radio frequency radiation and combinations thereof.

59. (New) The process of claim 56, wherein said visco-elastic film is further dried.

60. (New) The process of claim 56, wherein said visco-elastic film is a solid.

61. (New) The process of claim 56, wherein said visco-elastic film is formed within about 4 minutes.

62. (New) A process for making a film having a substantially uniform distribution of components, comprising the steps of:
(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and an active, said matrix having a uniform distribution of said active;
(b) casting said flowable polymer matrix;
(c) evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film within about 10 minutes or fewer to maintain said uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film; and

(d) forming a resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained.

63. (New) The process according to Claim 62, wherein said resulting film has a thickness of about 2 mils to about 10 mils.

64. (New) The process of claim 62, wherein said evaporating is conducted by applying radiant energy selected from the group consisting of air currents, heat, infrared radiation, radio frequency radiation and combinations thereof.

65. (New) The process of claim 62, wherein the visco-elastic film is formed within about 4 minutes.

66. (New) The process of claim 62, wherein the visco-elastic film is further dried.

67. (New) The process of claim 62, wherein the visco-elastic film is a solid.

Remarks/Arguments:

Claims 28-32 and 37-51 are currently pending. Claims 29, 30, 37, 38, 40, 42-49 and 51-54 have been amended. Claims 28, 33-36, 39, 41 and 55 have been cancelled. New claims 56-67 have been added. Claims 31 and 32 have been withdrawn as the result of a restriction requirement. Applicants reserve the right to pursue claims 31 and 32 in a divisional application. No new matter has been added. Applicants respectfully request reconsideration of the application based on the above amendments and the following remarks.

Discussion of Telephonic Interview

Applicants' representatives Daniel A. Scola, Jr. and Nichole E. Martiak, wish to thank Examiner Lee for granting a Telephone Interview on September 2, 2009 to discuss proposed claim amendments for the subject application.

Applicants' Remarks in Regards to the Advisory Action

In the Advisory Action dated June 26, 2009, the Examiner entered the previous amendments and acknowledged that the Applicants had overcome the 35 U.S.C. §112, first paragraph rejections. As such, the §112, first paragraph rejections from the Final Office Action will not be discussed.

Applicants' Response to 35 U.S.C. §103 Rejection over Staab

Claims 28-30, 38, 40, 41, 43, 44, 48 and 51 are rejected under 35 U.S.C. § 103(a), as allegedly being anticipated by U.S. Patent No. 5,393,528 to Staab et al. (hereinafter "Staab"). Applicants respectfully request reconsideration based on the following remarks.

The Examiner acknowledges that Staab does not disclose removing a portion of the liquid carrier within 10 minutes, but alleges that:

> ...such is a well-known result effective variable that may be dependent on the material, thickness, temperature and pressure. Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to dry the film of Staab within about 10 minutes since it has been held that discovering an optimum value of a result effective variable involves only routine skill in the art. In the present invention, one would have been motivated to optimize the drying time in order in order to reduce cycle time without compromising film quality.
>
> (Office Action, at page 3)

In regards to claims 37, 39, 42 and 48, the Examiner alleges that:

> ...the use of a specific material in a molding process is a mere obvious matter of choice dependent on the desired final product and of little patentable consequence to the claimed process since it is not a manipulative step or feature of the claimed process. Further, the claimed materials are well-known in the molding and water-soluble film art. Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to include the claimed materials into the film of Staab in order to form films having desired properties...it would have been obvious to one of ordinary skill in the art at the time the invention was made to form the film of Staab without bubbles in order to better control the uniformity of active components in the film.
>
> (Office Action, at pages 3-4) (citations omitted).

Claim 28 has been cancelled. Claims 29, 30, 37, 38, 40, 42-49 and 51-54 have been amended to depend upon new claim 56. New claim 56 is directed to a process for making a film having a substantially uniform distribution of components, including the following steps:

> (a) forming a flowable polymer matrix comprising a water-soluble polymer composition comprising polyethylene oxide, at least 30% solvent and an active component, said matrix having a uniform distribution of said active component;
> (b) casting said flowable polymer matrix;
> (c) evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film within about 10 minutes

> or fewer to maintain said uniform distribution of said active component by locking-in or substantially preventing migration of said active component within said visco-elastic film; and
> (d) forming a resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said uniform distribution of active by said locking-in or substantially preventing migration of said active component is maintained.

Staab is directed to a dissolvable device for contraception or delivery of medication. Although Staab mentions film as a possible form of its dissolvable device, nowhere in Staab is it disclosed, taught or suggested to utilize a water-soluble polymer composition, a solvent, and remove at least a portion of the liquid solvent to provide a visco-elastic film that maintains a uniform distribution of the active component in the resulting film product. Nowhere in Staab is it disclosed, taught or suggested to maintain the uniform distribution of active components by locking-in or substantially preventing migration of the active components within the visco-elastic film and resulting film product. Moreover, Staab fails to disclose or suggest that the visco-elastic film must be formed within a 10 minute time period and the resulting film present has a 10% water content.

On the contrary, the film of Staab is dried using one of the "conventional" drying techniques, i.e. drying for approximately 20-40 minutes at a temperature of approximately 160°F in an oven. The method of drying as described by Staab would trap moisture inside the film. (Staab, col. 11, ll. 44-46). Once the trapped moisture begins to evaporate, the surface of the film will rip open and reform. Uniform distribution of actives within the final film would neither be expected, nor likely even possible, with Staab's process. In fact, conventional processing does not produce films with uniformity of content. This is well described in Applicants' specification.

Applicants believe the present claims to be in condition for allowance and respectfully request withdrawal of all rejections. Early allowance is therefore solicited. Should the Examiner have any questions or comments concerning the above, the Examiner is respectfully invited to contact the undersigned attorney at the telephone number given below.

Respectfully submitted,

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EXHIBIT N

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Hoffmann & Baron LLP
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DIAMOND, ALAN D	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

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CENTRAL REEXAMINATION UNIT

Transmittal of Communication to Third Party Requester
Inter Partes Reexamination

REEXAMINATION CONTROL NO. : 95001753
PATENT NO. : 7824588
TECHNOLOGY CENTER : 3999
ART UNIT : 3991

Enclosed is a copy of the latest communication from the United States Patent and Trademark Office in the above identified Reexamination proceeding. 37 CFR 1.903.

Prior to the filing of a Notice of Appeal, each time the patent owner responds to this communication, the third party requester of the inter partes reexamination may once file written comments within a period of 30 days from the date of service of the patent owner's response. This 30-day time period is statutory (35 U.S.C. 314(b)(2)), and, as such, it cannot be extended. See also 37 CFR 1.947.

If an ex parte reexamination has been merged with the inter partes reexamination, no responsive submission by any ex parte third party requester is permitted.

All correspondence relating to this inter partes reexamination proceeding should be directed to the Central Reexamination Unit at the mail, FAX, or hand-carry addresses given at the end of the communication enclosed with this transmittal.

PTOL-2070(Rev.07-04)

Transmittal of Communication to Third Party Requester Inter Partes Reexamination	Control No.	Patent Under Reexamination
	95/001,753	7,824,588
	Examiner	Art Unit
	ALAN DIAMOND	3991

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address. --

Enclosed is a copy of the latest communication from the United States Patent and Trademark Office in the above-identified reexamination proceeding. 37 CFR 1.903.

Prior to the filing of a Notice of Appeal, each time the patent owner responds to this communication, the third party requester of the *inter partes* reexamination may once file written comments within a period of 30 days from the date of service of the patent owner's response. This 30-day time period is statutory (35 U.S.C. 314(b)(2)), and, as such, it cannot be extended. See also 37 CFR 1.947.

If an *ex parte* reexamination has been merged with the *inter partes* reexamination, no responsive submission by any *ex parte* third party requester is permitted.

All correspondence relating to this inter partes reexamination proceeding should be directed to the **Central Reexamination Unit** at the mail, FAX, or hand-carry addresses given at the end of the communication enclosed with this transmittal.

INTER PARTES REEXAMINATION COMMUNICATION	Control No.	Patent Under Reexamination
	95/001,753	7,824,588
	Examiner	Art Unit
	ALAN DIAMOND	3991

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address. --

BELOW/ATTACHED YOU WILL FIND A COMMUNICATION FROM THE UNITED STATES PATENT AND TRADEMARK OFFICE OFFICIAL(S) IN CHARGE OF THE PRESENT REEXAMINATION PROCEEDING.

All correspondence relating to this *inter partes* reexamination proceeding should be directed to the **Central Reexamination Unit** at the mail, FAX, or hand-carry addresses given at the end of this communication.

ACTION CLOSING PROSECUTION (37 CFR 1.949)	Control No.	Patent Under Reexamination
	95/001,753	7,824,588
	Examiner	Art Unit
	ALAN DIAMOND	3991

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address. --

Responsive to the communication(s) filed by:
Patent Owner on 10 January, 2012
Third Party(ies) on 09 February, 2012

Patent owner may once file a submission under 37 CFR 1.951(a) within 1 month(s) from the mailing date of this Office action. Where a submission is filed, third party requester may file responsive comments under 37 CFR 1.951(b) within 30-days (not extendable- 35 U.S.C. § 314(b)(2)) from the date of service of the initial submission on the requester. **Appeal cannot be taken from this action.** Appeal can only be taken from a Right of Appeal Notice under 37 CFR 1.953.

All correspondence relating to this inter partes reexamination proceeding should be directed to the **Central Reexamination Unit** at the mail, FAX, or hand-carry addresses given at the end of this Office action.

PART I. THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892
2. ☐ Information Disclosure Citation, PTO/SB/08
3. ☐ _____

PART II. SUMMARY OF ACTION:

1a. ☒ Claims 1-193 are subject to reexamination.
1b. ☐ Claims _____ are not subject to reexamination.
2. ☐ Claims _____ have been canceled.
3. ☐ Claims _____ are confirmed. [Unamended patent claims]
4. ☐ Claims _____ are patentable. [Amended or new claims]
5. ☒ Claims 1-193 are rejected.
6. ☐ Claims _____ are objected to.
7. ☐ The drawings filed on _____ ☐ are acceptable ☐ are not acceptable.
8 ☐ The drawing correction request filed on _____ is: ☐ approved. ☐ disapproved.
9 ☐ Acknowledgment is made of the claim for priority under 35 U.S.C. 119 (a)-(d). The certified copy has:
☐ been received. ☐ not been received. ☐ been filed in Application/Control No _____
10. ☐ Other _____

Summary of Proceedings

A Request pursuant to 37 CFR 1.913 for inter partes reexamination of claims 1-191 of U.S. Patent 7,824,588 (hereinafter "the '588 patent") was filed September 12, 2011 by Third Party Requester. An Order granting inter partes reexamination of claims 1-191 and a first Office action rejecting claims 1-191 of the '588 patent were mailed 11/10/11.

On 01/10/12, Patent Owner filed a response including an amendment which amends claim 1 and adds new claims 192 and 193, and a Rule 1.132 Declaration by Rhyta S. Rounds, hereafter "Rounds Declaration".

On 02/09/12, Third Party Requester filled comments including a Rule 1.132 Declaration by Edward D. Cohen, hereafter "Cohen Declaration".

Art Cited

Each of the following prior art references has a 35 USC 102(b) publication date with respect to the earliest possible priority date of October 12, 2001 for the '588 patent:

Chen et al, WO 00/42992, hereafter "Chen".

Bernstein et al., U.S. Patent 5,656,297, hereafter "Bernstein".

Hijiya et al, U.S. Patent 4,562,020, hereafter "Hijiya.

Peh et al, "Polymeric films as vehicle for buccal delivery: swelling, mechanical and bioadhesive properties," J. Pharm. Pharmaceut. Sci., 2(2), pp. 53-61, (1999), hereafter "Peh".

Strobush et al, U.S. Patent 5,881,476, hereafter "Strobush".

Staab, U.S. Patent 5,393,528.

Fuchs et al, U.S. Patent 4,136,145, hereafter "Fuchs".

Le Person et al, "Near infrared drying of pharmaceutical thin films: experimental analysis of internal mass transport," Chemical Engineering and Processing, Vol. 37, pp. 257-263, (1998), hereafter "Le Person".

Scope of Claims

In reexamination, patent claims are construed broadly. *In re Yamamoto*, 740 F.2d 1569, 1571, 222 USPQ 934, 936 (Fed. Cir. 1984) (claims given "their broadest reasonable interpretation consistent with the specification"). This reexamination proceeding contains claims 1-193 directed to a method of making a self-supporting therapeutic active-containing film. Claims 1, 25, 50, 192 and 193 are representative:

1. A method of making a self-supporting therapeutic active-containing film comprising:

(a) Mixing at least one edible polymer component, a therapeutic active composition, and at least one polar solvent to form a matrix;

(b) Forming a wet film from said matrix, said wet film having a substantially uniform content of therapeutic active composition throughout said wet film;

(c) Removing said polar solvent from said matrix with heat and/or radiation energy by exposing said matrix to a temperature greater than the degradation temperature of said therapeutic active composition to form a self-supporting film;

wherein the temperature of the matrix is 100° C. or less during said step of removing said polar solvent from said matrix;

wherein the resulting self-supporting film maintains the substantially uniform content of therapeutic active composition per unit of film.

25. A method of making a self-supporting therapeutic active-containing film comprising:

(a) Mixing at least one edible polymer component, a therapeutic active composition, and at least one polar solvent to form a matrix;

(b) Forming a wet film from said matrix;

(c) Removing said polar solvent from said matrix with heat and/or radiation energy by heating said matrix to a temperature that is less than the boiling point of said at least one polar solvent so as to form a viscoelastic film.

50. A method of making a self-supporting therapeutic active-containing film comprising:

(a) Mixing at least one edible polymer component, a therapeutic active composition, and at least one polar solvent to form a matrix;

(b) Forming a wet film from said matrix;

(c) Using heat and/or radiation energy to remove said polar solvent from said matrix to form a visco-elastic state without forming bubbles.

192. (New) A method of making a self-supporting therapeutic active-containing film comprising:

(a) Mixing at least one edible polymer component, a therapeutic active composition, and at least one polar solvent to form a matrix;

(b) Forming a wet film from said matrix, said wet film having a substantially uniform content of therapeutic active composition throughout said wet film;

(c) Removing said polar solvent from said matrix with heat and/or radiation energy by heating said matrix to a temperature that is less than the boiling point of said at least one polar solvent so as to form a viscoelastic film;

wherein the resulting viscoelastic film maintains the substantially uniform content of therapeutic active composition per unit of film.

193. (New) A method of making a self-supporting therapeutic active-containing film comprising:

(a) Mixing at least one edible polymer component, a therapeutic active composition, and at least one polar solvent to form a matrix;

(b) Forming a wet film from said matrix, said wet film having a substantially uniform content of therapeutic active composition throughout said wet film;

(c) Using heat and/or radiation energy to remove said polar solvent from said matrix to form a self-supporting therapeutic active-containing film without forming bubbles;

wherein the resulting self-supporting film maintains the substantially uniform content of therapeutic active composition per unit of film.

With respect to the requirement in claim 1 of "exposing said matrix to a temperature greater than the degradation temperature of said therapeutic active composition", the '588 patent states the following at col. 11, line 45 to col. 12, line 43:

> During film preparation, it may be desirable to dry films at high temperatures. High heat drying produces uniform films, and leads to greater efficiencies in film production. Films containing sensitive active components, however, may face degradation problems at high temperatures. Degradation is the "decomposition of a compound ... exhibiting well-defined intermediate products." The American Heritage Dictionary of the English Language (4th ed 2000). Degradation of an active component is typically undesirable as it may cause instability, inactivity, and/or decreased potency of the active component. ... Degradation of an active component may occur through a variety of processes, such as, hydrolysis, oxidation, and light degradation, depending upon the particular active component. Moreover, temperature has a significant effect on the rate of such reactions. The rate or degradation typically doubles for every 10° C. increase in temperature. Therefore, it is commonly understood that exposing an active component to high temperatures will initiate and/or accelerate undesirable degradation reactions. ... Proteins are one category of useful active ingredients that will degrade, denature, or otherwise become inactive when they are exposed to high temperatures for extended periods of time. ... [T]he films may be exposed to temperatures that would typically lead to degradation, denaturization, or inactivity of the active component ... .

Accordingly, the "degradation temperature" of the therapeutic active composition is taken to be the temperature at which the isolated therapeutic active composition would typically decompose to well defined intermediate products by processes such as hydrolysis, oxidation, and light degradation, which thus, may cause instability, inactivity and/or decreased potency of the active component.

Each of independent claims 1, 25, 50, 192 and 193 recites the step of mixing at least one edible polymer component, a therapeutic active composition, and at least one polar solvent to form a "matrix". With respect to the "matrix", the '588 patent, for example, states the following:

> When the active is combined with the polymer in the solvent, the type of matrix that is formed depends on the solubilities of the active and the polymer. If the active and/or polymer are soluble in the selected solvent, this may form a solution. However, if the components are not soluble, the matrix may be classified as an emulsion, a colloid, or a suspension (see col. 20, lines 52-58).
>
> After the desired components are combined to form a multi-component matrix, including the polymer, water, and an active or other components as desired ... (see col. 23, lines 57-59).

Accordingly, the "matrix" is taken to be the material that results from mixing the at least one edible polymer component, the therapeutic active composition, and the at least one polar solvent.

Claim 1 has been amended to recite and new claims 192 and 193 recite the term "substantially uniform content of therapeutic active composition" in the wet film and in the resulting film after removing the polar solvent. This term is not defined in the '588 patent, nor does the '588 patent provide any criteria to determine what is a "substantially uniform content of therapeutic active composition". Accordingly, a film

that has been prepared according to the processing steps of claims 1, 192 or 193, i.e., mixing, forming and removing, or mixing, forming and using, is taken to be a film having "substantially uniform content of therapeutic active composition".

Proposed Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-24, 75, 78, 81, 84, 87, 90, 93, 96, 99, 102, 105, 106, 111-132, 177, 178, 183, 186, 189, 192 and 193 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The rejection of claims 1, 192 and 193 was proposed by Third Party Requester in the Comments filed 02/09/12 and **is adopted** for the reasons that follow. While the rejection of claims 2-24, 75, 78, 81, 84, 87, 90, 93, 96, 99, 102, 105, 106, 111-132, 177, 178, 183, 186 and 189 was not proposed by Third Party Requester, these claims are included in the rejection since they depend from claim 1.

Claim 1 has been amended to recite "said wet film having a substantially uniform content of therapeutic active composition through said wet film" and "wherein the resulting self-supporting film maintains the substantially uniform content of therapeutic active composition per unit of film". Similar recitations are present in new claims 192 and 193 with the exception of replacing "self-supporting" with "visco-elastic" in claim 192. It is not clear exactly what is encompassed by a substantially uniform content of

therapeutic active composition, and the '588 patent does not provide a definition for a substantially uniform content of therapeutic active composition. The same applies to claims 2-24, 75, 78, 81, 84, 87, 90, 93, 96, 99, 102, 105, 106, 111-132, 177, 178, 183, 186 and 189, which depend from claim 1.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-24, 75, 78, 81, 84, 87, 90, 93, 96, 99, 102, 105, 106, 111-132, 177, 178, 183, 186, 189, 192 and 193 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-24, 75, 78, 81, 84, 87, 90, 93, 96, 99, 102, 105, 106, 111-132, 177, 178, 183, 186, 189, 192 and 193 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The 35 USC 112, first paragraph, rejections of claims 1, 192 and 193 with respect to written description and enablement were proposed by the Third Part

Requester in the Comments filed 01/27/12 and **are adopted** for the reasons that follow. While the rejections of claims 2-24, 75, 78, 81, 84, 87, 90, 93, 96, 99, 102, 105, 106, 111-132, 177, 178, 183, 186 and 189 were not proposed by Third Party Requester, these claims are included in the rejections since they depend from claim 1.

As noted above, claim 1 has been amended to require, and new claims 192 and 193 require, that the wet film and the resulting self-supporting or viscoelastic film have substantially uniform content of therapeutic active composition. Substantially uniform content of therapeutic active composition lacks adequate written description and enablement in the '588 patent. The same applies to claims 2-24, 75, 78, 81, 84, 87, 90, 93, 96, 99, 102, 105, 106, 111-132, 177, 178, 183, 186 and 189, which depend from claim 1.

On pages 10 and 12-15 of the Comments filed 02/09/12, Third Party proposes that claims 1, 192 and 193 be rejected under 35 USC 112, second paragraph as being indefinite due to the term "unit of film".

This proposed rejection **is not adopted** for the reasons that follow.

Third Party Requester argues that the '588 patent fails to teach one of ordinary skill in the art what is intended by "unit of film" (Comments of 02/09/12). In particular, Third Party Requester argues the following at p. 13 of the Comments filed 02/09/12: "Is it a roll of finished film? A standard area of dried film before being cut? A dosage unit? And in any of these cases, of what size?"

These arguments are unpersuasive. First, the term "unit of film" is no different from the term "film unit" which appears in claim 3. Thus, even though claim 1 has been amended to recite "unit of film" and new claims 192 and 193 recite this term, the term cannot be rejected under 35 U.S.C § 112 because such a rejection is not within the scope of reexamination. As noted in MPEP 2258(II), "[i]f a limitation that appears in an existing patent claim also appears in a claim newly presented in a reexamination proceeding, that limitation cannot be examined as to 35 U.S.C. 112." See also MPEP 2658 (II).

Second, the term "unit of film", though broad, is definite. It could be a roll of finished film, it could be a standard area of dried film before being cut, or it could be a dosage unit. Any size can be a unit.

On pages 15-19 of the Comments filed 02/09/12, Third Party proposes that claims 1, 25, 50, 192 and 193 be rejected under 35 USC 112, as being indefinite and lacking written description due to the claim term "visco-elastic".

This proposed rejection **is not adopted** for the reasons that follow.

The term "visco-elastic" or "viscoelastic" appears in, for example, patented claims 25 and 50 and thus, cannot be reexamined as to 35 USC 112. On pp. 15-19 of the Comments filed 02/09/12, it is apparent that Third Party Requester disputes the interpretation of the meaning of the term "visco-elastic" given by Patent Owner on p. 6, lines 8-14, of the Remarks filed 01/10/12. The meaning of term "visco-elastic" is a

scope of claims issue and is discussed below in response to Patent Owner's arguments.

Proposed Claim Rejections - 35 USC § 102 and § 103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1. Claims 25-28, 30-33, 35, 36, 40, 42-53, 55-58, 60, 61, 65, 67-74, 76, 77, 79, 80, 82, 83, 85, 86, 88, 89, 91, 92, 94, 95, 97, 98, 100, 101, 103, 104, 107-110, 133-139, 141-143, 155-161, 163-165, 179-182, 184, 185, 187, 188 and 190-193 are rejected under 35 U.S.C. 102(b) as being anticipated by Chen.

In the request and Comments filed 02/09/12, Third Party Requester proposes that claims 25-33, 35, 36, 40, 42-58, 60, 61, 65, 67-74, 76, 77, 79, 80, 82, 83, 85, 86, 88, 89, 91, 92, 94, 95, 97, 98, 100, 101, 103, 104, 107-110, 133-143, 155-165, 179-182, 184, 185, 187, 188 and 190-193 be rejected under 35 USC 102(b) as being anticipated by Chen. For the reasons that follow, the proposed rejection **is not adopted** for claims

29, 54, 140 and 162. For the reasons that follow, the proposed rejection **is adopted** for claims 25-28, 30-33, 35, 36, 40, 42-53, 55-58, 60, 61, 65, 67-74, 76, 77, 79, 80, 82, 83, 85, 86, 88, 89, 91, 92, 94, 95, 97, 98, 100, 101, 103, 104, 107-110, 133-139, 141-143, 155-161, 163-165, 179-182, 184, 185, 187, 188 and 190-193.

With respect to claims 29, 54, 140 and 162, the only teaching in Chen with respect to a mixture of polar solvents is Example 2, Table 1, at p. 18, wherein said Example 2 uses water and ethanol. However, Example 2, like Chen's Example 1, does not contain a therapeutic active composition (see also p. 27, lines 12-13).

Chen teaches a dosage unit including a water-soluble hydrocolloid, mucosal surface-coat-forming film, such film including an effective dose of an active agent (see p. 3, lines 30-32). In Examples 5-8, Chen prepares hydroxypropyl methylcellulose based quick dissolving intraoral films containing therapeutic agents (see p. 20, lines 17-20 and Tables 5 and 7). In particular, the films in Examples 5-8 contain a therapeutic agent, e.g., nicotine, hydromorphone, oxybutynin or estradiol; an edible polymer, i.e., hydroxypropyl methylcellulose (HPMC); and a polar solvent, i.e., water (see Tables 5 and 7). Further, the film in Tables 7 and 8 of Chen uses Sildenafil citrate as the active ingredient and is prepared using HPMC (in this case Methocel E15) and water as the solvent. In the method of preparation of the films, the HPMC (i.e., hydrocolloid) is dissolved in water under agitated mixing to form a uniform and viscous solution and the additional ingredients are then added under agitated mixing until they are uniformly dispersed or dissolved in the hydrocolloid (see p. 14, line 22 to p. 15, line 3; and p. 17, lines 6-19). The resultant mixture, i.e. the instant matrix, is degassed in a vacuum

chamber until trapped air bubbles are removed, and then coated on the non-siliconized side of a polyester film at a wet thickness of 10 mil and dried in a hot air circulating oven at 50°C for 9 minutes (see p. 17, lines 13-15). The 50°C is less than the boiling point of water, as per independent claims 25 and 192. Also, since the drying is at 50°C for 9 minutes, the matrix temperature is at most 50°C, which is less than about 100°C, as per instant claims 26 and 51; and the water is removed from the matrix in less than about 10 minutes, as per instant claims 27, 52, 135 and 157. In view of said degassing in a vacuum chamber until trapped air bubbles are removed, the film is formed without forming bubbles as per claim 50, and is deaerated as per claims 30 and 55. The dried films in Chen's Examples 5-8 are "self-supporting" films as here claimed (see p. 17, lines 15-16 of Chen). Likewise, Chen's films are "viscoelastic" as in claims 25 and 50 because they are flexible, stand alone, self-supporting films made using hydroxypropyl methylcellulose (see pp. 20-21), which is disclosed in the '588 patent as a suitable film-forming polymer (see col. 15, lines 12-17).

With respect to claims 28, 53, 138 and 160, Chen prepares its self-supporting, therapeutic active containing film from a coating solution with a homogeneous mixture of ingredients (see p. 17, lines 6-11 and 26-28, Examples 5-8; and p. 20, lines 17-20). Accordingly, the films in Examples 5-8 inherently have a variation of active content of less than 10% per film unit, as here claimed. Likewise, with respect to claims 1, 192 and 193, Chen's wet film has "substantially uniform content of therapeutic active composition" throughout the wet film, and the dried film has "substantially uniform content of therapeutic active composition" per unit of film, in view of the fact, as noted

above, the coating solution is a homogeneous mixture, the fact that Chen performs the same process steps as here claimed, and the fact that, for example, as seen in Chen's Table 4 on p. 20, Example 1 has a weight of 0.028 $\pm$ 0.001 g/dosage film, a thickness of 2.1 $\pm$ 0.12 mil, and a density of 1.0485 $\pm$ 0.009 g/cm^2, and a water content of 1.7 $\pm$ 0.24%.

With respect to claims 31 and 56, Chen's Examples 1-8 use hydroxypropyl methylcellulose (Methocel E5, HPMC), which is water soluble (p. 17, lines 6-8). In fact, HPMC is identified as a water soluble polymer in the '588 patent at col. 15, lines 16-18. Example 9 uses, for example, different hydroxypropyl methylcellulose types, such as the Methocel E5 and E15 (see Tables 7 and 8 on p. 23, and Table 9a on p. 24).

With respect to claims 32, 57, 141, 163 and 179-182, Chen's matrix includes a hydrocolloid, and the ingredients are uniformly dispersed or dissolved in the hydrocolloid (see p. 17, lines 6-11). Chen teaches that the active agent may be dispersed as colloidal particles or microencapsulated within the film (see p. 7, lines 19-21).

With respect to claims 33, 35, 36, 40, 58, 60, 61 and 65, Chen's active agent can include insulin, proteins, hormones, and peptide active agent (see p. 11, lines 3-5).

With respect to claims 42, 67 and their dependent claims, and with respect to claims 142 and 164, Chen discloses (a) forming a master batch premix including a polymer, e.g., hydrocolloid HPMC, and a solvent, i.e. water, (b) adding the active agent to the premix - presumably in a mixer, given the next step - and (c) mixing the premix and active agent to form a coatable mixture (see p. 4, lines 24-28; p. 17, lines 7-11; and

p. 20, lines 19-20). Chen does not specify whether a separate mixer is used, only that premix and active agent are mixed. However, step (b) in instant claims 42, 67, 142 and 164 does not require that the premix be made in a first vessel and then fed to a second mixer. Accordingly, adding water and polymer to the mixer of step (b) in Chen is "directing" the premix to the mixer as here claimed.

With respect to claims 43, 68, 143 and 165, Chen teaches that the matrix can include at least one taste-masking agent, e.g., peppermint and aspartame (see p. 10, lines 7-14; p. 17, lines 8-9; Examples 5-8 in Table 5).

With respect to claims 44 and 69, Chen teaches that its therapeutic active composition can be in a controlled release form, e.g., encapsulated for release after the dissolution of the film as described, e.g., at p. 9, lines 11-14.

With respect to claims 45, 48, 70 and 73, Chen prepares a stand alone, self-supporting therapeutic active-containing film from a coating solution with a homogeneous mixture of ingredients (see p. 17, lines 6-28, Examples 5-8, p. 20, lines 19-20, and p. 15, line 25). Accordingly, Chen's method prevents substantial aggregation of the active components and has a "substantially uniform mass to volume ratio of components", as here claimed.

With respect to claims 46 and 71, Chen teaches that the films are suitable for administration of the active material through the buccal cavity (see p. 8, lines 9-10 and Fig. 1).

With respect to claims 47 and 72, the films prepared in Chen's Examples 5-9 have a thickness of 3.2 mils with a standard deviation of 0.1 mils (see Tables 6 and 8 on pp. 22-23), and thus have "substantially uniform thickness" as here claimed.

With respect to claims 49 and 74, which require that any air flow present during the step of removing the polar solvent from the matrix does not overcome the inherent viscosity of the wet film, the '588 patent provides the following discussion relating to this limitation at col. 11, lines 21-33:

> Any top fluid flow, such as air, also must not overcome the inherent viscosity of the film-forming composition. In other words, the top air flow cannot break, distort or otherwise physically disturb the surface of the composition. Moreover, air velocities are desirably below the yield values of the film, i.e., below any force level that can move the liquids in the film-forming compositions. For thin or low viscosity compositions, low air velocity must be used. For thick or high viscosity compositions, higher air velocities may be used.

Chen teaches that its wet films before drying are viscous, and that the product films after drying are glossy (see p. 17, lines 6-15 and Examples 5-8). A glossy surface evidences the absence of mottle caused by surface disturbances during drying. Therefore, in the Examples of Chen, any air flow present during the rapid drying step in the hot air circulating oven (p. 17, line 14) necessarily did not overcome the inherent viscosity of the viscous wet films. In fact, as noted above, Chen's Example 1 has a weight 0.028 g/dosage film with a standard deviation of only $\pm$ 0.001 g/dosage film (see Table 4 on p. 20).

With respect to claims 76, 77, 79, 80, 136, 137, 158 and 159, the films formed in Chen's Examples 5-8 have a water content of less than 3% (see Table 6 on p. 22).

With respect to claims 82 and 83, Chen teaches application of its films to provide administration of the active material through a mucosal surface (see p. 8, lines 6-9 and Example 12 at p. 27, lines 11-27).

With respect to claims 85 and 86, Chen teaches administration of the film through sublingual application (see p. 8, lines 8-10 and Fig. 1).

With respect to claims 88 and 89, Chen's films are capable of being administered at any time, including surgery. Chen discloses several active agents that are highly suitable for use "during surgery", including sedatives, local anesthetics, antiseptics, anti-inflammatory agents, anti-viral agents, muscle relaxants, and steroids (see p. 10, line 29 through p. 11, line 12). Further, Chen teaches that "[e]mbodiments of the invention include .... for a quick dissolving film for local and systemic delivery of pharmaceutical agents to a mucosal surface in a subject .... The dosage unit of the invention may be applied to any mucosal surface as deemed appropriate for the systemic or local delivery of an active agent including vaginal, rectal and ocular surfaces ... [e]mbodiments [may be administered easily by] physicians, parents, patients ..." (*see* p. 8, lines 2-4, 6-10, and 19-20). Chen also teaches the application of films to a wound surface "where lymph fluid bathes the tissue surface" at p. 7, lines 32 to p. 8, line 1. Thus, the films of Chen are clearly "capable of" being administered during surgery, whether orally or at the site of the surgery.

With respect to claims 91 and 92, Chen teaches that "[d]epending on the optimal program for a specific application of the invention, the disintegration time and dissolution time can be controlled within a prescribed range by adjustment of the

formulation and the thickness of the film" and also encapsulation of the active material (see p. 9, lines 9-14). Slow release films are also discussed, e.g., at p. 7, lines 16-21.

With respect to claims 94, 95, 139 and 161, Chen prepares its self-supporting, therapeutic active containing film from a coating solution with a homogeneous mixture of ingredients (see p. 17, lines 6-11 and 26-28, Examples 5-8; and p. 20, lines 17-20). Accordingly, the films in Examples 5-8 inherently have a variation of active content of no more than 10% per individual dosage unit, as here claimed. In fact, as noted above, Chen's Example 1 has a weight 0.028 g/dosage film with a standard deviation of only $\pm$ 0.001 g/dosage film (see Table 4 on p. 20). Chen teaches forming a plurality of individual dosage units of substantially the same size (see p. 16, lines 2-8 and Fig. 3).

With respect to claims 97 and 98, Chen forms its wet film by casting (see p. 15, lines 13-14; p. 15, line 24 to p. 16, line 3; p. 17, lines 3-15; and Fig. 2).

With respect to claims 100 and 101, the casting method shown in Fig. 2 of Chen (see also p. 15, lines 13-14) extrudes the wet matrix through a "coating slot" onto a backing belt.

With respect to claims 103 and 104, the wet film on the backing belt is in the form of a sheet (see Fig. 2 and accompanying description on p. 15, line 19 to p. 16, line 3).

With respect to claims 107-110, Chen teaches that its active material can be a contraceptive (see p. 10, line 32).

With respect to claims 133, 155 and their dependent claims, Chen uses heat, i.e., heating in a hot circulating oven at 50°C for 9 minutes, to remove the water in Examples 5-8 (see p. 17, lines 13-15).

With respect to claims 134 and 154, Chen uses a hot circulating oven with aeration controller, and thus the heat comprises hot air currents, as here claimed (see p. 17, lines 13-15 and Fig. 2).

With respect to claims 184 and 185, in Chen's Examples 5-8, the hydroxypropyl methylcellulose (Methocel E5), the active ingredient which is nicotine, hydromorphone, oxybutynin or estradiol, and the water, are each ingestible materials.

With respect to claims 187 and 188, Chen's films are orally administrable (see p. 8, lines 8-10 and Example 12).

With respect to claims 190 and 191, Chen teaches that the active composition can be in the form of a particle, e.g., a colloid particle or microencapsulated (see p. 7, lines 17-21).

2. Claims 1-3, 5-8, 10, 11, 15, 17-24, 75, 78, 81, 84, 87, 90, 93, 96, 99, 102, 105, 106, 111-117, 119-121, 177, 178, 183, 186 and 189 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Chen.

In the request and Comments filed 02/09/12, Third Party Requester proposes that claims 1-8, 10, 11, 15, 17-24, 75, 78, 81, 84, 87, 90, 93, 96, 99, 102, 105, 106, 111-121, 177, 178, 183, 186 and 189 be rejected under 35 USC 102(b) as being anticipated by Chen. For the reasons that follow, the proposed rejection **is not adopted** for claims 4 and 118. For the reasons that follow, the proposed rejection **is adopted** for claims 1-3, 5-8, 10, 11, 15, 17-24, 75, 78, 81, 84, 87, 90, 93, 96, 99, 102, 105, 106, 111-117,

119-121, 177, 178, 183, 186 and 189. The 35 USC 103(a) rejection of claims 1-3, 5-8, 10, 11, 15, 17-24, 75, 78, 81, 84, 87, 90, 93, 96, 99, 102, 105, 106, 111-117, 119-121, 177, 178, 183, 186 and 189 was Examiner-initiated in the Office action mailed 11/10/11.

With respect to claims 4 and 118, the only teaching in Chen with respect to a mixture of polar solvents is Example 2, Table 1, at p. 18, wherein said Example 2 uses water and ethanol. However, Example 2, like Chen's Example 1, does not contain a therapeutic active composition (see also p. 27, lines 12-13).

Chen is relied upon for the reasons stated above. With respect to claim 1 and its dependent claim, and as discussed above with respect to claims 192 and 193, Chen's wet film has "substantially uniform content of therapeutic active composition" throughout the wet film (p. 17, lines 6-11 and 26-28, Examples 5-8; and p. 20, lines 17-20), and the dried film has "substantially uniform content of therapeutic active composition" per unit of film, in view of the fact, as noted above, the coating solution is a homogeneous mixture, the fact that Chen uses the same process steps as in claims 192 and 193, and the fact that, for example, as seen in Chen's Table 4 on p. 20, Example 1 has a weight of 0.028 $\pm$ 0.001 g/dosage film, a thickness of 2.1 $\pm$ 0.12 mil, and a density of 1.0485 $\pm$ 0.009 g/cm^2, and a water content of 1.7 $\pm$ 0.24%.

Claim 1 and its dependent claims require removing the polar solvent from the matrix by heat and/or radiation energy by exposing the matrix to a temperature "greater than the degradation temperature of said therapeutic active composition", and that the temperature of the matrix is 100°C or less during the removing of the polar solvent. In addition to the nicotine, hydromorphone, oxybutynin, estradiol, and Sildenafil citrate

exemplified in Chens example films, other therapeutic agents taught by Chen include peptide active agents, polypeptide active agents, and proteins such as insulin, calcitonin, LHRH (i.e., luteinizing-hormone-releasing hormone, also known as gonadotropin-releasing hormone or luliberin) and the like (see p. 11, lines 4-5). Chen also teaches that when removing the water from its films, the drying is at a temperature of "between 40-100°C so as to avoid destabilizing the agents contained within the formulation" (see p. 15, lines 19-29). The temperature range of between 40-100°C is entirely within the instantly claimed range of 100°C or less. The '588 patent states that temperatures that approach 100°C will generally cause degradation of proteins (see col. 12, lines 26-29). Accordingly, Chen's temperature of "between 40-100°C so as to avoid destabilizing the agents contained within the formulation" anticipates the claimed requirements of less than 100°C but greater than the degradation temperature of the therapeutic active agent when Chen's active agent is a peptide active agent, polypeptide active agent, or protein such as insulin, calcitonin or LHRH.

With respect to claims 2 and 113, Chen exemplifies removing water from the matrix in 9 minutes (see p. 17, lines 13-15).

With respect to claims 3 and 116, Chen prepares its self-supporting, therapeutic active containing film from a coating solution with a homogeneous mixture of ingredients (see p. 17, lines 6-11 and 26-28, Examples 5-8; and p. 20, lines 17-20). Accordingly, Chen's films, such as those in Examples 5-8, inherently have a variation of active content of less than 10% per film unit, as here claimed.

With respect to claim 5, Chen teaches degassing in a vacuum chamber until trapped air bubbles were removed, i.e., the instant deaerating (see p. 17, lines 11-12).

With respect to claim 6, Chen's Examples 1-8 use hydroxypropyl methylcellulose (Methocel E5, HPMC), which is water soluble (see p. 17, lines 6-8) In fact, HPMC is identified as a water soluble polymer in the '588 patent at col. 15, lines 16-18. Example 9 uses, for example, different hydroxypropyl methylcellulose types, such as the Methocel E5 and E15 (see Tables 7 and 8 on p. 23, and Table 9a on p. 24). Other water soluble polymers are taught by Chen at p. 14, line 12 to p. 15, line 3).

With respect to claims 7,119, 177 and 178, Chen's matrix includes a hydrocolloid, and the ingredients are uniformly dispersed or dissolved in the hydrocolloid (see p. 17, lines 6-11). Chen that the active agent may be dispersed as colloidal particles or microencapsulated within the film (see p. 7, lines 19-21).

With respect to claims 8, 10, 11 and 15, as noted above, Chen's active agent can include peptide active agents, polypeptide active agents, and proteins such as insulin, calcitonin, LHRH (i.e., luteinizing-hormone-releasing hormone, also known as gonadotropin-releasing hormone or luliberin) and the like (see p. 11, lines 4-5).

With respect to claim 17 and its dependent claims, and with respect to claim 120, Chen discloses (a) forming a master batch premix including a polymer, e.g., hydrocolloid HPMC, and a solvent, i.e. water, (b) adding the active to the premix - presumably in a mixer, given the next step - and (c) mixing the premix and active agent to form a coatable mixture (see p. 4, lines 24-28; p. 17, lines 7-11; and p. 20, lines 19-20). Chen does not specify whether a separate mixer is used, only that premix and

active agent are mixed. However, step (b) in instant claims 17 and 120 does not require that the premix be made in a first vessel and then fed to a second mixer. Accordingly, adding water and polymer to the mixer of step (b) in Chen is "directing" the premix to the mixer.

With respect to claims 18 and 121, Chen teaches that the matrix can include at least one taste-masking agent, e.g., peppermint and aspartame (see p. 10, lines 7-14; p. 17, lines 8-9; Examples 5-8 in Table 5).

With respect to claim 19, Chen teaches that its therapeutic active composition can be in a controlled release form, e.g., encapsulated for release after the dissolution of the films as described, e.g., at p. 9, lines 11-14.

With respect to claims 20 and 23, Chen prepares a stand alone, self-supporting therapeutic active-containing film from a coating solution with a homogeneous mixture of ingredients (see p. 17, lines 6-28, Examples 5-8, p. 20, lines 19-20, and p. 15, line 25). Accordingly, Chen's method prevents substantial aggregation of the active components and has a "substantially uniform mass to volume ratio of components", as here claimed.

With respect to claim 21, Chen teaches that the films are suitable for administration of the active material through the buccal cavity (see p. 8, lines 9-10 and Fig. 1).

With respect to claim 22, the films prepared in Chen's Examples 5-9 have a thickness of 3.2 mils with a standard deviation of 0.1 mils (see Tables 6 and 8 on pp. 22-23), and thus have "substantially uniform thickness" as here claimed.

With respect to claim 24, which requires that any air flow present during the step of removing the polar solvent from the matrix does not overcome the inherent viscosity of the wet film, the '588 patent provides the following discussion relating to this limitation at col. 11, lines 21-33:

> Any top fluid flow, such as air, also must not overcome the inherent viscosity of the film-forming composition. In other words, the top air flow cannot break, distort or otherwise physically disturb the surface of the composition. Moreover, air velocities are desirably below the yield values of the film, i.e., below any force level that can move the liquids in the film-forming compositions. For thin or low viscosity compositions, low air velocity must be used. For thick or high viscosity compositions, higher air velocities may be used.

Chen teaches that its wet films before drying are viscous, and that the product films after drying are glossy (see p. 17, lines 6-15 and Examples 5-8). A glossy surface evidences the absence of mottle caused by surface disturbances during drying. Therefore, in the Examples of Chen, any air flow present during the rapid drying step in the hot air circulating oven (p. 17, line 14) necessarily did not overcome the inherent viscosity of the viscous wet films. In fact, as noted above, Chen's Example 1 has a weight 0.028 g/dosage film with a standard deviation of only $\pm$ 0.001 g/dosage film (see Table 4 on p. 20).

With respect to claims 75, 78, 114 and 115, the films formed in Examples 5-8 have a water content of less than 3% (see Table 6 on p. 22).

With respect to claim 81, Chen teaches application of its films to provide administration of the active material through a mucosal surface (see p. 8, lines 6-9 and Example 12 at p. 27, lines 11-27).

With respect to claim 84, Chen teaches administration of the film through sublingual application (see p. 8, lines 8-10 and Fig. 1).

With respect to claim 87, Chen's films are capable of being administered at any time, including surgery. Chen discloses several active agents that are highly suitable for use "during surgery", including sedatives, local anesthetics, antiseptics, anti-inflammatory agents, anti-viral agents, muscle relaxants, and steroids (see p. 10, line 29 through p. 11, line 12). Further, Chen teaches that "[e]mbodiments of the invention include .... for a quick dissolving film for local and systemic delivery of pharmaceutical agents to a mucosal surface in a subject .... The dosage unit of the invention may be applied to any mucosal surface as deemed appropriate for the systemic or local delivery of an active agent including vaginal, rectal and ocular surfaces ... [e]mbodiments [may be administered easily by] physicians, parents, patients ..." (see p. 8, lines 2-4, 6-10, and 19-20). Chen also teaches the application of films to a wound surface "where lymph fluid bathes the tissue surface" at p. 7, lines 32 to p. 8, line 1. Thus, the films of Chen are clearly "capable of" being administered during surgery, whether orally or at the site of the surgery.

With respect to claim 90, Chen teaches that "[d]epending on the optimal program for a specific application of the invention, the disintegration time and dissolution time can be controlled within a prescribed range by adjustment of the formulation and the thickness of the film" and also encapsulation of the active agent (see p. 9, lines 9-14). Slow release films are also discussed, e.g., at p. 7, lines 16-21.

With respect to claims 93 and 117, Chen prepares its self-supporting, therapeutic active containing film from a coating solution with a homogeneous mixture of ingredients (see p. 17, lines 6-11 and 26-28, Examples 5-8; and p. 20, lines 17-20). Accordingly, Chen's films, such as those in Examples 5-8, inherently have a variation of active content of no more than 10% per individual dosage unit. In fact, as noted above, Chen's Table 4 on p. 20, shows that Example 1 has a weight of 0.028 $\pm$ 0.001 g/dosage film, a thickness of 2.1 $\pm$ 0.12 mil, and a density of 1.0485 $\pm$ 0.009 g/cm^2, and a water content of 1.7 $\pm$ 0.24%. Additionally, Chen teaches forming a plurality of individual dosage units of substantially the same size (see p. 16, lines 2-8 and Fig. 3).

With respect to claim 96, Chen forms its wet film by casting (see p. 15, lines 13-14; p. 15, line 24 to p. 16, line 3; p. 17, lines 3-15; and Fig. 2).

With respect to claim 99, the casting method shown in Fig. 2 of Chen (see also p. 15, lines 13-14) extrudes the wet matrix through a "coating slot" onto a backing belt.

With respect to claim 102, the wet film on the backing belt is in the form of a sheet (see Fig. 2 and accompanying description on p. 15, line 19 to p. 16, line 3).

With respect to claims 105 and 106, Chen teaches that its active material can be a contraceptive (see p. 10, line 32).

With respect to claim 111 and its dependent claims, Chen uses heat, i.e., heating in a hot circulating oven to remove the water (see p. 17, lines 13-15 and the drying oven in Fig. 2).

With respect to claim 112, Chen uses a hot circulating oven with aeration controller, and thus the heat comprises hot air currents as here claimed (see p. 17, lines 13-15 and Fig. 2).

With respect to claim 183, the hydroxypropyl methylcellulose (Methocel E5) used in Chen's examples, the active ingredient which is insulin, calcitonin or LHRH, and the water, are each ingestible materials.

With respect to claim 186, Chen's films are orally administrable (see p. 8, lines 8-10 and Example 12).

With respect to claims 189, Chen teaches that the active composition can be in the form of a particle, e.g., a colloid particle or microencapsulated (see p. 7, lines 17-21).

To the extent it can be argued that Chen does not anticipate the requirement in claim 1 and its dependent claims of removing the polar solvent from the matrix by heat and/or radiation energy by exposing the matrix to a temperature "greater than the degradation temperature of said therapeutic active composition", then such is rendered obvious by Chen. In particular, as noted above, the therapeutic agents taught by Chen include peptide active agents, polypeptide active agents, and proteins such as insulin, calcitonin, LHRH (i.e., luteinizing-hormone-releasing hormone, also known as gonadotropin-releasing hormone or luliberin) and the like (see p. 11, lines 4-5). Chen also teaches that when removing the water from its film, the drying is at a temperature of "between 40-100°C so as to avoid destabilizing the agents contained within the formulation" (see p. 15, lines 19-29). Thus, temperature is a results-effective variable

with respect to destabilization of the therapeutic agent. Temperature is also a well-known results-effective variable with respect to drying time as higher temperatures generally permit shorter drying times. It is also well known in the art that proteins begin to degrade as temperatures approach 100°C. It is noted that Chen's temperature range of between 40-100°C for removing the water from the film is entirely within temperature range "100°C or less" set forth in claim 1.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have optimized Chen's drying step by using as high a drying temperature as possible within Chen's disclosed the range of 40-100°C without destabilizing the active agent because temperature is a results-effective variable with respect to active agent destabilization as taught by Chen; and so as to dry Chen's film as quickly as possible.

3. Claims 4, 14, 29, 39, 54, 64, 118, 140 and 162 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen. This rejection was Examiner-initiated in the Office action mailed 11/10/11.

Chen is relied upon for all the reasons stated above. With respect to claims 4, 29, 54, 118, 140 and 162, Chen exemplifies the use of a mixture of polar solvents, i.e., water and ethanol, in Example 2 (see Table 1 at p. 18). The film of Example 2 does not contain therapeutic active composition. However, as seen in the description of Table 1 at the top of p. 18, Example 2 is a formulation of a quick dissolving film using a hydrocolloid.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have prepared Chen's film containing therapeutic agent using a mixture of ethanol and water because a mixture of solvents permits the formation of a quick dissolving film using a hydrocolloid as shown by Example 2 in Table 1 of Chen; and so as to facilitate the dissolving of the ingredients when preparing the film.

With respect to claims 14, 39 and 64, Chen does not specifically require that its active material comprises a polysaccharide. However, Chen teaches that its active material can be an anti-diarrheal or a laxative (see p. 10, line 27 and p. 11, line 7). Well known laxatives in the art are polysaccharides and include bran; psyllium husk, i.e. Metamucil; methyl cellulose, which is also one of the water-soluble hydrocolloids taught by Chen at p. 14, line 27; and sterculia (i.e., Normacol). Methyl cellulose, as well as guar gum (which is also one of the water-soluble hydrocolloids taught by Chen at p. 14, line 14), bran and sterculia are also well known anti-diarrhea agents. Chen also teaches that its hydrocolloid can be polysaccharides such as chondroitin sulfate (see p. 14, line 20), which is well known for treating osteoarthritis; and teaches hyaluronic acid, which is another well-known therapeutic active material used for joint disorders including osteoarthritis and in plastic surgery.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have used bran, psyllium husk, methyl cellulose, sterculia, or guar gum as the active ingredient in Chen's film because Chen teaches that the active ingredient in its film can be a laxative or anti-diarrhea agent; and bran, psyllium husk, methyl cellulose, sterculia, and guar gum are well known laxatives and/or anti-diarrhea

agents in the art. Furthermore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have used chondroitin sulfate or hyaluronic acid for Chen's hydrocolloid because such is clearly within the scope of Chen's disclosure. As noted above chondroitin sulfate and hyaluronic acid are also well known therapeutic active materials.

4. Claims 1, 122-132, 144-154 and 166-176 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Chen and Le Person.

This rejection was proposed by Third Party Requester in the request and **is adopted** for the reasons that follow.

Chen is relied upon for all the reasons stated above.

With respect to claim 1, as noted above, Chen uses a hot air circulating oven at 50°C for 9 minutes, i.e., uses heat, to remove the water from its wet film (see p. 17, lines 13-15). As an alternative to heat, instant claim 1 recites radiation energy for removing the polar solvent, i.e., claim 1 recites "[r]emoving said polar solvent from said matrix with heat and/or radiation energy ...". Claims 122-132, 144-154 and 166-176 specifically require the use of radiation energy. Chen does not teach the use of radiation energy for removing the water or water/ethanol solvent mixture from the wet film.

Le Person compares the drying of pharmaceutical wet films comprising polymer, a mixture of solvents and an active material, by convection, conduction and infrared radiation (see p. 258, first sentence of § 2.1, Table 1, and first sentence of § 2.2). Le Person teaches that "[a]fter preparation, the coating mixture is spread on a web, and

submitted to drying in a tunnel or an oven", and that "[f]requently, impinging jets and Infra Red Radiation accomplish the work in a short drying time (100 s as an order of magnitude)." (see p. 257, col. 1). Water is identified as the major solvent (38 wt.% based on the wet composition) on p. 260, Table 1, i.e., Le Person discloses removing polar solvent with heat and/or radiation energy. Le Person teaches that in 10 minutes, 99% of the initial water from a 100 μm thick coating is evaporated using a short infrared drying process (see § 3.1 at pp. 260-261, in particular Fig. 5). The 10 minutes renders obvious the instantly claimed "less than about 10 minutes". Le Person teaches that the initial drying velocity with infrared is about twice the velocity with other heating modes and that "[b]etween conduction and SIR [short infrared] the latter one is far more preferable." (see p. 258, col. 2, last paragraph). Figure 2 on p. 259 of Le Person shows that combined convection plus medium infrared drying is just as fast and complete as short infrared, and that conduction and convection alone are comparable.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have dried Chen's film using short infrared drying, or combined convection and medium infrared drying, instead of oven drying because these are known, alternative drying techniques in the art with short infrared drying being preferred, as taught by Le Person. In fact, as noted above, Le Person shows that combined convection plus medium infrared drying is just as fast and complete as short infrared drying, and that conduction and convection alone are comparable.

5. Claims 2, 5, 8, 9, 12, 15, 16, 18, 34, 37, 41, 59, 62, 66, 84, 99, 113 and 121 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Chen and Bernstein.

This rejection was proposed by Third Party Requester in the request and **is adopted** for the reasons that follow.

Chen is relied upon for all the reasons stated above. Chen does not specifically teach, for example, that the protein or peptide active agent to be delivered by its film is an enzyme, a cytokine or glycoprotein.

Bernstein teaches the preparation of a film for the modulated release of a biologically active agent (see abstract; col. 1, lines 29-43; and Example I). An example of the biocompatible polymer used to form the film is poly(lactide-co-glycolide), i.e., "PLGA", which is an edible polymer; and examples of the biologically active agent include nucleases, which are enzymes; interferons, interleukins and tumor necrosis factor, which are each cytokines; and erythropoietin, which in addition to interferons, is glycoprotein (see col. 3, line 56 to col. 4, line 58; col. 6, lines 27-29; and Examples I and VII).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have used nucleases, interleukins, tumor necrosis factor or erythropoietin for the active material in Chen's film because Chen teaches that its active material can be a protein or peptide; and because nucleases, interleukins, tumor necrosis factor or erythropoietin can be delivered in film form, as taught by Bernstein.

6. Claims 13, 14, 17, 38, 39, 42, 63, 64 and 67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen in combination with Staab or Hijiya.

This rejection was proposed by Third Party Requester in the request and **is adopted** for the reasons that follow.

Chen is relied upon for all the reasons stated above. With respect to claims 13, 14, 38, 39, 63 and 64, Chen does not specifically teach that the active material in its film can comprise an immunoglobin, or teach that the active material is, for example, a polysaccharide.

Staab teaches films made of dissolvable polymer material and/or complex carbohydrate material which are food grade materials, wherein the films also contain an agent such as a drug or medication (see abstract). The drug/medication can be monoclonal antibodies (col. 6, lines 49-53), which are immunoglobins. It is noted that immunoglobins are glycoproteins, and glycoproteins contain oligosaccharides. As discussed above, Chen teaches that its active agent can be a protein (see p. 11, line 4).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have used a monoclonal antibody for the active material in Chen's film because Chen teaches that proteins can be used as the active material, and Staab teaches that monoclonal antibodies can be delivered in film form.

Alternatively, Hijiya teaches a process of producing a glucan film of self-supporting thickness (see col. 2, lines 13-3). An aqueous glucan solution is used, and the solution can further contain an ingredient such as cyclodextrin, protein, hormone, antigenic substance, antibiotic, biologically active substance, etc (see col. 3, lines 5-34).

Cyclodextrins can be oligosaccharides, like those taught in Examples 4 and 5 of Hijiya, but can also be polysaccharides and have been well characterized as having up to 39 saccharide units, as is well known in the art. In Hijiya's Examples 4 and 5, the cyclodextrin is part of an inclusion complex with L-menthol and cinnamaldehyde, respectively. As is well known in the art, the inclusion complex is for controlled release of the active material complexed with the cyclodextrin.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have used a cyclodextrin inclusion complex with active material for Chen's active material because such complexes are well known in the art for controlled release of the active material, and incorporation of the complex in Chen's film would provide an alternative to other forms of delivery of the complex, e.g., an alternative to pills or injections.

With respect to claims 17, 42 and 67, to the extent that forming a master batch of the polymer and water is not anticipated or rendered obvious by Chen, then such is rendered obvious by Chen in combination with Staab.

Staab further teaches forming a premix including polymer and water at a first temperature and then transferring to another vessel of a cooler temperature, and then stirring in heat sensitive ingredients (see col. 7, lines 37-48). Pharmaceuticals and other agents may be heat sensitive (see col. 7, lines 48-51).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have prepared Chen's film by first forming a premix of the polymer and water in one vessel, and then transferring the premix to another vessel of a

cooler temperature, and then stirring in heat sensitive ingredients, i.e., drugs, as in Staab, so as to protect the drug, which is usually the most expensive component.

7. Claims 2, 5, 8, 15, 84, 99 and 113 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Chen and Hijiya.

This rejection was proposed by Third Party Requester in the request and **is adopted** for the reasons that follow.

Chen is relied upon for all the reasons stated above. Chen does not specifically teach that the active material in its film can comprise, for example, a polysaccharide.

Hijiya teaches a process of producing a glucan film of self-supporting thickness (see col. 2, lines 13-3). An aqueous glucan solution is used, and the solution can further contain an ingredient such as cyclodextrin, protein, hormone, antigenic substance, antibiotic, biologically active substance, etc (see col. 3, lines 5-34). Cyclodextrins can be oligosaccharides, like those taught in Examples 4 and 5 of Hijiya, but can also be polysaccharides and have been well characterized as having up to 39 saccharide units, as is well known in the art. In Hijiya's Examples 4 and 5, the cyclodextrin is part of an inclusion complex with L-menthol and cinnamaldehyde, respectively. As is well known in the art, the inclusion complex is for controlled release of the active material complexed with the cyclodextrin.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have used a cyclodextrin inclusion complex with active material for Chen's active material because such complexes are well known in the art for

controlled release of the active material, and incorporation of the complex in Chen's film would provide an alternative to other forms of delivery of the complex, e.g., an alternative to pills or injections.

Proposed rejections relying on Bernstein:

8. Third Party Requester proposes that claims 1, 3, 4, 7, 9-12, 15-17, 19, 21-23, 75, 78, 81, 84, 87, 90, 96, 111, 114-116, 118-120, 177, 178, 183, 186 and 189 be rejected under 35 USC 102(b) as being anticipated by Bernstein.

9. Third Party Requester proposes that claims 6, 14, 18, 22, 102, 112, 121, 183 and 186 be rejected under 35 USC 103(a) as being obvious over the combination of Bernstein and Hijiya.

10. Third Party Requester proposes that claims 3, 6, 13, 17, 18, 20, 22, 23, 93, 102, 105, 106, 116, 117, 121 and 183 be rejected under 35 USC 103(a) as being obvious over the combination of Bernstein and Staab.

11. Third Party Requester proposes that claims 3, 6, 8, 93, 102, 105, 106, 116, 117, 183 and 186 be rejected under 35 USC 103(a) as being obvious over the combination of Bernstein and Fuchs.

12. Third Party Requester proposes that claims 5, 6 and 21 be rejected under 35 USC 103(a) as being obvious over the combination of Bernstein and Peh.

13. Third Party Requester proposes that claim 24 be rejected under 35 USC 103(a) as being obvious over the combination of Bernstein and Strobush.

14. Third Party Requester proposes that claims 1, 2, 122-126 and 129-131 be rejected under 35 USC 103(a) as being obvious over the combination of Bernstein and Le Person.

These seven proposed rejections, i.e., Nos. 8-14, based on Bernstein were proposed by Third Party Requester in the request and **are not adopted** for the reasons that follow.

Steps (b) and (c) of Claim 1 and its dependent claims require removing the polar solvent from the matrix with heat and/or radiation energy by exposing the matrix to a temperature greater than the degradation temperature of the therapeutic active composition; wherein the temperature of the matrix is 100°C or less during the step of removing said polar solvent from said matrix. Bernstein's film can contain biologically active agent, i.e., therapeutic active composition, and the biologically active agent can be, for example, proteins, nucleic acids, etc (see col. 4, lines 28-57). However, the only working example making a film in Bernstein is Example I at cols. 8-9, and Example I does not contain biologically active agent. The temperatures used in Example I for removing methylene chloride solvent are 30°C for 6 hours, 40°C for 3 days, and then at 50°C for 3 days (see col. 8, lines 55-60). While some proteins would normally degrade at these temperature, other wouldn't. See, for example, col. 12, lines 26-29 of the '588 patent which teach that glycoproteins will degrade if exposed to a temperature of 70°C for 30 minutes. In the only example where Bernstein uses a biologically active material that would normally degrade at a temperature of 100°C or less, i.e., Example VII at col. 12 which uses RNase-A and prepares microspheres, a temperature of -80°C and

lyophilization (freeze drying) are used (see col. 12, lines 9-22). Examples I and VII use the same polymer, i.e., PLGA (poly lactide-co-glycolide). Accordingly, a skilled artisan practicing Bernstein's invention would seek to avoid normal degradation temperatures when working with temperature sensitive biologically active materials such as proteins. None of Hijiya, Staab, Fuchs, Peh, Strobush or Le Person solves Bernstein's deficiency.

Proposed rejections relying on Hijiya:

15. Third Party Requester proposes that claims 1, 6, 10, 11, 14, 18, 22, 96, 102, 111, 112, 121, 183 and 186 be rejected under 35 USC 102(b) as being anticipated by Hijiya.

16. Third Party Requester proposes that claims 4, 7, 9, 12, 16, 17, 19, 75, 78, 81, 87, 90, 114, 115, 118-120, 177, 178 and 189 be rejected under 35 USC 103(a) as being obvious over the combination of Hijiya and Bernstein.

17. Third Party Requester proposes that claims 3, 13, 20, 22, 23, 93, 105, 106, 116 and 117 be rejected under 35 USC 103(a) as being obvious over the combination of Hijiya and Staab.

18. Third Party Requester proposes that claims 3, 4, 8, 93, 105, 106 and 116-118 be rejected under 35 USC 103(a) as being obvious over the combination of Hijiya and Fuchs.

19. Third Party Requester proposes that claim 21 be rejected under 35 USC 103(a) as being obvious over the combination of Hijiya and Peh.

20. Third Party Requester proposes that claim 24 be rejected under 35 USC 103(a) as being obvious over the combination of Hijiya and Strobush.

21. Third Party Requester proposes that claims 1, 2, 122-126 and 132 be rejected under 35 USC 103(a) as being obvious over the combination of Hijiya and Le Person.

22. Third Party Requester proposes that claims 129-131 be rejected under 35 USC 103(a) as being obvious over the combination of Hijiya, Le Person and Bernstein.

23. Third Party Requester proposes that claims 127 and 128 be rejected under 35 USC 103(a) as being obvious over the combination of Hijiya, Le Person and Staab.

These nine proposed rejections, i.e., Nos. 15-23, based on Hijiya were proposed by Third Party Requester in the request and **are not adopted** for the reasons that follow.

Steps (b) and (c) of Claim 1 and its dependent claims require removing the polar solvent from the matrix with heat and/or radiation energy by exposing the matrix to a temperature greater than the degradation temperature of the therapeutic active composition; wherein the temperature of the matrix is 100°C or less during the step of removing said polar solvent from said matrix. Hijiya produces a self-supporting glucan film by casting an aqueous glucan solution on the surface of a corona-treated endless heat-resistant plastic belt, drying the glucan solution thereon while heating, and releasing the film therefrom (see abstract). The drying can be at a temperature of about

40-100°C (see col. 3, lines 42-47). The glucan solution prior to drying can further contain "one or more ingredients, for example, flavor, coloring agent, seasoning, natural paste, cyclodextrin, protein, fat, vitamin, hormone, antigenic substance, antibiotics, biologically-active substance, virus, microorganism, spore, seed, lecithin, microcapsule and plasticizer, and then heat-dried to obtain the glucan film" (see col. 3, lines 27-34). Many of these materials are heat stable, and in fact, in the examples in Hijiya where the ingredient is present, such as Examples 3 to 5, the drying temperature would not be expected to degrade the ingredient in the example. For example, in Hijiya's Example 4, a drying temperature of 85°C would not be expected to degrade either L-menthol or β-cyclodextrin. While ingredients such as proteins are temperature sensitive, no examples are given, and, as noted at col. 12, lines 26-27 of the '588 patent, it is temperatures that approach 100°C that will generally cause degradation of proteins. Accordingly, the use of a drying temperature above the degradation temperature of Hijiya's ingredient is neither anticipated nor rendered obvious. None of Bernstein, Staab, Fuchs, Peh, Strobush or Le Person solves Hijiya's deficiency.

Proposed rejections relying on Peh:

24. Claims 25, 26, 30, 31, 46, 47, 50, 51, 55, 56, 71, 72, 76, 77, 79, 80, 82, 83, 85, 86, 97, 98, 133, 134, 136, 137, 155, 156, 158, 159, 184, 185, 187, 188, 192 and 193 are rejected under 35 U.S.C. 102(b) as anticipated by Peh.

The rejection of claims 25, 26, 31, 46, 47, 50, 51, 56, 71, 72, 76, 77, 79, 80, 82, 83, 85, 86, 97, 98, 133, 134, 136, 137, 155, 156, 158, 159, 184, 185, 187 and 188 was

proposed by Third Party Requester in the request and **is adopted** for the reasons that follow. While the rejection of claims 30, 55, 192 and 193 was not proposed by Third Party Requester, these claims are included in rejection for the reasons that follow.

Peh teaches the preparation of polymeric films for the buccal delivery of a drug (see the title; abstract; and the Conclusion at p. 59). An aqueous solution containing hydroxypropyl methylcellulose (Methocel K15M), polyacrylic acid (carbopol 934P), and polyethylene glycol (PEG 400) is allowed to stir for 6 hours and stand overnight to remove all the air bubbles entrapped; the solution, i.e. the claimed matrix, is then cast onto a petri dish, i.e. a wet film is formed; and the water is then removed by drying in "the oven at 60°C until completely dry" so as to form the polymeric film (see the method of preparation on p. 54). 60°C is less than the boiling point of water, as per claims 25 and 192. Since Peh removes all entrapped air bubbles prior to heating in the oven, then Peh's heating step in the oven occurs "without forming air bubbles", as per claims 50 and 193. In fact, Peh's films were checked for imperfections, and samples with air bubbles, nicks or tears and having a mean thickness variation greater than 5% were excluded from analysis (see p. 54, the paragraph bridging the two columns). Consistent with Peh, the '588 patent teaches that "air bubble reduction can further be achieved by allowing the mix to stand for a sufficient time for bubbles to escape prior to drying the film." (see col. 9, line 66 to col. 10, line 2 of the '588 patent).

The hydroxypropyl methylcellulose used by Peh is "Methocel K15M" from Colorcon, UK (see p. 54, Materials section), and hydroxypropyl methylcellulose is well known to be food-grade (edible), medically safe, low cost and very stable. Furthermore,

it is the Examiner's position that Peh's polymeric film is "viscoelastic" as here claimed in view of the fact that it is prepared using the same materials disclosed in the '588 patent specification (see col. 15, lines 12-27 of the '588 patent). Indeed, even the polyacrylic acid and polyethylene glycol, which Peh mixes with the hydroxypropyl methylcellulose (see p. 54), are taught at col. 15, lines 12-27 of the '588 patent as suitable film-forming polymers. A viscoelastic film is formed in Peh as also evidenced by the elasticity, softness and bioadhesive strength measured and discussed by Peh (see Results at p. 53, col. 1; and Tables 1 and 2).

While an objective of Peh is to investigate the suitability of hydroxypropyl methylcellulose as a vehicle for the buccal delivery of drugs (see p. 54, col. 1, first paragraph), no drugs were used in Peh, but rather, Peh measured mechanical and bioadhesive properties of drug-free polymer films (see pp. 54-60). However, the Examiner at once envisages mixing the drug (i.e., instant therapeutic active composition) with the hydroxypropyl methylcellulose, polyacrylic acid, polyethylene glycol and water so as to prepare the material that will subsequently be dried to form the polymeric film for buccal delivery of the drug. Since Peh's process steps for forming its film are the same as in claims 192 and 193, the resulting film containing drug will have a substantially uniform content of the drug, as per claims 192 and 193.

With respect to claims 26 and 51, as noted above, Peh teaches drying the film in an oven at 60°C until completely dry (see the method of preparation on p. 54). Therefore, the matrix is necessarily less than 100°C.

With respect to claims 30 and 55, Peh teaches that its polymer solution in water was "allowed to stir for 6 h and stand overnight to remove all the air bubbles entrapped." (see the method of preparation on p. 54). It is the Examiner's position that this reads on "deaerating", particularly in view of the fact that the '588 patent specification deaerates by slow stirring for 45 or 30 minutes (see col. 33, lines 14-16; and col. 34, lines 6-10).

With respect to claims 31 and 56, the hydroxypropyl methylcellulose is water soluble, and, as noted above, Peh teaches forming an aqueous solution (see the method of preparation on p. 54).

With respect to claims 46 and 71, Peh is directed to buccal delivery of the drug (see the title; abstract; and the Conclusion at p. 59).

With respect to claims 47 and 72, Peh's film is "substantially uniform" in thickness as here claimed because Peh teaches that the thickness of each sample of the film was measured at five locations, and the mean thickness calculated (see p. 54, col. 2, lines 5-8). Samples with mean thickness variations of greater than 5% were excluded (see p. 54, col. 2, lines 8-11). Therefore, all samples with less than 5% mean thickness variation were kept.

With respect to claims 76, 77, 79, 80, 136, 137, 158 and 159, Peh removes water from the matrix by drying in "the oven at 60°C until completely dry" so as to form the polymeric film (see the method of preparation on p. 54). The "completely dry" taught by Peh anticipates the 10% or less polar solvent and 6% or less polar solvent as here claimed.

With respect to claims 82 and 83, administration through the buccal cavity as discussed in Peh, is administration through a mucosal surface.

With respect to claims 85 and 86, a film that is "capable of providing administration...through the buccal cavity" in Peh is "capable of providing administration ...through sublingual application" as here claimed. There is no teaching in the '588 patent to suggest that films capable of buccal and sublingual applications are materially different, or are made by different processes.

With respect to claims 97 and 98, Peh teaches forming a wet film from the matrix by casting it onto a petri dish (see the method of preparation on p. 54).

With respect to claims 133, 134, 155 and 156, Peh removes the water from the matrix by drying in "the oven at 60°C until completely dry" (see the method of preparation on p. 54). An oven that uses heat necessarily has hot air currents, as per claim 134.

With respect to claims 184 and 185, as discussed above, Peh discloses edible polymers, e.g., hydroxypropyl methylcellulose, a drug and water. Hydroxypropyl methylcellulose is well known to be food-grade, medically safe, low cost, and very stable. The drug is for buccal delivery as disclosed in the title and throughout Peh, and so would necessarily be ingestible, and water is ingestible.

With respect to claims 187 and 188, Peh teaches that its films were administered to ten healthy adult volunteers and the volunteers were asked to record the residence time of the film on the buccal mucosa in the oral cavity (see p. 55, col. 2, lines 28-32).

25. Claims 27, 52, 134, 135, 144-148, 156-159 and 166-170 are rejected under 35 U.S.C. 103(a) as being unpatentable over Peh as applied to claims 25, 26, 30, 31, 46, 47, 50, 51, 55, 56, 71, 72, 76, 77, 79, 80, 82, 83, 85, 86, 97, 98, 133, 134, 136, 137, 155, 156, 158, 159, 184, 185, 187, 188, 192 and 193 above, and further in combination with Le Person.

This rejection was proposed by Third Party Requester in the request and **is adopted** for the reasons that follow.

Peh, as relied upon for the reasons stated above, teaches the limitations of claims 27, 52, 134, 135, 144-148, 156-159 and 166-170 the differences being that Peh does not specifically teach removing the water from the matrix in less than about 10 minutes or the use of radiation energy instead of oven heating to remove the water. Furthermore, with respect to claims 134 and 156, to the extent that Peh does not teach or render obvious hot air currents during the drying, then such is rendered obvious by the combination of Peh and Le Person.

Le Person compares the drying of pharmaceutical wet films comprising polymer, a mixture of solvents and an active material, by convection, conduction and infrared radiation (see p. 258, first sentence of § 2.1, Table 1, and first sentence of § 2.2). Le Person teaches that "[a]fter preparation, the coating mixture is spread on a web, and submitted to drying in a tunnel or an oven", and that "[f]requently, impinging jets and Infra Red Radiation accomplish the work in a short drying time (100 s as an order of magnitude)." (see p. 257, col. 1). Water is identified as the major solvent (38 wt.% based on the wet composition) on p. 260, Table 1, i.e., Le Person discloses removing

polar solvent with heat and/or radiation energy. Le Person teaches that in 10 minutes, 99% of the initial water from a 100 μm thick coating is evaporated using a short infrared drying process (see § 3.1 at pp. 260-261, in particular Fig. 5). The 10 minutes renders obvious the instantly claimed "less than about 10 minutes". Le Person teaches that the initial drying velocity with infrared is about twice the velocity with other heating modes and that "[b]etween conduction and SIR [short infrared] the latter one is far more preferable." (see p. 258, col. 2, last paragraph). Figure 2 on p. 259 of Le Person shows that combined convection plus medium infrared drying is just as fast and complete as short infrared, and that conduction and convection alone are comparable. Heat convection uses "hot air currents", as is well known.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have dried Peh's film using short infrared drying, or combined convection and medium infrared drying instead of oven drying because these are known, alternative drying techniques in the art, as shown by Le Person. As noted above, Le Person teaches that Infra Red Radiation accomplishes the work in a short drying time (100 s as an order of magnitude) and in 10 minutes, 99% of the initial water from a 100 μm thick coating is evaporated using a short infrared drying process; short infrared drying is preferred; and Le Person shows that combined convection plus medium infrared drying is just as fast and complete as short infrared drying, and that conduction and convection alone are comparable.

26. Claims 28, 36, 38, 42, 43, 45, 47, 48, 53, 61, 63, 67, 68, 70, 72, 73, 94, 95, 103, 104, 107-110, 138, 139, 160, 161, 192 and 193 are rejected under 35 U.S.C. 103(a) as being unpatentable over Peh as applied to claims 25, 26, 30, 31, 46, 47, 50, 51, 55, 56, 71, 72, 76, 77, 79, 80, 82, 83, 85, 86, 97, 98, 133, 134, 136, 137, 155, 156, 158, 159, 184, 185, 187, 188, 192 and 193 above, and further in combination with Staab.

The rejection of claims 28, 36, 38, 43, 45, 47, 48, 53, 61, 63, 68, 70, 72, 73, 94, 95, 103, 104, 107-110, 138, 139, 160 and 161 was proposed by Third Party Requester in the request and **is adopted** for the reasons that follow. While the rejection of claims 42, 67, 192 and 193 was not proposed by Third Party Requester, these claims are included in the rejection for the reasons that follow.

Peh, as relied upon for the reasons stated above, teaches the limitations of claims 28, 36, 38, 43, 45, 47, 48, 53, 61, 63, 68, 70, 72, 73, 94, 95, 103, 104, 107-110, 138, 139, 160, 161, 192 and 193 other than the differences discussed below.

With respect to claims 28, 53, 94, 95, 138, 139, 160 and 161, Peh does not specifically teach that its film has a variation of active content of less than 10% per film unit, or forming a plurality of individual dosage units of substantially the same size. With respect to claims 45 and 70, Peh does not specifically teach that its method of preparation prevents substantial aggregation of the drug. With respect to claims 192 and 193, to the extent that a "substantially uniform" content of therapeutic active composition per unit of film is taken to mean some amount of variance, then this requirement is rendered obvious by the combination of Peh and Staab.

Staab teaches films made of dissolvable polymer material and/or complex carbohydrate material which are food grade materials, wherein the films also contain an agent such as a drug or medication (see abstract). Staab teaches that "[t]he agent material is evenly distributed throughout the film, so as the film slowly dissolves, it releases the agent material in the proper dosage ...." (see col. 5, line 68 through col. 6, line 3). Staab also discloses that "[t]he device of the invention thus is composed of a biologically compatible material that has been blended homogeneously" with the drug (see col. 6, lines 6-10). The disclosure of a film with active material "evenly distributed throughout" meets the instantly claimed limitation of a variation of less than 10% and renders obvious the prevention of substantial aggregation of the active composition. Further, Staab teaches forming a plurality of individual dosing units of substantially the same size (see Figs. 1-4 and col. 11, lines 12-18).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified Peh's film so that the active material, e.g., drug, is evenly distributed throughout the film, as taught by Staab, so as to ensure the same and consistent dispensing of a predictable active material to patients. Furthermore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have prepared Peh's film as a plurality of same size dosage units, as in Staab, for a variety of commercially important reasons, including safety.

With respect to claims 47 and 72, to the extent that Peh does not anticipate that its film has "substantially uniform thickness", then such is rendered obvious by the

combination of Peh and Staab. With respect to claims 103 and 104, Peh does not specifically teach that its wet film is in the form of a sheet.

Staab teaches that "[a]t the casting area, the mixture is poured onto the surface of a continuous stainless steel casting belt (4 feet wide) and spread to a constant 3 mil thickness." (*see,* col. 11, lines 61-63). Thus, the wet films of Staab are in the form of a sheet and the films of Staab are of "substantially uniform thickness."

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have prepared Peh's film so that it has a uniform thickness, as in Staab, so as to ensure the safe and consistent dispensing of a predictable amount of active to patients, and to have a uniform commercial product for ease of manufacture and packaging, and for patient acceptance and trust. Additionally, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have prepared Peh's wet film in the form of a sheet, as in Staab, so as to scale up the process to produce large quantities of film for commercial manufacture.

With respect to claims 48 and 73, Peh does not specifically teach that its film has substantially uniform mass to volume ratio of components.

Staab further describes in its general methods of making films that the desired agent materials are dissolved in a base polymer material, e.g., hydroxypropyl methylcellulose, with additives in a premix tank, then spread evenly and dried (see col. 10, line 66 - col. 11, line 5). Since, as discussed above, the active agent is blended homogeneously in the finished product, then all the other components are also blended

homogeneously since they are blended in the same step. Staab, therefore, discloses a film having a substantially uniform mass to volume ratio of components as here claimed.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have prepared Peh's film so that it has substantially uniform mass to volume ratio of components, as in Staab, so as to ensure safe and consistent dispensing of a predictable amount of active to patient.

With respect to claims 42 and 67, and their dependent claims 108 and 110, Peh does not specifically teach forming a master batch premix comprising the polymer and water, and directing the premix and drug to a mixer. As noted above, Chen exemplifies preparation of its film without the drug, and stirs (mixes) the polymer and water (see p. 54).

Staab further teaches forming a premix including polymer and water at a first temperature and then transferring to another vessel of a cooler temperature, and then stirring in heat sensitive ingredients (see col. 7, lines 37-48). Pharmaceuticals and other agents may be heat sensitive (see col. 7, lines 48-51). Accordingly, one skilled in the art would have been motivated to use a premix to allow the addition of the active material after the other ingredients are well mixed, since the active material, e.g. drug, is usually the most expensive component.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have prepared Peh's film by first forming a premix of the polymers and water in one vessel, and then transferring the premix to another vessel of

a cooler temperature, and then stirring in heat sensitive ingredients, e.g. a drug, as in Staab, so as to protect the drug, which is usually the most expensive component.

With respect to claims 36 and 61, Peh does not specifically teach that its "drug" can comprise a hormone. With respect to claims 38 and 63, Peh does not specifically teach that its "drug" can comprise immunoglobin. With respect to claims 107-110, Peh does not specifically teach that its drug includes a contraceptive. With respect to claims 43 and 68, Peh does not specifically teach that its matrix can further contain a taste-masking agent.

As noted above, Staab's films can contain an agent such as a drug or medication (see abstract). The agent can be estrogenic and progestational (see col. 3, lines 37-45), e.g., hormones (col. 6, line 68), and estrogen and progestin are present in most oral contraceptives, as is well known. The agent can also be, for example, monoclonal antibodies (col. 6, lines 49-53), which renders obvious immunoglobin. Staab further teaches that its film can contain a flavorant (col. 3, lines 46-47) to provide a more acceptable product for consumers.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the film of Peh so that the "drug" is a hormone, estrogen, progestin or immunoglobulin, as taught by Staab, because buccal delivery of such materials by film as in Peh presents an attractive alternative to conventional forms of delivery such as pill, cream or injection.

Additionally, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have included a flavorant in Peh's matrix so as to make the final film product more acceptable to consumers, as taught by Staab.

27. Claims 27, 30, 33, 40, 43, 52, 55, 58, 65, 68, 85, 86, 100, 101, 134, 143, 156, 165, 192 and 193 are rejected under 35 U.S.C. 103(a) as being unpatentable over Peh as applied to claims 25, 26, 30, 31, 46, 47, 50, 51, 55, 56, 71, 72, 76, 77, 79, 80, 82, 83, 85, 86, 97, 98, 133, 134, 136, 137, 155, 156, 158, 159, 184, 185, 187, 188, 192 and 193 above, and further in combination with Chen.

The rejection of claims 27, 30, 33, 40, 43, 52, 55, 58, 68, 85, 86, 100, 101, 134, 143, 156 and 165 was proposed by Third Party Requester in the request and **is adopted** for the reasons that follow. The rejection of claims 192 and 193 was proposed by Third Party Requester on p. 46 of the Comments filed 02/09/11 and **is adopted** for the reasons that follow. While the rejection of claim 65 was not proposed by Third Party Requester, this claim is included in the rejection for the reasons that follow.

Peh, as relied upon for the reasons stated above, teaches the limitations of claims 27, 30, 33, 40, 43, 52, 55, 58, 68, 85, 86, 100, 101, 134, 143, 156, 165, 192 and 193 other than the differences discussed below.

With respect to claims 27 and 52, Peh does not specifically teach that drying of its matrix in the oven, i.e., removal of the water, occurs in less than about 10 minutes. With respect to claims 134 and 156, to the extent it can be argued that Peh's oven for

drying the matrix does not provide hot air currents, then such is rendered obvious by the combination of Peh and Chen.

Chen teaches a dosage unit including a water-soluble hydrocolloid, mucosal surface-coat-forming film, such film including an effective dose of an active agent (see p. 3, lines 30-32). In Example 5-8, Chen prepares hydroxypropyl methylcellulose based quick dissolving intraoral films containing therapeutic agents (see p. 1, lines 5-6; p. 3, lines 13-36; p. 20, lines 17-20; Table 5). In particular, the films in Examples 5-8 contain a therapeutic agent, e.g., nicotine, hydromorphone, oxybutynin or estradiol; an edible polymer, i.e., hydroxypropyl methylcellulose (HPMC); and a polar solvent, i.e., water (see Table 5). In the method of preparation of the films of Examples 5-8, the HPMC (i.e., hydrocolloid) is dissolved in water under agitated mixing to form a uniform and viscous solution and the additional ingredients are then added under agitated mixing until they are uniformly dispersed or dissolved in the hydrocolloid (see p. 14, line 22 to p. 15, line 3; and p. 17, lines 6-19). The resultant mixture is degassed in a vacuum chamber until trapped air bubbles are removed and then coated on the non-siliconized side of a polyester film at a wet thickness of 10 mil and dried in a hot air circulating oven at 50°C for 9 minutes (see p. 17, lines 13-15). In general, Chen teaches that the drying is done at a temperature of 40-100°C so as to avoid destabilizing the agents contained within the formulation (see p. 15, lines 24-29).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified Peh's process as to remove the water in the polymer solution in, for example, 9 minutes using a hot air circulating oven as in Chen,

so as to provide for efficient, rapid and controlled dying of the matrix in a short period of time.

With respect to claims 30 and 55, to the extent that it can be argued that Peh's teaching of stirring its polymer solution for 6 hours and letting it stand overnight to remove all the air bubbles entrapped is not "aerating" as here claimed, then such is rendered obvious by the combination of Peh and Chen. Chen further teaches its matrix was degassed in a vacuum chamber prior to forming a film "until trapped air bubbles were removed." (see p. 17, lines 11-13).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified Peh's process so as to deaerate the matrix, as in Chen, in order to obtain a more uniform product. As noted on p. 54 of Peh, samples containing air bubbles, nicks or tears and having mean thickness variation of greater than 5% are excluded from Peh's analysis.

With respect to claims 33, 40, 58 and 65, Peh does not specifically teach that its "drug" can be insulin or a peptide.

Chen further teaches that the active agent in its intraoral film can be a therapeutic agent such as insulin or peptide (see p. 10, line 23 to p. 11, line 4).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have used insulin or peptide as the drug in Peh's film for buccal delivery because insulin and peptide can be delivered orally by film, as taught by Chen, and so as to provide a very attractive alternative to the use of, for example, needles/injection or pills.

With respect to claims 43, 68, 143 and 165, Peh does not specifically teach that its matrix further comprises at least one taste-masking agent.

Chen further teaches the use of a taste-masking agent (see p. 10, lines 7-8).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have further included a taste-masking agent in Peh's matrix because a taste-masking agent is a conventional ingredient in the art as shown by Chen, and so as to provide a more commercially attractive, better tasting product.

With respect to claims 85 and 86, to the extent it can be argued that Peh does not anticipate that its film "is capable of providing administration of said active composition to an individual through sublingual application", then such is rendered obvious by the combination of Peh and Chen.

Chen teaches that its films containing active agent can be used for oral delivery, wherein the films are applied on buccal (as in Peh) or sublingual surfaces (see p. 8, lines 8-10).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to administer the films of Peh sublingually in view of Peh's disclosure that administration of the films bucally is appropriate, and further in view of Chen explicitly teaching this embodiment. Sublingual administration of the film of Peh is merely a simple substitution of one known mode of mucosal delivery for another.

With respect to claims 100 and 101, Peh does not specifically teach forming its wet film from the matrix by extruding the matrix. Peh exemplifies casting the matrix to form the wet film (see the method of preparation on p. 54).

Chen further teaches the alternative use of casting and extrusion for forming its film (see p. 15, lines 13-18). In fact, the casting method shown in Fig. 2 of Chen (see also p. 15, lines 13-14) extrudes the wet matrix through a "coating slot" onto a backing belt.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified Peh's process so as to include extrusion to form Peh's wet film because extrusion and casting are well known methods in the art for forming a film, and Chen's casting method uses extrusion, as shown by Chen.

With respect to claims 192 and 193, to the extent that a "substantially uniform" content of therapeutic active composition per unit of film is taken to mean some amount of variance, the this requirement is rendered obvious by the combination of Peh and Chen for the reasons that follow. The desirability of preparing films that are as close to the same as possible, including drug content, is well known in the art. As noted above, Chen's coating solution is uniform, and, as seen in Table 4 on p. 20, the film prepared in Chen's Example 1 has a weight of 0.028 $\pm$ 0.001 g/dosage film, a thickness of 2.1 $\pm$ 0.12 mil, and a density of 1.0485 $\pm$ 0.009 g/cm^2, and a water content of 1.7 $\pm$ 0.24%.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have prepared Peh's films so that they are as close to the same as possible because such is desired in the art, as shown by Chen, and so as to ensure the same and consistent dispensing of a predictable active material to patients.

28. Claims 49 and 74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Peh as applied to claims 25, 26, 30, 31, 46, 47, 50, 51, 55, 56, 71, 72, 76, 77, 79, 80, 82, 83, 85, 86, 97, 98, 133, 134, 136, 137, 155, 156, 158, 159, 184, 185, 187, 188, 192 and 193 above, and further in combination with Strobush.

This rejection was proposed by Third Party Requester in the request and **is adopted** for the reasons that follow.

Peh, as relied upon for the reasons stated above, teaches the limitations of claims 49 and 74, the difference being that Peh does not specifically teach that air flow in its oven during the step of drying the wet film does not overcome the inherent viscosity of the wet film.

The '588 patent provides the following discussion relating to this limitation at col. 11, lines 21-33:

> Any top fluid flow, such as air, also must not overcome the inherent viscosity of the film-forming composition. In other words, the top air flow cannot break, distort or otherwise physically disturb the surface of the composition. Moreover, air velocities are desirably below the yield values of the film, i.e., below any force level that can move the liquids in the film-forming compositions. For thin or low viscosity compositions, low air velocity must be used. For thick or high viscosity compositions, higher air velocities may be used.

Strobush teaches methods "for evaporating a coating solvent from a coating of a first substrate surface on a substrate and minimizing the formation of mottle as the coating solvent is evaporating." (See Summary of the Invention, col. 6, lines 28-32). Strobush teaches that mottle is an irregular pattern or non-uniform density defect that appears blotchy when viewed (see col. 1, lines 59-60). Strobush teaches that "[m]ottle is usually caused by air movement over the coating before it enters the dryer, as it

enters the dryer, or in the dryer." (See col. 1, line 67 to col. 2, line 3). In other words, mottle is the result of overcoming the inherent viscosity of the wet film. Strobush teaches a number of methods and apparatus for minimizing the formation of mottle (see e.g., col. 6, line 28 - col. 7, line 33). Strobush discloses that its methods can be applied to dry any mottle-susceptible material (see e.g., col. 16, lines 62-64).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified Peh's process so that any air flow in the oven during the step of drying the wet film does not overcome the inherent viscosity of the wet film so as to avoid the formation of mottle, i.e., avoid the formation of a defective, irregular or non-uniform product, as taught by Strobush.

29. Claims 29, 32, 34-37, 40-42, 44, 54, 57, 59-62, 65-67, 69, 88, 89, 91, 92, 140-142, 162-164, 179-182, 190 and 191 are rejected under 35 U.S.C. 103(a) as being unpatentable over Peh as applied to claims 25, 26, 30, 31, 46, 47, 50, 51, 55, 56, 71, 72, 76, 77, 79, 80, 82, 83, 85, 86, 97, 98, 133, 134, 136, 137, 155, 156, 158, 159, 184, 185, 187, 188, 192 and 193 above, and further in combination with Bernstein.

This rejection was proposed by Third Party Requester in the request and **is adopted** for the reasons that follow.

Bernstein teaches the preparation of a film for the modulated release of a biologically active agent (see abstract; col. 1, lines 29-43; and Example I). In other words, the biologically active material is in controlled release form as per instant claims 44, 69, 91 and 92 (see also col. 1, line 30 of Bernstein). In particular, Bernstein teaches

that "[t]he composition comprises a biocompatible polymeric matrix, a biologically active agent which is dispersed within the polymeric matrix, and a metal cation component which is separately dispersed within the polymeric matrix, whereby the metal cation component modulates the release of the biologically active agent from the polymeric matrix." (see col. 1, lines 37-43). An example of the biocompatible polymer used to form the film is poly(lactide-co-glycolide), i.e., "PLGA", which is an edible polymer; and examples of the biologically active agent include erythropoietin, human growth hormone, RNase-A, interferons, interleukins, tumor necrosis factor, erythropoietin and nucleases, as per instant claims 34-37, 40, 41, 59-62, 65 and 66 (see col. 3, line 56 to col. 4, line 58; col. 6, lines 27-29; and Examples I and VII). It is noted that interferons, interleukins and tumor necrosis factor are cytokines; human growth hormone is a peptide; and erythropoietin is a glycoprotein and hormone. The biologically active agent can be in the form of particles, as per claims 190 and 191 (see col. 4, lines 39-41 and col. 6, lines 9-12).

In Bernstein's method of preparing the film, the biocompatible polymer is dissolved in a polar solvent, i.e., a master batch premix is formed as per claims 42, 67, 142 and 164, and the biologically active agent and metal cation can then be added to the polymer solution (see col. 5, lines 36-42, col. 6, lines 6-12). Two polar solvents such as methylene chloride and acetone can be used, as per instant claims 29, 54, 140 and 162, wherein the polymer is dissolved in the methylene chloride, and the metal cation is suspended or dissolved in the second solvent, i.e., the acetone (see col. 5, lines 44-62). The mixture of polymer, biologically active agent and metal cation, i.e., the

instantly recited matrix, can be in the form of a suspension or dispersion, as per claims 32, 57, 141, 163 and 179-182 (see col. 7, lines 3-13; and col. 8, lines 47-60).

With respect to claims 88 and 89, which require that the film is capable of providing administration of the active composition to an individual by administration within the body of the individual during surgery, Bernstein teaches that "[t]he composition of the invention can be administered to a human, or other animal, by injection, and/or implantation, subcutaneously, intramuscularly, intraperitoneally, intradermally, intravenously, intraarterially or intrathecally; by administration to mucosal membranes, such as intranasally, or by means of a suppository, or by in situ delivery..." (see col. 7, line 66 through col. 8, line 5). Thus, the films of Bernstein are clearly "capable of" being administered during surgery, whether orally or at the site of the surgery.

With respect to claims 29, 32, 34-37, 40-42, 44, 88, 91, 140-142, 179, 180, and 190, which require removing the polar solvent from the matrix with heat and/or radiation energy by heating to a temperature that is less than the boiling point of the at least one polar solvent so as to form a viscoelastic film, it is noted that in preparing the films of Bernstein's Example I, methylene chloride is used as the solvent and the films are transferred to a vacuum oven and dried at 30°C for 6 hours, 40°C for 3 days, and then at 50°C for 3 days (see col. 8, lines 55-60). Methylene chloride has a boiling point of 39.6°C, and thus the heating at 30°C for 6 hours is at a temperature less than methylene chloride's boiling point, as here claimed. It is the Examiner's position that Bernstein's film product, after all the heating steps are completed, is a viscoelastic film.

In fact, the poly(lactide-co-glycolide) polymer used in Bernstein's Example I (see also col. 4, lines 21-22) is also taught as a suitable polymer at col. 16, line 7, of the '588 patent. However, Bernstein does not specifically teach that its heating step below the boiling point results in a viscoelastic film.

It is well known in the art that heating below the boiling point can be used to remove solvent and obtain a viscoelastic film. A skilled artisan would have recognized that the results-effective variables for removal of the solvent are temperature, time and pressure. For example, as discussed above, Peh's film is viscoelastic; Peh uses water as a solvent in preparing the film, and dries the film at 60°C until completely dry, i.e., well below the boiling point of water (see the method of preparation section on p. 54).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified Bernstein's drying steps so that a viscoelastic film is obtained by heating below the boiling point of the methylene chloride solvent because it is known in the art that heating below the boiling point of a solvent can be used to remove the solvent and obtain a viscoelastic film, as shown by Peh; and determination of appropriate temperature, time and pressure for the removal of solvent is a matter of optimization of well-known results-effective variables.

With respect to claims 54, 57, 59-62, 65-67, 69, 89, 92, 162-164, 181, 182, and 191, Bernstein does not specifically teach forming its film without forming bubbles.

Peh, as discussed above, teaches stirring for 6 hours and letting its polymer-water solution stand overnight to remove all entrapped air bubbles prior to heating in the oven (see the method of preparation on p. 54), and thus, Peh's heating step in the oven

occurs without forming air bubbles. In fact, Peh's films were checked for imperfections, and samples with air bubbles, nicks or tears and having a mean thickness variation greater than 5% were excluded from analysis (see p. 54, the paragraph bridging the two columns). Consistent with Peh, the '588 patent teaches that "air bubble reduction can further be achieved by allowing the mix to stand for a sufficient time for bubbles to escape prior to drying the film." (see col. 9, line 66 to col. 10, line 2).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have removed Bernstein's solvent without forming air bubbles, as in Peh, so as to help minimize defects in the films and prepare uniform films.

30. Claims 39 and 64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Peh as applied to claims 25, 26, 30, 31, 46, 47, 50, 51, 55, 56, 71, 72, 76, 77, 79, 80, 82, 83, 85, 86, 97, 98, 133, 134, 136, 137, 155, 156, 158, 159, 184, 185, 187, 188, 192 and 193 above, and further in combination with Hijiya.

This rejection was proposed by Third Party Requester in the request and **is adopted** for the reasons that follow.

Peh, as relied upon for the reasons stated above, does not specifically teach that its drug contains a polysaccharide.

Hijiya teaches a process of producing a glucan film of self-supporting thickness (see col. 2, lines 13-3). An aqueous glucan solution is used, and the solution can further contain an ingredient such as cyclodextrin, protein, hormone, antigenic substance, antibiotic, biologically active substance, etc (see col. 3, lines 5-34).

Cyclodextrins can be oligosaccharides, like those taught in Examples 4 and 5 of Hijiya, but can also be polysaccharides and have been well characterized as having up to 39 saccharide units, as is well known in the art. In Hijiya's Examples 4 and 5, the cyclodextrin is part of an inclusion complex, i.e., with L-menthol and cinnamaldehyde, respectively. As is well known in the art, the inclusion complex is for controlled release of the active material complexed with the cyclodextrin.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have used a cyclodextrin inclusion complex for Peh's drug because such complexes are well known in the art for controlled release of the drug, and incorporation of the complex in the Peh's film would provide an alternative to other forms of delivery of the complex, e.g., an alternative to pills or injections.

31. Claims 149-154 and 171-176 are rejected under 35 U.S.C. 103(a) as being unpatentable over Peh in combination with Le Person as applied to claims 27, 52, 134, 135, 144-148, 156-159 and 166-170 above, and further in combination with Staab or Bernstein.

Peh in combination with Le Person, as relied upon for the reasons stated above, teaches the limitations of claims 149, 150, 154, 171, 172 and 176, other than the differences discussed below.

With respect to claims 149, 150, 171 and 172, Peh and Le Person do not specifically teach that the film has a variation of active content of less than 10% per unit film, or preparing a plurality of individual dosage units of substantially the same size.

Staab teaches films made of dissolvable polymer material and/or complex carbohydrate material which are food grade materials, wherein the films also contain an agent such as a drug or medication (see abstract). Staab teaches that "[t]he agent material is evenly distributed throughout the film, so as the film slowly dissolves, it releases the agent material in the proper dosage ...." (see col. 5, line 68 through col. 6, line 3). Staab also discloses that "[t]he device of the invention thus is composed of a biologically compatible material that has been blended homogeneously" with the drug (see col. 6, lines 6-10). The disclosure of a film with active material "evenly distributed throughout" meets the instantly claimed limitation of a variation of less than 10%. Further, Staab teaches forming a plurality of individual dosing units of substantially the same size (see Figs. 1-4 and col. 11, lines 12-18).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the film of Peh and Le Person so that the active material, e.g., drug, is evenly distributed throughout the film, as taught by Staab, so as to ensure the same and consistent dispensing of a predictable amount of active material to patients. Furthermore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have prepared the film of Peh and Le Person as a plurality of same size dosage units, as in Staab, for a variety of commercially important reasons, including safety.

With respect to claims 154 and 176, Peh and Le Person do not specifically teach that the matrix comprises at least one taste-masking agent.

Staab further teaches that its film can contain a flavorant (col. 3, lines 46-47) to provide a more acceptable product for consumers.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have included a flavorant in the matrix of Peh and Le Person so as to make the final film product more acceptable to consumers, as taught by Staab.

With respect to claims 151-153 and 173-175, Bernstein teaches the preparation of a film for the modulated release of a biologically active agent (see abstract; col. 1, lines 29-43; and Example I). In particular, Bernstein teaches that "[t]he composition comprises a biocompatible polymeric matrix, a biologically active agent which is dispersed within the polymeric matrix, and a metal cation component which is separately dispersed within the polymeric matrix, whereby the metal cation component modulates the release of the biologically active agent from the polymeric matrix." (see col. 1, lines 37-43). An example of the biocompatible polymer used to form the film is poly(lactide-co-glycolide), i.e., "PLGA", which is an edible polymer; and examples of the biologically active agent include erythropoietin, human growth hormone, RNase-A, interferons, interleukins, tumor necrosis factor, erythropoietin and nucleases (see col. 3, line 56 to col. 4, line 58; col. 6, lines 27-29; and Examples I and VII).

In Bernstein's method of preparing the film, the biocompatible polymer is dissolved in a polar solvent, i.e., a master batch premix is formed as per claims 153 and 175, and the biologically active agent and metal cation can then be added to the polymer solution (see col. 5, lines 36-42, col. 6, lines 6-12). Two polar solvents such as methylene chloride and acetone can be used, as per instant claims 151 and 173,

wherein the polymer is dissolved in the methylene chloride, and the metal cation is suspended or dissolved in the second solvent, i.e., the acetone (see col. 5, lines 44-62). The mixture of polymer, biologically active agent and metal cation, i.e., the instantly recited matrix, can be in the form of a suspension or dispersion, as per claims 152 and 174 (see col. 7, lines 3-13; and col. 8, lines 47-60).

It is further noted that in preparing the films of Bernstein's Example I, methylene chloride is used as the solvent and the films are transferred to a vacuum oven and dried at 30°C for 6 hours, 40°C for 3 days, and then at 50°C for 3 days (see col. 8, lines 55-60). Methylene chloride has a boiling point of 39.6°C, and thus the heating at 30°C for 6 hours is at a temperature less than methylene chloride's boiling point, as here claimed. It is the Examiner's position that Bernstein's film product, after all the heating steps are completed, is viscoelastic, as per claims 173-175. In fact, the poly(lactide-co-glycolide) polymer used in Bernstein's Example I (see also col. 4, lines 21-22) is also taught as a suitable polymer at col. 16, line 7, of the '588 patent. However, with respect to claims 151-153, Bernstein does not specifically teach that its heating step below the boiling point results in a viscoelastic film.

It is well known in the art that heating below the boiling point can be used to remove solvent and obtain a viscoelastic film. A skilled artisan would have recognized that the results-effective variables for removal of the solvent are temperature, time and pressure. For example, as discussed above, Peh's film is viscoelastic; Peh uses water as a solvent in preparing the film, and dries the film at 60°C until completely dry, i.e., well below the boiling point of water (see the method of preparation section on p. 54).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified Bernstein's drying steps so that a viscoelastic film is obtained by heating below the boiling point of the methylene chloride solvent because it is known in the art that heating below the boiling point of a solvent can be used to remove the solvent and obtain a viscoelastic film, as shown by Peh; and determination of appropriate temperature, time and pressure for the removal of solvent is a matter of optimization of well-known results-effective variables.

With respect to claims 173-175, Bernstein does not specifically teach forming its film without forming bubbles.

Peh teaches stirring for 6 hours and letting its polymer-water solution stand overnight to remove all entrapped air bubbles prior to heating in the oven (see the method of preparation on p. 54), and thus, Peh's heating step in the oven occurs without forming air bubbles. In fact, Peh's films were checked for imperfections, and samples with air bubbles, nicks or tears and having a mean thickness variation greater than 5% were excluded from analysis (see p. 54, the paragraph bridging the two columns). Consistent with Peh, the '588 patent teaches that "air bubble reduction can further be achieved by allowing the mix to stand for a sufficient time for bubbles to escape prior to drying the film." (see col. 9, line 66 to col. 10, line 2).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have removed Bernstein's solvent without forming air bubbles, as in Peh, so as to help minimize defects in the films and prepare uniform films.

With respect to claims 151-153 and 173-175, Bernstein and Peh do not specifically teach using radiation energy to remove Bernstein's solvents.

Le Person is relied upon for the reasons stated above.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have dried Bernstein's film using short infrared drying, or combined convection and medium infrared drying, instead of oven drying, because these are known, alternative drying techniques in the art, as shown by Le Person.

Response to Arguments

Patent Owner's arguments filed January 10, 2012 have been fully considered but they are not persuasive.

The terms "Viscoelastic Solid" and "Substantially Uniform Distribution":

Patent Owner argues that "as defined in the applications as filed and present in the issued claims, a viscoelastic solid is one that has been controllably dried to lock its components into a substantially uniform distribution throughout the film while avoiding problems with conventional drying methods." (Remarks of 01/10/12, pp. 6 and 17).

Patent Owner's argument is unpersuasive. Nowhere does the '588 patent provide a special definition for the terms "viscoelastic" or "viscoelastic solid", and these terms do not require "substantially uniform distribution". As noted in ¶¶ 13-14 of Third Party Requester's Cohen Declaration, viscoelasticity is independent of particle aggregation, agglomeration, uniformity of active content or uniformity of components in a film sample; and there are many properties that can influence uniform content of

active in a coating, including but not limited to: the characteristics of the particle (e.g., size, shape, density, and solubility of active), the degree of dispersion in the solution preparation process, solvent properties, binder properties, drying conditions, particle stability, and thickness of the intended film. Accordingly, as noted in ¶ 9 of the Cohen Declaration, "[t]he standard definition of viscoelastic behavior is that it is a material that reflects the combined viscous and elastic responses, under mechanical stress, of materials which are intermediate between liquids and solids in character." Furthermore, as noted by Third Party Requester on p. 17 of the Comments filed 02/09/12, references to viscoelasticity in the '588 patent appear to adhere to this established definition in the art:

> The viscosity of the liquid phase is critical and is desirably modified by customizing the liquid composition to a viscoelastic non-Newtonian fluid with low yield stress values .... Formation of a viscoelastic or a highly structured fluid phase provides additional resistive forces to particle sedimentation. (Col. 8, lines 36-42).
>
> Compositions P-R show the effects of visco-elastic properties on the ability to coat the film composition mixture onto the substrate for film formation .... This product coated the substrate but would not stay level due to the change in the visco-elastic properties of the wet foam. (Col. 32, lines 59-61, and 65-67).
>
> The addition of hydrocolloids to the aqueous phase of the suspension increases viscosity, may produce viscoelasticity, and can impart stability depending on the type of hydrocolloid, its concentration and the particle composition, geometry, size and volume reaction. (Col. 8, lines 46-50).
>
> For viscoelastic fluid systems, a rheology that yields stable suspensions for extended time period, such as 24 hours, must be balanced with the requirements of high-speed film casting operations. (Col. 9, lines 3-6).

Patent Owner argues that "[c]ompositional uniformity means that the film product is substantially uniform throughout its entire volume, including at its top and bottom

surfaces and therebetween." (See p. 7 of the Remarks filed 01/10/11; and ¶ 24 of the Rounds Declaration).

This is unpersuasive. The term "compositional uniformity" is not present in any claim. Further, it is not clear how close to being uniform the product must be in order to be considered "substantially uniform". "Substantially uniform" is not defined in the '588 patent.

Arguments with respect to the rejections based on Chen:

Patent Owner argues the following on pp. 10-11 of the Remarks filed 01/10/12:

> Chen's drying process is so general and devoid of detail so as to provide no guidance other than that to dry, one places a film in a conventional hot air circulating oven at temperatures of from 40-100°C and leaves it for a period of time. (Rounds Dec. ¶10). As shown in the Patentee's actual photographs (Figures 9-16), drying in a hot air oven does not produce uniform films through the locking in of the active in a substantially uniform distribution throughout the viscoelastic film.

Citing the term "visco-elastic", Patent Owner further argues that Chen does not disclose a resulting film product that has any compositional uniformity (Remarks of 01/10/12, p. 17). In particular, citing the Rounds Declaration, Patent Owner argues the following at p. 18 of the Remarks filed 01/10/12:

> Chen simply explains that the coated film is dried "in a hot air circulating oven", but does not disclose the formation of and maintenance of a substantially uniform film. The use of a hot air circulating oven likely includes certain undesirable drying features, such as a high presence of air flowing over the surface(s) of the wet film product. (Rounds Dec. ¶15-16). As uneven air currents flow over the wet film surface, it can cause disruption of the fluid matrix and the components held therein, causing non-uniformity of the final, resulting product. (Rounds Dec. ¶16). In addition, use of non-controlled drying methods such as those in the present invention can lead to compositional non-uniformity, as

> explained above, due to the number of problems associated with conventional drying, as well as at Column 39, lines 21-40 of the Issued Patent. In fact, as explained in the Issued Patent, depending upon the drying methods used, various "hot spots" can form due to uneven air flow and temperatures, which destroy the compositional uniformity of the resulting product. (See Column 13, lines 13-23, as well as Figures 9-16 of the Issued Patent). Conventional drying methods, such as the use of general ovens, do not inherently provide compositionally uniform films. In fact, the Patentee has demonstrated quite the contrary occurs.

These arguments are unpersuasive. It is the drying process recited in the instant claims that is general and devoid of detail. Each of the independent claims recites three basic steps, i.e., mixing the polymer component, therapeutic active composition and polar solvent to form a matrix; forming a wet film from the matrix; and removing the polymer solvent. These three steps encompass conventional film preparation in the art. They are the steps that Chen performs to prepare its films (see p. 17, lines 6-19). In particular, Chen's hydoxypropyl methyl cellulose (HPMC i.e., hydrocolloid) is dissolved in water (polar solvent) under agitated mixing to form a uniform and viscous solution and the additional ingredients are then added under agitated mixing until they are uniformly dispersed or dissolved in the hydrocolloid (see p. 14, line 22 to p. 15, line 3; and p. 17, lines 6-19). The resultant mixture, i.e. the instant matrix, is degassed in a vacuum chamber until trapped air bubbles are removed, and then coated on the non-siliconized side of a polyester film at a wet thickness of 10 mil and dried in a hot air circulating oven (see p. 17, lines 13-15). Chen's removes the water from its wet film by exposing the wet film to a temperature of 40-100°C (p. 15, lines 24-29 and p. 17, lines 13-15), as per instant independent claims 1, 25 and 192; and, as noted above, Chen avoids the formation of bubbles (p. 17, lines 11-12), as per instant independent claims

50 and 193. In fact, Chen exemplifies drying at 50°C for 9 minutes, which is within the '588 patent's most desirable temperature range of about 80°C or less (col. 25, lines 42-44) and within the '588 patent's time range of about 10 minutes or fewer (col. 4, line 37).

As discussed above, the term "visco-elastic" does not require any degree of compositional uniformity. Chen's films are visco-elastic because they are flexible, stand alone, self-supporting films made using hydroxypropyl methylcellulose (see pp. 20-21), which is disclosed in the '588 patent as a suitable film-forming polymer (see col. 15, lines 12-17).

Furthermore, recitation of "substantially uniform content" of therapeutic active composition per unit of film in claims 1, 192 and 193 does not distinguish over Chen. In particular, Chen's coating solution is a homogeneous mixture (p. 17, lines 8-11); Chen uses the same basic process steps as here claimed (as noted above); and in Chen's Table 4 on p. 20, the films prepared by Chen in Example 1 have a weight of 0.028 $\pm$ 0.001 g/dosage film, a thickness of 2.1 $\pm$ 0.12 mil, and a density of 1.0485 $\pm$ 0.009 g/cm^2, and a water content of 1.7 $\pm$ 0.24%.

Patent Owner cites the Rounds Declaration and argues that "glossy" does not mean compositionally uniform; that "glossy" is referring to the bottom side of Chen's film which is in contact with the polyester film during drying, not the top side exposed to air; and that mottle is a surface defect, not a compositional uniformity defect (Remarks of 01/10/12, pp. 11-12 and 18-19). As noted above, the fact that Chen's films are glossy was cited in the rejection with respect to instant claims 49 and 74.

These arguments are unpersuasive. Chen does not distinguish between film sides when referring to its films as being glossy. Chen further teaches that is films are substantially transparent (p. 17, line 15), and as noted above, the films of Chen's Example 1 have a weight of 0.028 $\pm$ 0.001 g/dosage film, a thickness of 2.1 $\pm$ 0.12 mil, and a density of 1.0485 $\pm$ 0.009 g/cm^2, and a water content of 1.7 $\pm$ 0.24% (Table 4). In view of these teachings and the fact that Chen's wet films are viscous to begin with (p. 17, lines 6-8), the Examiner maintain that any air flow present during Chen's 9-minute drying step does not overcome the inherent viscosity of Chen's viscous wet film, as per instant claims 49 and 74. In fact, as seen schematically in Chen's Fig. 2, the air flow is less direct at the film surface at the beginning of the drying and becomes more direct as the film proceeds through the drying oven having an aeration controller.

Patent Owner argues the following at p. 12 of the Remarks filed 01/10/12:

> In fact, Chen's Figure 5 (Examples 5-8) clearly shows a lack of compositional uniformity of active. (Rounds Dec. ¶17). While statistics are not defined in the text, the error bars represent either high or low values, standard deviation or some measure of variation. Given that the compositions of Examples 5-8 are the same, except for the amount of active, it is reasonable to assume that the active is not uniformly present in the individual films due to the wide variation of release of active from the same film compositions. For example, with regard to the release of nicotine in the same film compositions, release reaches in excess of 100% with the upper error bar near 120%. Similarly, estradiol at 4 minutes released in ranges from about 40-60%. It is reasonable to conclude that a major reason for these release differences is that the amount of active differs in each film tested, despite the identical film-forming compositions. (Rounds Dec. ¶17).

This argument is unpersuasive for the reasons set forth by Third Party Requester at pp. 21-22 of the Comments filed 02/09/12, which are reproduced below:

The Patent Owner and its expert assert, incorrectly, that Chen's Figure 5 shows "a lack of compositional uniformity of active" in view of the "wide variation of release of [different] active[s]" (A&R, p. 12, lines 8-17; Rounds Decl. ¶ 17). The Patent Owner and its expert have misread this Figure, or relied upon an unsupported and inappropriately narrow construction, or both. First, there are no issued claims, amended claims, or new claims that recite a "uniform release rate of active." It would be clearly unreasonable to construe "substantially uniform content of active per unit of film" as requiring "uniform release rate of active." A reasonable interpretation of the claim language "substantially uniform content of active per unit of film" is that each dosage unit, for example, has substantially the same amount of active as another dosage unit. Therefore, at best, the most relevant measurement in Figure 5 is the total amount of active released by each dosage unit. At the last time noted, 10 minutes, all measurements of active appear approximately within ± 10% of 100 percent. There are many factors involved in release rate, some of which may account for the modest variation in percentage release. Although not a direct measurement, this Figure 5 evidences clear support that the films of Chen have substantial uniformity of content per dosage unit.

With respect to claim 1 and its dependent claims, which require the film be dried at a temperature greater than the degradation temperature of the therapeutic active composition, Patent Owner argues that Chen's teaching of drying at a temperature between 40-100°C so as to avoid destabilizing the agents contained within the formulation (p. 15, lines 24-29), and Chen's teaching that its active can be peptide active agents, polypeptide active agents, and proteins such as insulin, calcitonin, LHRH and the like (see p. 11, lines 4-5) amounts to selection from an infinite number of temperatures from which to choose an enormous number of actives (Remarks of 01/10/12, p. 20). Patent Owner cites cols. 12-13 of the '588 patent and argues that "the controlled manner of drying of the invention maintains not only the uniformity of the active of the film but also the activity of the materials in the film"; and argues that "[t]he present inventors have, in fact, discovered that the films may be exposed to such higher

heat and that the active(s) within the film remain(s) viable (Remarks of 01/10/12, p. 20). Patent Owner argues that they "discovered that the temperature within the film did not reach the higher external temperature which would have caused degradation of the active (Remarks of 01/10/12, p. 21). Patent Owner then argues the following at p. 21 of the Remarks of 01/10/12:

> Chen does not disclose exposing the film to a temperature above a degradation temperature of the active. Although Chen discloses the use of proteins and glycoproteins, Chen does not disclose their respective degradation temperatures or the temperature at which one dries a film with such components to maintain active potency and uniformity. In fact, the Issued Patent states (at column 12, lines 27-30) that glycoproteins may degrade at temperature of 70°C. Further, Examples CE and CF of the Issued Patent disclose drying films with proteins from bovine extract at temperatures of 60 and 80°C without degradation of the active. Chen's only disclosure is a general drying at from 40-100°C, but there is no disclosure or even a suggestion that the temperature is above the degradation temperature of an active. Moreover, destabilization may mean include [sic] interaction with other materials, including hydrolysis and oxidation, not degradation due to temperature.

These arguments are unpersuasive. Temperature is a well-known results-effective variable with respect to drying time as higher temperatures generally permit shorter drying times. It is also well-known in the art that proteins begin to degrade as temperatures approach 100°C. In fact, it is well-known that insulin, which is an active agent specifically taught by Chen at p. 11, line 4, begins to degrade at a temperature of 70°C. However, it is also common knowledge that the temperature to which a solvent-containing composition is exposed is higher than the internal temperature of the solvent-containing composition, when exposed for relatively short periods of time (see, for example, ¶ 15 of the Cohen Declaration). Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have optimized

Chen's drying step by using as high a drying temperature as possible within Chen's disclosed the range of 40-100°C without destabilizing the active agent because temperature is a results-effective variable with respect to active agent destabilization as taught by Chen; and so as to dry Chen's film as quickly as possible. Chen's exemplifies operating its hot air circulating oven at 50°C for 9 minutes (p. 17, lines 13-15), and a skilled artisan would expect that a higher temperature would permit even shorter drying times.

Chen's temperature range of 40-100°C is not an infinite number of temperatures from which to choose. Rather, it is a definite range that is either entirely within (anticipates) or closely overlaps with the '588 patent's teaching (col. 25, lines 42-44) of drying at a temperature of "about 100°C or less, desirably about 90°C or less, and most desirably about 80°C or less." Additionally, selection of active agents such as "peptide active agents, polypeptide active agents, proteins such as insulin, calcitonin, LHRH and the like" from the relatively short list of actives in the bridging pages 10 and 11 of Chen is anticipated or would have been obvious. For example, it would have been obvious to select insulin for the treatment of diabetes, or to select calcitonin for the treatment of hypercalcemia or osteoporosis.

Patent Owner's argument that "the controlled manner of drying of the invention maintains not only the uniformity of the active of the film but also the activity of the materials in the film", is unpersuasive because, as discussed above, Chen's manner of drying is essentially the same as recited in instant claim 1, which does not recite anything concerning control. In particular, Chen removes the water from its wet film

using heat by exposing the wet film to a temperature in the range of 40-100°C (see p. 15, lines 24-29). In fact, as seen in Chen's Fig. 2, Chen's drying is done in a drying oven have an aeration controller.

Even if there was a risk that the hot air in Chen's oven could degrade a protein such as insulin or calcitonin, then, in order to use as high an air temperature as possible so as to dry the wet film as quickly as possible, a skilled artisan would add a well-known protein heat stabilizer to the formulation. In the only examples of the '588 patent where a temperature above the degradation temperature is used, i.e., Examples CE and CF at col. 38, one of the most well-known protein heat stabilizers in the art, i.e., trehalose, is used. Chen teaches that stabilizers and preservatives can be present in its formulations (see p. 11, lines 23-31).

Even further, Patent Owner's argument that "destabilization may mean include [sic] interaction with other materials, including hydrolysis and oxidation, not degradation due to temperature" suggests that some degradation may occur at lower temperatures than those typical of heat degradation. As noted by Third Party Requester on p. 31 of the Comments filed 02/09/12, "[l]ogically, some degradation necessarily occurs to bovine extract [used in Examples CE-CF at col. 38 of the '588 patent] (or indeed other proteins and peptides) at temperatures even lower that 60°C, creating an even greater degree of homology between Chen's temperature range [of 40-100°C] and the claim limitation for bovine extract and other proteins."

With respect to claims 4, 29, 54, 118, 140 and 162, Patent Owner argues that "Chen does not actually teach using the mixture of polar solvents with an active, as acknowledged by the Examiner." (Remarks of 01/10/12, p. 22).

This is not persuasive. In the Office action mailed 11/10/11 and above, the Examiner notes that Chen exemplifies the use of a mixture of polar solvents, i.e., water and ethanol, in Example 2 (see Table 1 at p. 18), and that the film of Example 2 does not contain therapeutic active composition. However, as seen in the description of Table 1 at the top of p. 18, Example 2 is a formulation of a quick dissolving film using a hydrocolloid. Accordingly, the Examiner maintains that it would have been obvious to one of ordinary skill in the art at the time the invention was made to have prepared Chen's film containing therapeutic agent using a mixture of ethanol and water because a mixture of solvents permits the formation of a quick dissolving film using a hydrocolloid as shown by Example 2 in Table 1 of Chen; and so as to facilitate the dissolving of the ingredients when preparing the film.

With respect to claims 14, 39 and 64, Patent Owner argues the following at p. 23 of the Remarks filed 01/10/12:

> [T]he Examiner's substitution of Chen's active (a laxative) for the Patentee's polysaccharide polymer is not a logical or rational substitution, since nowhere does Chen suggest using actives in combination with each other nor does it suggest using an active as the film forming polymer. The Issued Patent, on the other hand, provides a matrix including a film forming polymer and an active. To read Chen as using an active as the polymeric component would defy logic and would effectively read out a limitation in the claim.

This argument is unpersuasive. Not only does Chen teach that its active material can be an anti-diarrheal or a laxative (see p. 10, line 27 and p. 11, line 7), which are well

known to be polysaccharides, but several of Chen's hydrocolloids, i.e., film forming polymers, such as methyl cellulose, guar gum, condroitin sulfate and hyaluronic acid (p. 14, lines 12-27), are also well-known active agents. As noted in the rejection, methyl cellulose and guar gum are well known anti-diarrhea agents, chondroitin sulfate is well known for treating osteoarthritis, and hyaluronic acid is used for joint disorders including osteoarthritis and in plastic surgery. Accordingly, the Examiner maintains that it would have been obvious to one of ordinary skill in the art at the time the invention was made to have used bran, psyllium husk, methyl cellulose, sterculia, or guar gum as the active ingredient in Chen's film because Chen teaches that the active ingredient in its film can be a laxative or anti-diarrhea agent; and bran, psyllium husk, methyl cellulose, sterculia, and guar gum are well known laxatives and/or anti-diarrhea agents in the art. Furthermore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have used chondroitin sulfate or hyaluronic acid for Chen's hydrocolloid because such is clearly within the scope of Chen's disclosure. As noted above chondroitin sulfate and hyaluronic acid are also well known therapeutic active materials. A skilled artisan would seek to take advantage of the known activity of each ingredient in Chen's formulations, whether it be a sole active ingredient, or used in combination with other actives. In fact, Chen explicitly teaches that its dosage unit can comprise more than one active agent (see Chen's claim 34 on p. 32).

With respect to the rejection of claims 1, 122-132, 144-154 and 166-176 over Chen in combination with Le Person, Patent Owner argues that Le Person's methods resulted in a non-uniform product prior to 10 minutes; that the active substance in Le

Person homogenizes and only after 15 minutes is quasi-equilibrium obtained; that Chen discloses drying in 9 minutes; and that a skilled artisan would not arrive at the limitation of the present claims (Remarks of 01/10/12, pp. 15-16 and 24-25).

Patent Owner's argument is unpersuasive. Claims 1, 122, 123, 125-132, 144, 145, 147-154, 166, 167 and 169-176 do not recite a drying time. Claims 124, 146 and 168 recite a time of less than about 10 minutes for removal of polar solvent. Chen exemplifies water as the solvent and achieves its drying in 9 minutes (see also p. 17, line 15 of Chen). As discussed above, the film prepared in Chen's Example 1 has "substantially uniform content" of therapeutic active composition per unit of film in view of the fact that Chen uses the same basic process steps as here claimed, and in Chen's Table 4 on p. 20, the films prepared by Chen in Example 1 have a weight of 0.028 $\pm$ 0.001 g/dosage film, a thickness of 2.1 $\pm$ 0.12 mil, and a density of 1.0485 $\pm$ 0.009 g/cm^2, and a water content of 1.7 $\pm$ 0.24%.

Le Person uses a combination of water and heavy solvent, and, for the drying temperature used (Table 2 on p. 259), achieved quasi-equilibrium at a slightly longer time, i.e., 15 minutes, than the 9-minute drying time of Chen (see p. 263 of Le Person). The Examiner maintains that it would have been obvious to one of ordinary skill in the art at the time the invention was made to have dried Chen's film using short infrared drying, or combined convection and medium infrared drying, instead of oven drying because these are known, alternative drying techniques in the art with short infrared drying being preferred, as taught by Le Person.

With respect to the rejection of claims 2, 5, 8, 9, 12, 15, 16, 18, 34, 37, 41, 59, 62, 66, 84, 99, 113 and 121 over Chen in combination with Bernstein, Patent Owner argues that Bernstein does not disclose or suggest the formation of a substantially uniform product (Remarks of 01/10/12, p. 26).

This argument is unpersuasive. Claims 34, 37, 41, 59, 62 and 66 do not require a substantially uniform product. Claims 2, 5, 8, 9, 12, 15, 16, 18, 84, 99, 113 and 121 recite "substantially uniform". However, as discussed above, Chen's product is a substantially uniform product, and Bernstein has been relied upon to show other protein biologically active agents, such as nucleases, interferons, interleukins, tumor necrosis factor, and erythropoietin, that can be incorporated into films (see col. 3, line 56 to col. 4, line 58; col. 6, lines 27-29; and Examples I and VII). Furthermore, there is reason to believe that Bernstein's films are "substantially uniform" in view of the fact that Bernstein teaches that its films can be administered to humans and animals to deliver the desired dosage (see col. 7, line 66 through col. 8, line 7).

With respect to the rejection of claims 13, 14, 17, 38, 39, 42, 63, 64 and 67 over Chen in combination with Staab or Hijiya, and the rejection of claims 2, 5, 8, 15, 84, 99 and 113 over Chen in combination with Hijiya, Patent Owner argues that Staab and Hijiya fail to disclose compositional uniformity in the final product (Remarks of 01/10/12, pp. 27-29).

This argument is unpersuasive. Claims 38, 39, 42, 63, 64 and 67 are silent concerning any type of uniformity. Claims 2, 5, 8, 13, 14, 15, 17, 84, 99 and 113 require a "substantially uniform" product, and, as discussed above, Chen's product is

substantially uniform. Furthermore, Staab teaches that its active agent is evenly distributed throughout the film (see sentence bridging cols. 5 and 6; and col. 9, lines 11-14). Even further, Hijiya teaches that its layer is uniform (col. 2, lines 53-60). In fact, Hijiya uses the same drying temperature, i.e., 40-100°C, as Chen and the '588 patent (see col. 3, lines 42-44 of Hijiya; p. 15, line 28 of Chen; and col. 25, lines 42-44 of the '588 patent).

Patent Owner cites col. 7, lines 37-48 of Staab and argues that Staab does not disclose addition of active separately from polymer and water (Remarks of 01/10/12, p. 28).

This argument is unpersuasive for the reasons set forth by Third Party Requester on p. 36 of the Comments filed 02/19/12, reproduced below:

> Contrary to the Reply, and as the Examiner correctly stated (OA: p. 28, line 16 - p. 29, line 6), Staab discloses a polymer solution that may contain an active, wherein the solution can be cast directly, or transferred to a cooling bath where other "heat sensitive ingredients (e.g., pharmaceuticals) can be introduced with stirring" (Col. 7, lines 38-52). Thus, Staab discloses preparing a premix and subsequently adding a pharmaceutical active that is heat sensitive. In addition, it is also possible to rely upon Hijiya for disclosing a pre-mix, namely, "an aqueous glucan solution may be admixed with ... [active]" see Hijaya [sic] 3, lines 26-31.
>
> Moreover, in the Decision on Appeal in the related '292 case [application Serial No. 10/074,272] (p. 26, Exhibit C), the Appeals Board held: "we determine that the use of premixes, deaerating by mixing (at least to some extent), and adding the active component at the end of this mixing, were all well known in this art. We also determine that the particular order of adding components would have been well within the ordinary skill in this art, absent some showing of criticality." If the Patent Owner disagreed, it should have appealed at that time.

Arguments with respect to the rejections based on Peh:

Patent Owner argues that claims 25 and 50 recite forming a viscoelastic product, which "is intended to be a product that has maintained substantial active uniformity." (Remarks of 01/10/12, p. 30).

This argument is not persuasive. As discussed above, the term "viscoelastic" is not given a special definition in the '588 patent and does not require substantial uniformity of active material in the product. Rather, as noted in ¶ 9 of the Cohen Declaration, "[t]he standard definition of viscoelastic behavior is that it is a material that reflects the combined viscous and elastic responses, under mechanical stress, of materials which are intermediate between liquids and solids in character." Peh's films are viscoelastic in view of the fact that they are prepared from the same film-forming polymers, i.e., hydroxypropylmethyl cellulose, carboxymethyl cellulose and polyacrylic acid, as disclosed in the '588 patent (Abstract, p. 54 and Table 1 of Peh; and col. 15, lines 13-28 of the '588 patent), and in view of the fact that Peh's films are flexible, elastic and soft (abstract and Introduction on p. 53 and Conclusions on p. 59).

Further, even if "viscoelastic" required substantial active uniformity (the Examiner maintains it doesn't), Patent Owner's argument remains unpersuasive. As discussed above, the term "substantially uniform content of therapeutic active composition" is not defined in the '588 patent, nor does the '588 patent provide any criteria to determine what is a "substantially uniform content of therapeutic active composition". Thus, a film that has been prepared according to the process steps in claims 192 and 193 is taken to be a film having "substantially uniform content of therapeutic active composition".

Peh anticipates the mixing, forming and removing steps of claim 192 (and claim 25), and the mixing, forming and using steps of claim 193 (and claim 50), and thus, Peh's film containing a drug has a substantially uniform content of the drug.

In particular, as noted in the anticipatory rejection, Peh teaches an aqueous solution containing hydroxypropyl methylcellulose (Methocel K15M), polyacrylic acid (carbopol 934P), and polyethylene glycol (PEG 400) is allowed to stir (i.e. is mixed) for 6 hours and stand overnight to remove all the air bubbles entrapped; the solution, i.e. the claimed matrix, is then cast onto a petri dish, i.e. a wet film is formed; and the water is then removed by drying (i.e., using heat) in "the oven at 60°C until completely dry" so as to form the polymeric film (see the method of preparation on p. 54). Since Peh removes all entrapped air bubbles prior to heating in the oven, then Peh's heating step occurs "without forming air bubbles", as per claims 50 and 193. In fact, Peh's films were checked for imperfections, and samples with air bubbles, nicks or tears and having a mean thickness variation greater than 5% were excluded from analysis (see p. 54, the paragraph bridging the two columns). While an objective of Peh is to investigate the suitability of hydroxypropyl methylcellulose as a vehicle for the buccal delivery of drugs (see p. 54, col. 1, first paragraph), no drugs were used in Peh, but rather, Peh measured mechanical and bioadhesive properties of drug-free polymer films (see pp. 54-60). However, one having ordinary skill in the art would at once envisage mixing the drug (i.e., instant therapeutic active composition) with the hydroxypropyl methylcellulose, polyacrylic acid, polyethylene glycol and water so as to

prepare the material that will subsequently be dried to form the polymeric film for buccal delivery of the drug.

Patent Owner cites the Rounds Declaration and provides various arguments concerning "substantially uniform content" of the active material. In particular, on p. 13 of the Remarks filed 01/10/12, Patent Owner argues the following:

> Peh completely fails to disclose any particular drying parameters that are necessary for the formation of the desired active uniformity. (Rounds Dec. ¶20). Peh's ultimate goal was the formation of a film that satisfied particular mechanical properties, such as tensile strength, elastic modulus and elongation at break. (Rounds Dec. ¶20). Nowhere in Peh is there a disclosure as to the substantial uniformity of content. There is no disclosure as to the composition of the ultimate film product, and in particular, there is no disclosure, either expressly or inherently, as to the substantial uniformity of active of the film product. (Rounds Dec. ¶20).
>
> Of particular importance in Peh is that the film includes a very low concentration of polymers. The low concentration of polymer is what allows the film to be deaerated simply by sitting overnight. (Rounds Dec. ¶21). With a higher concentration of polymers, air bubbles would not be allowed to escape without force being acted thereon. (Rounds Dec. ¶21). Given the low concentration of polymers and the ability of air to escape without outside force, it is evident that any actives within the wet film are able to move around, settle, and/or agglomerate during the deaeration stage. (Rounds Dec. ¶22). For the film forming matrix to be so non-viscous as to allow the air to escape by sitting inherently implies that actives (or other components therein) would be allowed to move around and settle and/or agglomerate. (Rounds Dec. ¶22).
>
> The resulting film in Peh would not be substantially uniform in content, including an active content, although its thickness may be substantially uniform and it may appear on its surface to be free of defects. (Rounds Dec. ¶23). Peh's disclosure teaches nothing to the manufacture of a film product to provide a substantially compositionally uniform viscoelastic film product. Although Peh's mixture may be homogeneous prior to casting and prior to drying, it is not practical or likely that the resulting film product would maintain that content homogeneity. (Rounds Dec. ¶23).

On p. 30 of the Remarks, Patent Owner further argues:

> As with the Chen reference, described above, Peh does not teach the formation of a substantially uniform active content having such a substantially uniform mass to volume ratio of active. As explained above and in more detail in the application as filed, various drying methods may impart significantly different final products, and especially conventional drying methods (such as uncontrolled drying in a conventional hot air oven) may cause agglomeration and non-uniformity of components.
>
> Peh discloses drying "in an oven" at 60°C, but does not disclose or even suggest any controlled drying parameters. Further, Peh does not disclose or suggest the substantial uniformity of the final film's active composition. Peh does disclose that the thickness is substantially uniform, but uniform thickness is certainly not equivalent to uniform content. Agglomeration of components may occur but may have nominal, if any, effect on the film's thickness.

These arguments are unpersuasive and the Rounds Declaration is unsupported by factual evidence. The instant claims do not recite any particular drying parameters/control or polymer concentration. In fact, contrary to the opinion in the Rounds Declaration, the polymer concentration disclosed by Peh, i.e., 1% w/v before drying, is on par with the polymer concentration in Examples CE and CF at col. 38 of the '588 patent. The weight of polymer in examples CE and CF is a total of 7.84 grams from hydroxypropylmethyl cellulose plus pullulan (see Table 14). Water is added to the composition in Examples CE and CF at "q.s." of about 1000 grams (see col. 38, lines 42-47 and Table 14). This results in about 0.7 or 0.8% w/w of the polymer. The about 0.7 or 0.8% w/w is the same as or close to 0.7 or 0.8% w/v of polymer due to the fact that a majority of the composition is water.

Since Peh performs the same process steps as here claimed, Peh's films have a substantially uniform content of drug to the best that the term "substantially uniform content" can be understood. This is further supported by the fact that, as admitted by

Patent Owner, "Peh does disclose that the thickness is substantially uniform" (Remarks of 01/10/12, p. 30; and the "Preparation of Drug Free Film" section on p. 54 of Peh). In particular, the '588 patent teaches that, like Peh, the films of the '588 patent have a "substantially uniform thickness", and that the absence of such a thickness detrimentally affects uniformity of component distribution throughout the area of a given film (see col. 6, lines 41-46).

With respect to the rejection of claims 27, 52, 134, 135, 144-148, 156-159 and 166-170 over Peh in combination with Le Person, Patent Owner argues that Le Person's method resulted in a non-uniform product prior to 10 minutes; that the active substance in Le Person homogenizes, and only after 15 minutes is quasi-equilibrium obtained (Remarks of 01/10/12, pp. 15-16 and 31-32).

Patent Owner's argument is unpersuasive. Claims 27, 52, 135, 146, 157 and 168 recite removing the polar solvent (e.g. water) in less than about 10 minutes but are silent with respect to uniformity. Claims 134, 144, 145, 147, 148, 156, 158, 159, 166, 167, 169 and 170 are silent with respect to drying time and uniformity. In any event, as discussed above, the films prepared in Peh have "substantially uniform content" of drug. Further, Le Person teaches drying for 5 or 10 minutes, and, in fact, teaches that after 10 minutes of drying 99% of the initial water from a 100 μm thick coating is evaporated using a short infrared drying process (see § 3.1 at pp. 260-261, in particular Fig. 5).

With respect to the rejection of claims 28, 36, 38, 42, 43, 45, 47, 48, 53, 61, 63, 67, 68, 70, 72, 73, 94, 95, 103, 104, 107-110, 138, 139, 160 and 161 over the Peh in combination with Staab, Patent Owner argues that "Staab provides no teaching or

suggestion as to how to arrive at a final product that contains the recited level of active uniformity" (Remarks of 01/10/12, p. 33).

This argument is unpersuasive. Claims 28, 53, 94, 95, 138, 139, 160 and 161 recite a variation of active content of less than 10% either per unit of film or in individual dosage units. Staab specifically teaches that its active agent is evenly distributed throughout the film (see sentence bridging cols. 5 and 6; and col. 9, lines 11-14). As noted in the rejection, the disclosure of a film with active material "evenly distributed throughout" meets the instantly claimed limitation of a variation of less than 10%. Further, Staab teaches forming a plurality of individual dosing units of substantially the same size (see Figs. 1-4 and col. 11, lines 12-18).

Patent Owner cites col. 7, lines 37-48, of Staab and argues that Staab does not disclose addition of active separately from polymer and water (Remarks of 01/10/12, p. 33).

This argument is unpersuasive for the same reasons set forth above with respect to the combination of Chen and Staab. In particular, Staab discloses a polymer solution that may contain an active, wherein the solution can be cast directly, or transferred to a cooling bath where other "heat sensitive ingredients (e.g., pharmaceuticals) can be introduced with stirring" (Col. 7, lines 38-52). Thus, Staab discloses preparing a premix and subsequently adding a pharmaceutical active that is heat sensitive. Moreover, in the Decision on Appeal in the related '292 case (application Serial No. 10/074,272), the Appeals Board held: "we determine that the use of premixes, deaerating by mixing (at least to some extent), and adding the active component at the end of this mixing, were

all well known in this art. We also determine that the particular order of adding components would have been well within the ordinary skill in this art, absent some showing of criticality."

With respect to the rejection of claims 27, 30, 33, 40, 43, 52, 55, 58, 65, 68, 85, 86, 100, 101, 134, 143, 156 and 165 over the combination of Peh and Chen, Patent Owner argues that Peh and Chen do not teach "substantial compositional uniformity" (Remarks of 01/10/12, pp. 33-34).

This argument is unpersuasive. None of claims 27, 30, 33, 40, 43, 52, 55, 58, 65, 68, 85, 86, 100, 101, 134, 143, 156 and 165 requires substantial compositional uniformity. In any event, the films of Peh and Chen have substantial compositional uniformity for the reasons discussed above.

Patent Owner argues that Chen does not disclose drying at a temperature above the degradation of the active (Remarks of 01/10/12, p. 34).

This argument is misplaced. None of claims 27, 30, 33, 40, 43, 52, 55, 58, 65, 68, 85, 86, 100, 101, 134, 143, 156 and 165 requires heating above the degradation temperature of the active. In any event, Chen anticipates/renders obvious heating above the degradation temperature of the active for the reasons discussed above.

With respect to the rejection of claims 49 and 74 over the combination of Peh and Strobush, Patent Owner cites ¶ 25 of the Rounds Declaration and argues that a product that is free of "mottle" as in Strobush does not necessarily mean that the product is substantially compositionally uniform throughout its thickness (Remarks of 01/10/12, pp. 14-15 and 34-35). Citing ¶ 32 of the Rounds Declaration, Patent Owner

argues that Strobush is concerned with photographic articles, not self-supporting ingestible films (Remarks of 01/10/12, p. 14).

This argument is unpersuasive because claims 49 and 74 do not require a product that is substantially compositionally uniform throughout its thickness. In any event, for the reasons discussed above, Peh's film has a substantially uniform content of drug. Furthermore, Strobush teaches that "[m]ottle is usually caused by air movement over the coating before it enters the dryer, as it enters the dryer, or in the dryer." (see col. 1, line 67 to col. 2, line 3). In other words, mottle is the result of overcoming the inherent viscosity of the wet film. Claims 49 and 74 require that any air flow present during the removal of the polar solvent from the matrix does not overcome the inherent viscosity of the wet film. Strobush teaches a number of methods and apparatus for minimizing the formation of mottle (see e.g., col. 6, line 28 - col. 7, line 33). Strobush discloses that its methods can be applied to dry any mottle-susceptible material, and teaches that mottle can occur to a significant extent in aqueous compositions (see e.g., col. 2, lines 6-15 and col. 16, lines 62-64). Strobush is not limited to photographic articles, but rather, generally teaches that its method is used for drying coatings on a substrate (col. 1, lines 8-11). Peh's aqueous film is coated onto a petri dish before drying (see p. 54). Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified Peh's process so that any air flow in the oven during the step of drying the wet film does not overcome the inherent viscosity of the wet film so as to avoid the formation of mottle,

i.e., avoid the formation of a defective, irregular or non-uniform product, as taught by Strobush.

With respect to the rejection of claims 29, 32, 34-37, 40-42, 44, 54, 57, 59-62, 65-67, 69, 88, 89, 91, 92, 140-142, 162-164, 179-182, 190 and 191 over Peh in combination of with Bernstein, Patent Owner argues that Bernstein does not disclose formation of a product having substantial compositional uniformity of active material (Remarks of 01/10/12, p. 35).

This argument is unpersuasive. None of claims 29, 32, 34-37, 40-42, 44, 54, 57, 59-62, 65-67, 69, 88, 89, 91, 92, 140-142, 162-164, 179-182, 190 and 191 requires substantial compositional uniformity of active material. In any event, as discussed above, the films prepared in Peh have substantially uniform content of drug. Further, Bernstein teaches that its films can be administered to humans and animals to deliver the desired dosage (col. 7, line 66 through col. 8, line 7).

With respect to the rejection of claims 25, 26, 30, 31, 46, 47, 50, 51, 55, 56, 71, 72, 76, 77, 79, 80, 82, 83, 85, 86, 97, 98, 133, 134, 136, 137, 155, 156, 158, 159, 184, 185, 187 and 188 over Peh in combination of with Hijiya, Patent Owner argues that Hijiya does not disclose formation of a product having substantial compositional uniformity of active material (Remarks of 01/10/12, p. 36).

This argument is unpersuasive. None of claims 25, 26, 30, 31, 46, 47, 50, 51, 55, 56, 71, 72, 76, 77, 79, 80, 82, 83, 85, 86, 97, 98, 133, 134, 136, 137, 155, 156, 158, 159, 184, 185, 187 and 188 requires substantial compositional uniformity of active material. In any event, as discussed above, the films prepared in Peh have

substantially uniform content of drug. Further, Hijiya teaches that its layer is uniform (col. 2, lines 53-60).

With respect to the rejection of claims 149-154 and 171-176 over Peh in combination with Le Person, and further in combination with Staab or Bernstein, Patent Owner inadvertently addresses the rejection as "Peh in combination with Staab and Bernstein" (see Remarks filed 01/10/12, p. 36). Patent Owner provides arguments with respect to Bernstein and Staab not teaching or suggesting substantial compositional uniformity of active (Remarks of 01/10/12, p. 37).

This argument is not persuasive because, as discussed above, Peh's films have substantially uniform content of drug. As admitted by Patent Owner on p. 15 of the Remarks filed 01/10/12, the active substance in Le Person's film is homogenized (see also p. 263 of Le Person). Further, as discussed above, Bernstein teaches that its films can be administered to humans and animals to deliver the desired dosage (col. 7, line 66 through col. 8, line 7). Even further, Staab specifically teaches that its active agent is evenly distributed throughout the film (see sentence bridging cols. 5 and 6; and col. 9, lines 11-14).

Conclusion

The patent owner is reminded of the continuing responsibility under 37 CFR 1.985 to apprise the Office of any litigation activity, or other prior or concurrent proceeding, involving Patent No. 7,824,588 throughout the course of this reexamination proceeding. The Third Party Requester is also reminded of the ability to similarly

apprise the Office of any such activity or proceeding throughout the course of this reexamination proceeding. MPEP 2686.

This is an ACTION CLOSING PROSECUTION (ACP); see MPEP § 2671.02.

(1) Pursuant to 37 CFR 1.951(a), the patent owner may once file written comments limited to the issues raised in the reexamination proceeding and/or present a proposed amendment to the claims which amendment will be subject to the criteria of 37 CFR 1.116 as to whether it shall be entered and considered. Such comments and/or proposed amendments must be filed within a time period of 30 days or one month (whichever is longer) from the mailing date of this action. Where the patent owner files such comments and/or a proposed amendment, the third party requester may once file comments under 37 CFR 1.951(b) responding to the patent owner's submission within 30 days from the date of service of the patent owner's submission on the third party requester.

(2) If the patent owner does not timely file comments and/or a proposed amendment pursuant to 37 CFR 1.951(a), then the third party requester is precluded from filing comments under 37 CFR 1.951(b).

(3) Appeal **cannot** be taken from this action, since it is not a final Office action.

All correspondence relating to this *inter partes* reexamination proceeding should be directed:

By EFS: Registered users may submit via the electronic filing system EFS-Web at https://efs.uspto.gov/efile/myportal/efs-registered

By Mail to: Attn: Mail Stop "Inter Partes Reexam"
Central Reexamination Unit
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Signed:

Alan Diamond
Patent Reexamination Specialist
Central Reexamination Unit 3991

Deborah D. Jones
Supervisory Patent Examiner
CRU - Art Unit 3991

JERRY D. JOHNSON
PRIMARY EXAMINER
CRU - AU 3991

EXHIBIT O

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	Fuisz, et al.	Examiner:	Melissa S. Mercier
Serial No.:	11/858,214	Group Art Unit:	1615
Confirmation No.:	2366	Docket:	1199-43 RCE
Filed:	September 20, 2007	Dated:	December 20, 2010
For:	EDIBLE WATER-SOLUBLE FILM CONTAINING A FOAM REDUCING FLAVORING AGENT		

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Certificate of EFS-Web Transmission

I hereby certify that this correspondence is being transmitted to the U.S. Patent and Trademark Office via the Office's electronic filing system on **December 20, 2010.**

Joyce Peterson (Printed Name)
/joyce peterson/ (Signature)

AMENDMENT

Sir:

This Amendment is in response to the non-final Office Action mailed September 27, 2010. This Amendment is being submitted within three months from the mailing date of the Office Action. It is therefore believed that no fee is necessary.

A Listing of the Claims begin on page 2 of this paper.

Remarks begin on page 4 of this paper.

IN THE CLAIMS:

Although no amendments to the claims are submitted herewith, a list of the claims as pending is set forth for the convenience of the Examiner:

1. (Previously Presented) A method of preparing an edible water-soluble film composition, said method comprising:

a) preparing a master batch of film-forming components comprising a water-soluble polymer, a foam reducing flavoring agent, and a polar solvent, wherein said foam reducing flavoring agent is added before mixing said polymer with said solvent;

b) mixing said film-forming components under vacuum;

c) wet casting said film-forming components; and

d) removing said polar solvent through a controlled drying process to form said edible water-soluble film; wherein said film is free of added defoaming agents.

2. (Original) The method of claim 1, wherein the foam reducing flavoring agent is present in amount of about 0.1 % to about 20% by weight of the film.

3. (Original) The method of claim 1, wherein the foam reducing flavoring agent is present in amount of about 0.5 % to about 15% by weight of the film.

4. (Canceled)

5. (Original) The method of claim 1, wherein the foam reducing flavoring agent is selected from the group consisting of menthol, cherry menthol, cinnamint, spearmint, peppermint, orange flavor, natural raspberry and combinations thereof.

6. (Canceled)

7. (Previously Presented) The method of claim 1, wherein said film composition further comprises an active.

8. (Previously Presented) The method of Claim 1, wherein said foam reducing flavoring agent comprises menthol.

REMARKS

No claims have been amended or cancelled herein. Accordingly, Claims 1-3, 5, and 7-8 remain pending. In view of the remarks set forth herein, reconsideration is respectfully requested.

Rejections under 35 U.S.C. §103

Claims 1-3, 5 and 7-8 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Leung et al. (WO 00/18365) The examiner asserts that the various elements of the claims are disclosed by a method of producing films disclosed by Leung et al. However, the examiner concedes that Leung does not disclose the flavoring agent being added prior to mixing of the polymer and solvent. To the contrary, the examiner confirms that Leung discloses the flavoring agent being added *after* mixing of the polymer and solvent. The examiner then asserts that it would have been obvious to one of ordinary skill in the art at the time the invention was made to have added the flavoring agent to the gelled formulation of the water soluble polymer and water in order to obtain a dried edible film with a uniform distribution of flavoring agents.

However, as explained in paragraph [0144] of the specification, flavoring agents are typically added *after* mixing because mixing can cause a decrease in the flavor. Accordingly, the prior art, including Leung, discloses adding flavoring agents after mixing so that the flavoring agents, typically volatile oils, do not dissipate during processing of the components utilized in forming the film. Therefore, contrary to what is stated in the Office Action, there would be no reason for one of ordinary skill in the art at the time the invention was made to add the flavoring agent before mixing the polymer with the solvent, as set forth in Claim 1.

The examiner further acknowledges the Declaration under 37 CFR 1.132 filed on November 12, 2009 by one of the inventors, Garry Myers. The examiner further acknowledges that the Declaration demonstrates that there is a criticality to the order in which the components are added and mixed together.

However, the examiner questions whether, if the air bubbles are removed by vacuum as disclosed by Leung, the product produced by Leung and that of the claimed invention would be the same. Applicants respectfully assert that this is an incorrect inquiry.

The question is not whether the methods disclosed in the prior art can somehow achieve an acceptable product by including additional steps, such as deaerating of the film. The point is that the claims include a step for preparing an edible water-soluble film composition that is not disclosed or suggested by the prior art, and which does impart different properties to the film, i.e., fewer air bubbles, than would otherwise be present.

Accordingly, withdrawal of the rejections under 35 U.S.C. §103 is respectfully requested.

New Claim Rejections under 35 U.S.C. §112

Claims 1-3, 5, and 7-8 also stand rejected under 35 U.S.C. §112, second paragraph as being indefinite for failing to point out and distinctly claim the subject matter which Applicants regard as the invention. More specifically, the examiner has noted that the claims have been amended to recite "wherein said film is free of added defoaming agents". The examiner further asserts that, since the claims recite in part (a) the use of a foam reducing agent, the claims are indefinite in view of the wherein clause which states that a form reducing agent cannot be included. Applicants respectfully traverse.

Step (a) in Claim 1 refers to a foam reducing *flavoring* agent, not a foam reducing agent. The term "foam reducing flavoring agent" is specifically defined in paragraphs [0130] and [0140]. More specifically, a foam reducing flavoring agent is defined as a component that can act to both flavor the film and prevent and/or remove air from the film-forming compositions. The film reducing flavoring agent is contrasted with conventional foam reducing agents, such as simethicone. (See paragraph [0142]). The term "defoaming agent" is defined in paragraph [0141] as a component used to reduce foam after it has already been formed. Such conventional defoaming/anti-foaming agents are well known in the art.

Accordingly, Claim 1 requires a foam reducing *flavoring agent* in step (a), while the wherein clause specifies that the film is free of any *additional* foaming agents, such as simethicone, etc. In view of the distinction between foam reducing flavoring agents and any other additional defoaming agents, Applicants respectfully assert that the two defoaming agents are not the same thing used for the same purpose, as asserted on page 5 of the Office Action.

Accordingly withdrawal of the rejections under 35 U.S.C. §112 is respectfully requested.

Conclusion

Applicants submit that the application is now in proper form for allowance, which action is earnestly solicited. If resolution of any remaining issue is required prior to allowance of the application, it is respectfully requested that the examiner contact Applicants' attorney at the telephone number provided below.

Respectfully submitted,

/james f. harrington/
James F. Harrington
Registration No.: 44,741
Attorney for Applicants

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346915_1.DOC

EXHIBIT Q

PTO/SB/08b (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	Not Yet Assigned
Filing Date	September 10, 2012
First Named Inventor	Robert K. Yang
Art Unit	Not Yet Assigned
Examiner Name	Not Yet Assigned
Attorney Docket Number	117744-00023

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	A1	5,393,528	02-28-1995	Staab et al.	
	A2	5,629,003	05-13-1997	Horstmann et al.	
	A3	7,666,337	02-23-2010	Yang et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	B1	WO2000/42992	07-27-2000	Chen et al.		

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	C1	LE PERSON et al., "Near infrared drying of pharmaceutical thin films: experimental analysis of internal mass transport", Chem. Eng. & Proc. 37:257-263 1998	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. * CITE NO.: Those application(s) which are marked with an single asterisk (*) next to the Cite No. are not supplied (under 37 CFR 1.98(a)(2)(iii)) because that application was filed after June 30, 2003 or is available in the IFW. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with § 1.6(a)(4).

Dated: September 10, 2012
Electronic Signature for Danielle L. Herritt: /Danielle L. Herritt/

EXHIBIT R

CERTIFICATE OF SERVICE

I hereby certify that a true and complete copy of the Request for *Inter Partes* Reexamination of U.S. Patent No. 7,897,080—including all Exhibits and Enclosures referenced in the Request (also listed below)—has been served via first class mail, on September 10, 2012, on the Patent Owner's attorney at the following address:

Daniel A. Scola, Jr.
HOFFMANN & BARON, LLP
6900 Jericho Turnpike
Syosset, NY 11791,

- Enclosure - *Inter Partes* Reexamination Request Transmittal Form; and
- Enclosure - Request for *Inter Partes* Reexamination of U.S. Patent No. 7,897,080, including Exhibits A-R thereto.

By: /Danielle L. Herritt/
Danielle L. Herritt
Registration No. 43,670
Attorney for Requester

McCarter & English, LLP
265 Franklin Street
Boston, Massachusetts 02110

Dated: September 10, 2012

EXHIBIT L

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re *Inter Partes* Reexamination of:	)	
	)	
US Patent No. 7,897,080	)	
	)	
Issued: March 1, 2011	)	
	)	
Named Inventor: Robert K. Yang *et al.*	)	Group Art Unit: To Be Assigned
	)	
Control No.: To Be Assigned	)	Examiner: To Be Assigned
	)	
Filed: September 10, 2012	)	
	)	
Title: Polyethylene-oxide based films and drug delivery systems made therefrom	)	

Mail Stop *Inter Partes* Reexam
Attn: Central Reexamination Unit
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION BY EDWARD D. COHEN, PH.D. UNDER 37 C.F.R. § 1.132

Sir/Madam:

I, Edward D. Cohen, Ph.D., do hereby make the following declaration:

I. Technical Background

1. I have worked for over 45 years in the field of coating and drying, in research, manufacturing, and more recently in industry consulting. I have a B.S. in Chemical Engineering from Tufts University and a Ph.D. in Physical Chemistry from the University of Delaware.

2. I have technical experience in thin film coating and drying process development, formulating coatings, coating machine design, new product process development, and troubleshooting manufacturing process problems. My experience includes more than 30 years at E.I. DuPont de Nemours and Co., from which I retired as a DuPont Fellow.

3. I have published extensively in the field of coating and converting, including several books and industry publications (see Appendix A for a shortened list of publications). I am a contributing editor for Converting Quarterly, a peer-reviewed journal. Converting is the field of coating and drying a substrate, and cutting the resulting product. I have chaired committees and symposia in both the American Institute of Chemical Engineers and the American Chemical Society. I was founding president of the International Society of Coating Science and Technology ("ISCST").

4. I have taught professional continuing education courses in the coating fields for more than 22 years, for the Association of Metallizers, Coaters, and Laminators ("AIMCAL); University of Minnesota; American Institute of Chemical Engineers; and the International Society of Coating Science and Technology.

5. My honors include the John Tallmadge Award for Contributions to Coating Technology; the AIMCAL President's Award in recognition of Meritorious Service to AIMCAL and the Converting Industry, and the ISCST Founders Award.

6. I am currently an independent consultant for the coating and converting industries and a Technical Consultant for AIMCAL. I was retained by BDSI as a consultant in 2011, for which I am paid on an hourly basis. I have been hired as a consultant by McCarter & English, LLP, to provide an expert analysis of certain issues in connection with the reexamination of U.S. Patent No. 7,897,080 ("'080 patent"). While I am being paid for my time, I am not an employee of BioDelivery Sciences, Inc., nor do I have any financial interest in BioDelivery Sciences, Inc.

7. I have read the '080 patent, and Chen *et al.* (PCT Publication No. WO2000/42992, or "Chen").

8. Chen provides coating mixtures containing active that are described as "homogeneous", "completely dissolved", or "completely dispersed". Drying such hydrocolloid coating mixtures would be expected to yield films with substantially uniform content of active per unit of film, where the unit of film is a typical dosage unit or per sheet of uncut film. It is my opinion that Chen teaches films with substantially uniform content of active per unit of film, where the unit of film is, for example, a dosage unit or an uncut sheet of film.

9. In general, as a homogeneous or completely dispersed coating mixture is dried, the solvent is removed, the viscosity increases and the active would be more firmly fixed in place. When working with a homogeneous or completely dissolved coating mixture, for example, it would be difficult for a person of

ordinary skill in the thin film art not to obtain a film that has uniform content of active.

10. It is my opinion that drying the film coating mixtures of Chen according to the drying methods of Chen would yield films with uniform content of active per unit dosage. When working with a homogeneous or completely dissolved or completely dispersed coating mixture, it is my opinion that the drying methods disclosed in Chen would not be expected to create any agglomeration, aggregation, or otherwise non-uniform content of active. There would have been a variety of drying processes or apparatus known in the art at the time the '080 Patent was filed, including bottom drying, that would have been able to provide a film with uniform content of active.

11. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine, or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful statements may jeopardize the validity of the application or any patents issued thereon.

Dated this 6 day of September, 2012. Edward D Cohen

Edward D. Cohen, Ph.D.

Appendix A

Publications List Condensed

Books

Cohen, E. and Lightfoot, E. J., 2011. Coating Processes, Kirk-Othmer Encyclopedia of Chemical Technology. 1-68.

Cohen, E. D. & Gutoff E. B., *Water and Solvent Based Coating Technology*, in J. R, Wagner, Jr., Multilayer Flexible Packaging, Elsevier, First edition, 2010.

Cohen, E. D. & Gutoff E. B., *Coating and Drying Defects Troubleshooting Operating Problems*, second edition, John Wiley and Sons, New York, 2006.

Cohen, E. D. & Gutoff E. B., *Coating and Drying Defects Troubleshooting Operating Problems*, John Wiley and Sons, New York, 1995.

Cohen, E. D. & Gutoff E. B., *Modern Coating & Drying Technology*, VCH Publishers, New York, April 1992.

Journal Articles

E. D. Cohen, *Web Coating Defects: Controlling Dryer Defects, Part2*, Converting Quarterly, 2011 Quarter 4.

E. D. Cohen, *What is the Impregnation-coating Process and Why is it Used?* Converting Quarterly, 2011 Quarter 3.

E. D. Cohen, *Why is Pre-metered Slot-die Coating Increasing in Popularity?* Converting Quarterly, 2011 Quarter 1.

E. D. Cohen, *Web Coating Defects: Streaks And How To Eliminate Them,* Converting Quarterly, 2011 Quarter 1.

E. D. Cohen, *Technology Trends,* Paper Film & Foil Converter, May 2010.

E. D. Cohen & D. Bemi, *Conserve Energy*, Paper Film & Foil Converter, February, 2009.

E. D. Cohen, *Older methods: Still effective for web coating*, Converting Magazine, June 2007.

E. D. Cohen & E. B. Gutoff, *Coating Process Survey*, Kirk Othmer Concise Encyclopedia of Chemical Technology, 4th Ed., John Wiley & Sons, Inc. NY (1999).

E. Cohen, E. J. Lightfoot, K. N. Christodoulou, *Important Issues in Drying of Thin Films: An Industrial Engineers Perspective*, Part 2 Models. Industrial Coating Research, Vol. 4, pp.47-72 (1998).

E. B. Gutoff & E. D. Cohen, R&*D Needs in the Drying of Coatings*, Drying Technology, 14(6), 1315-1328 (1996).

E. Cohen, E. J. Lightfoot, K. N. Christodoulou, *Important Issues in Drying of Thin Films: An Industrial Engineers Perspective*, Industrial Coating Research, Vol. 3, pp.45-68 (1995).

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM
First Named Inventor/Applicant Name:	Robert K. Yang
Filer:	Danielle L. Herritt
Attorney Docket Number:	

Filed as Large Entity

inter partes reexam Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Request for inter reexamination	1813	1	8800	8800
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**8800**

Electronic Acknowledgement Receipt

EFS ID:	13702980
Application Number:	95002170
International Application Number:	
Confirmation Number:	6418
Title of Invention:	POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM
First Named Inventor/Applicant Name:	Robert K. Yang
Customer Number:	86738
Filer:	Danielle L. Herritt
Filer Authorized By:	
Attorney Docket Number:	
Receipt Date:	10-SEP-2012
Filing Date:	
Time Stamp:	17:45:37
Application Type:	inter partes reexam

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$8800
RAM confirmation Number	5782
Deposit Account	504876
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal of New Application	117744_00023_080_Transmittal.PDF	24417 7711d56baae87dd9932fabd859a7f8c0253e3ed9	no	2
Warnings:					
Information:					
2	Receipt of Original Inter Partes Reexam Request	117744_00023_080_Request_for_Inter_Partes_Reexam.PDF	1049025 288752d562c91ac1113788dcdf3dd0699adcf2c0	no	245
Warnings:					
Information:					
3	Copy of patent for which reexamination is requested	Ex_A_US7897080.PDF	11506881 bc2cbfc21340eb803b50a5bb9257fa06829d6fcb	no	73
Warnings:					
Information:					
4	Reexam Miscellaneous Incoming Letter	Ex_B_Claims_US7897080-.PDF	799248 004b51d8f7878f306baa63df182ea06b43c5d7ef	no	9
Warnings:					
Information:					
5	Reexam Miscellaneous Incoming Letter	Ex_C_Chen_WO200042992.PDF	1685229 4d74ae1b1dc224f8fad666c46bcc63bc550712d0	no	45
Warnings:					
Information:					
6	Reexam Miscellaneous Incoming Letter	Ex_D_Staab_US5393528.PDF	1007341 1d1e7112fd9e7236e44d8ec093803905e1c74d18	no	12
Warnings:					
Information:					
7	Reexam Miscellaneous Incoming Letter	Ex_E_Le_Person_Chem_Eng_Proc.PDF	197622 e67c487390b31b0fb70ac41a8fca9c0f4dd3bf21	no	8
Warnings:					
Information:					
8	Reexam Miscellaneous Incoming Letter	Ex_F_Horstmann_US5629003.PDF	438833 ccdfe497ceb65a80beba583634ef42e002a2ba4e	no	5

Warnings:					
Information:					
9	Reexam Miscellaneous Incoming Letter	Ex_G_Terminal_Disclaimer.PDF	149327 77f7db14a2da79b9feb4334a982e211601eb1458	no	4
Warnings:					
Information:					
10	Reexam Miscellaneous Incoming Letter	Ex_H_Patent_Chart.PDF	25868 d6a14c778fc96abd6a6145e7e3029af4928959dd	no	2
Warnings:					
Information:					
11	Reexam Miscellaneous Incoming Letter	Ex_I_OA_mailed_9_29_10.PDF	230263 9592b8a71527118148e698586a24137f440264e9	no	8
Warnings:					
Information:					
12	Reexam Miscellaneous Incoming Letter	Ex_J_Response_IDS_US7897080_filed_11_16_10.PDF	1865575 5d6400dc361ada789e341d61327d06257fe8bf61	no	50
Warnings:					
Information:					
13	Reexam Miscellaneous Incoming Letter	Ex_K_OA_US7824588_mailed_2_4_10.PDF	474462 ad662f58fde26619b4d98ea0c04c9b556ee0bf29	no	13
Warnings:					
Information:					
14	Reexam Miscellaneous Incoming Letter	Ex_M_Response_US7666337_filed_9_4_09.PDF	372414 7f5fea379b8a418197a6eac0378c39b2bd9325e6	no	12
Warnings:					
Information:					
15	Reexam Miscellaneous Incoming Letter	Ex_N_OA_Closing_Prosecution_in_Reexam_US7824588_mailed_7_20_12.PDF	3916197 4933b2865dfb865ec6cc155c8239f18b3c61fd2a	no	99
Warnings:					
Information:					
16	Reexam Miscellaneous Incoming Letter	Ex_O_Response_USSN11858214_filed_12_20_10.PDF	199738 5e5d8be6a3a5f25d2c9c654ee41671391d03a566	no	7
Warnings:					
Information:					
17	Reexam Miscellaneous Incoming Letter	Ex_P_US_7666337.PDF	2299811 22bc6d7923844b7ba2aa27d64ce8b6b059ce82f	no	67

Warnings:					
Information:					
18	Information Disclosure Statement (IDS) Form (SB08)	Ex_Q_SB08---.PDF	21443 efb62fe91b5d16e970474744b9f8d89d3ccaaac1	no	2
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
19	Reexam Certificate of Service	Ex_R_Certificate_of_Service.PDF	11700 8e8c5ce4e215abb8be7fae18ba8c438cdf56d509	no	2
Warnings:					
Information:					
20	Reexam Miscellaneous Incoming Letter	Ex_L_Cohen_Dec-.PDF	365369 ae9a4bb34bccf36b011c965d17ef9e09ca396602	no	6
Warnings:					
Information:					
21	Fee Worksheet (SB06)	fee-info.pdf	29573 ffbc7987183b09bfdbf759ea0b6471becb8ef1e7	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	26670336		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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P.O. Box 1450
Alexandria, Virginia 22313-1450
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Bib Data Sheet

CONFIRMATION NO. 6418

SERIAL NUMBER	FILING OR 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
95/002,170	09/10/2012 RULE	264	3991	117744-00023

APPLICANTS

7897080, Residence Not Provided;
MONOSOL RX, LLC(OWNER), PORTAGE, IN;
DANIELLE L. HERRITT(3RD.PTY.REQ.), BOSTON, MA;
BIO DELIVERY SCIENCE INTERNATIONAL(REAL PTY IN INTEREST), RALEIGH, NC;
DANIELLE L. HERRITT, BOSTON, MA

**** CONTINUING DATA ***************************

This application is a REX of 12/614,928 11/09/2009 PAT 7897080
which is a CON of 10/856,176 05/28/2004 PAT 7666337
which claims benefit of 60/473,902 05/28/2003
and is a CIP of 10/768,809 01/30/2004 PAT 7357891
which claims benefit of 60/443,741 01/30/2003
and is a CIP of PCT/US02/32575 10/11/2002
and is a CIP of PCT/US02/32594 10/11/2002
and is a CIP of PCT/US02/32542 10/11/2002
which claims benefit of 60/371,940 04/11/2002
and said PCT/US02/32594 10/11/2002
claims benefit of 60/414,276 09/27/2002

**** FOREIGN APPLICATIONS *********************

Foreign Priority claimed	STATE OR COUNTRY	SHEETS DRAWING	TOTAL CLAIMS	INDEPENDENT CLAIMS
☐ yes ☐ no				
35 USC 119 (a-d) conditions met ☐ yes ☐ no ☐ Met after Allowance				
Verified and Acknowledged Examiner's Signature Initials				

ADDRESS
23869

TITLE

POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM

FILING FEE RECEIVED	FEES: Authority has been given in Paper No. _____ to charge/credit DEPOSIT ACCOUNT No. _____ for following:

☐ All Fees
☐ 1.16 Fees (Filing)
☐ 1.17 Fees (Processing Ext. of time)
☐ 1.18 Fees (Issue)
☐ Other _____
☐ Credit