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.

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 September 27, 2003, attorney docket No. 1199-15P) 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, 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 paroxtine hydrochloride (available as Paxil®); anti-migraines such as Imigra®, ACE-inhibitors such as enalaprilat (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, nizatidien, 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-ordibasic 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-methyl-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 300mg, desirably up to about 150mg 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.

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; and thermo-setting gels such as pectin, carageenan, and gelatin, which help in maintaining the dispersion of 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 tragancanth), pectin, water-soluble derivatives of cellulose: alkylcelluloses hydroxyalkylcelluloses and hydroxyalkylalkylcelluloses, such as methylcelulose, 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.

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.

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.

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 0.1mils to about 10mils. 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.

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, ophthalmological, 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 Figure 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 Figure 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 Figure 5 or stacked as shown in Figure 3 and sold in a dispenser 18 as shown in Figure 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

	Weight (g)								
Ingredient	**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 0.04gm, 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

	Weight (g)		
Ingredient	**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 %		
Ingredient	**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 3nm intervals from 203-1200nm. The frequency of maximum absorption was found to be 530nm. 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 0.1mg and then dissolved in 10ml 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 203-1200nm and later from only 500nm to 550nm at a 1nm scanning speed. The value recorded was the % transmission at the lowest wave length, which was most frequently 530nm.

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 6m 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)							
Ingredient	**P**	**Q**	**R**	**S**	**T**	**U**	**V**	**W**
Hydroxypropylmethyl 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

[1] First Heater Section (3m)
[2] Second Heater Section (3m)

TABLE 7 (continued)

	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 (3m)
[2] Second Heater Section (3m)

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 45min. 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 3m 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)			
Ingredient	**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 10mg 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" x .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.

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. x 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 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

Ingredient	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

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-forming 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

Ingredient	(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

Ingredient	(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

Ingredient	(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 Dave
[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 describe 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 ingredients that effects taste receptors to mask the receptors from registering a different, typically undesirable, taste.

TABLE 13

Ingredient	(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.

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 film product formed by the steps of:

(a) combining a polymer and a polar solvent to form a material with a non-self-aggregating uniform heterogeneity;

(b) forming said material into a film; and

(c) drying said film in a controlled manner to maintain said non-self-aggregating uniform heterogeneity.

2. The film product of claim 1, wherein said film includes a top side and a bottom side and said drying includes drying said bottom side first.

3. The film product of claim 1, wherein said drying includes applying heat to said bottom side.

4. The film product of claim 1, wherein said polar solvent is a combination of water and a polar organic solvent.

5. The film product of claim 1, wherein said polar solvent is water.

6. The film product of claim 1 further comprising an active component.

7. The film product of claim 1, wherein said polar solvent added in step (a) has a weight percent of at least about 30%.

8. The film product of claim 1, wherein said drying of said film reduces the weight percent of said polar solvent to about 10% or less.

9. The film product of claim 1, wherein said drying of said film reduces the weight percent of said polar solvent to about 8% or less.

10. The film product of claim 1, wherein said drying of said film reduces the weight percent of said polar solvent to about 6% or less.

11. The film product of claim 6, wherein said active component is a member selected from the group consisting of medicaments, flavors, fragrances, enzymes, preservatives, sweetening agents, colorants, spices, vitamins, and combinations thereof.

12. The film product of claim 1, wherein said drying occurs within about 10 minutes or fewer.

13. The film product of claim 1, wherein said polymer is a member selected from the group consisting of water soluble polymers, water insoluble polymers, and combinations thereof.

14. The film product of claim 1, wherein said polymer is a cellulose derivative.

15. The film product of claim 13, wherein said water soluble polymer is a member selected from the group consisting of hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, polyvinylpyrrolidone, 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 and combinations thereof.

16. The film product of claim 13, wherein said water insoluble polymer is a member selected from the group consisting of ethyl cellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, and combinations thereof.

17. The film product of claim 1, wherein said film product has a thickness of greater than about 0.1 mils.

18. The film product of claim 1, wherein said film product has a thickness of about 10 mils or fewer.

19. The film product of claim 1, wherein said film product has a substantially uniform thickness.

20. The film product of claim 6, wherein said film product is divided into dosage forms of substantially equal dimensions.

21. The film product of claim 20, wherein each of said dosage forms contains a substantially equal amount of said active.

22. The film product of claim 20, wherein said dosage forms contain an amount of said active that varies about 10% or less among said dosage forms.

23. A process for making a film having a substantially uniform distribution of components comprising:

(a) combining a polymer component and polar solvent to form a matrix with a uniform distribution of said components;

(b) forming a film from said matrix;

(c) providing a surface having top and bottom sides;

(d) feeding said film onto said top side of said surface; and

(e) drying said film by applying heat to said bottom side of said surface.

24. The process of claim 23, further comprising the step of adding an active component to said matrix of step (a).

25. The process of claim 23, wherein said film is ingestible.

26. The process of claim 23, wherein said drying step maintains a non-self-aggregating uniform heterogeneity of said components throughout said film.

27. The process of claim 23, wherein said film is flexible when dried.

28. The process of claim 23, wherein said film is self-supporting.

29. The process of claim 24, wherein uniform distribution determines the amount of active material component per area.

30. The process of claim 24, wherein a specific amount of the active material component may be obtained from said film by cutting said film to a predetermined size.

31. The process of claim 23, wherein said drying of said film occurs within about 10 minutes or fewer.

32. A method of orally administering an active comprising the steps of:

(a) preparing a film by the steps of:

(i) combining a polymer, an active component, and water to form a material with a non-self-aggregating uniform heterogeneity;

(ii) forming said material into a film; and

(iii) drying said film in a controlled manner to maintain said non-self-aggregating uniform heterogeneity; and

(b) introducing said film to the oral cavity of a mammal.

33. A method of introducing an active component to liquid comprising the steps of:

(a) preparing a film by the steps of:

(i) combining a polymer, an active component, and a polar solvent to form a material with a non-self-aggregating uniform heterogeneity;

(ii) forming said material into a film; and

(iii) drying said film in a controlled manner to maintain said non-self-aggregating uniform heterogeneity; and

(b) placing said film into a liquid; and

(c) allowing said film to dissolve.

34. The method of claim 33, wherein said active ingredient is a flavoring.

35. The method of claim 34, wherein said flavoring is selected from the group consisting of hot and cold beverage flavorings and soup flavoring.

36. The method of claim 33, wherein said liquid is ingestible.

37. A dosage form for the administration of an active comprising:

(a) a first layer comprising a film formed by the steps of:

(i) combining a polymer, an active component, and a polar solvent to form a material with a non-self-aggregating uniform heterogeneity;

(ii) forming said material into a film; and

(iii) drying said film in a controlled manner to maintain said non-self-aggregating uniform heterogeneity; and

(b) a substantially non-water soluble second layer.

38. The dosage form of claim 37, wherein said first layer is removable from said second layer.

39. The dosage form of claim 37, wherein said film may be applied to the tongue of a mammal.

40. The dosage form of claim 37, wherein said film has a shape comprising first and second opposing bases wherein first base is longer than said second base.

41. The dosage form of claim 37, wherein said film has a shape selected from the group consisting of trapezoid and triangle.

42. The dosage form of claim 37, wherein said film adheres to an oral cavity.

43. The dosage form of claim 37, wherein said film includes an adhesive to adhere said film to an oral cavity.

44. A method of preparing a dosage form for the administration of an active comprising the steps of:

a. combining a polymer, an active component, and a polar solvent to form a material with a non-self-aggregating uniform heterogeneity;

b. forming said material into a film;

c. applying said film to a substantially non-water soluble support; and

d. drying said film in a controlled manner to maintain said non-self-aggregating uniform heterogeneity.

45. A method of administering an active comprising the steps of:

(a) preparing dosage form by the steps of:

(i) combining a polymer, an active component, and a polar solvent to form a material with a non-self-aggregating uniform heterogeneity;

(ii) forming said material into a film;

(iii) applying said film to a substantially non-water soluble support; and

(iv) drying said film in a controlled manner to maintain said non-self-aggregating uniform heterogeneity;

(b) removing said film from said support; and

(c) applying said film to the oral cavity of a mammal.

46. The method of claim 45, wherein said active is released as said film dissolves.

47. A film product formed by the steps of:

(a) combining a water soluble polymer and water to form a material with a non-self-aggregating uniform heterogeneity;

(b) forming said material into a film; and

(c) drying said film in a controlled manner to maintain said non-self-aggregating uniform heterogeneity.

48. A film product formed by the steps of:

(a) combining a polymer and a polar solvent to form a material with a non-self-aggregating uniform heterogeneity, said polymer selected to provide a viscosity sufficient to maintain said non-self aggregating heterogeneity;

(b) forming said material into a film; and

(c) drying said film.

49. A film product formed by the steps of:

(a) combining a polymer and a polar solvent to form a material with a non-self-aggregating uniform heterogeneity;

(b) forming said material into a film by reverse roll coating; and

(c) drying said film in a controlled manner to maintain said non-self-aggregating uniform heterogeneity.

50. A film product formed by the steps of:

(a) combining a polymer and a polar solvent to form a material with a non-self-aggregating uniform heterogeneity, said polymer selected to provide a viscosity sufficient to maintain said non-self aggregating heterogeneity;

(b) forming said material into a film by reverse roll coating; and

(c) drying said film in a controlled manner to maintain said non-self-aggregating uniform heterogeneity.

51. A process for making a film having a substantially uniform distribution of components comprising:

(a) combining a polymer component, and polar solvent to form a matrix with a uniform distribution of said components, said polymer selected to provide a viscosity sufficient to maintain said uniform distribution;

(b) forming a film from said matrix;

(c) providing a surface having top and bottom sides;

(d) feeding said film onto said top side of said surface; and

(e) drying said film by applying heat to said bottom side of said surface.

52. A process for making a film having a substantially uniform distribution of components comprising:

(a) combining a polymer component, and polar solvent to form a matrix with a uniform distribution of said components;

(b) forming a film from said matrix by reverse roll coating;

(c) providing a surface having top and bottom sides;

(d) feeding said film onto said top side of said surface; and

(e) drying said film by applying heat to said bottom side of said surface.

53. A process for making a film having a substantially uniform distribution of components comprising:

(a) combining a polymer component, and polar solvent to form a matrix with a uniform distribution of said components, said polymer selected to provide a viscosity sufficient to maintain said uniform distribution;

(b) forming a film from said matrix by reverse roll coating;

(c) providing a surface having top and bottom sides;

(d) feeding said film onto said top side of said surface; and

(e) drying said film by applying heat to said bottom side of said surface.

54. A process for making a film having a substantially uniform distribution of components comprising:

(a) combining a polymer component and polar solvent to form a matrix with a uniform distribution of said components;

(b) forming a film from said matrix; and

(c) drying said film by feeding said film onto a surface having top and bottom sides; said bottom side being in substantially uniform contact with a water bath at a temperature sufficient to dry said film.

55. The process of claim 54, wherein said water bath is temperature controlled.

56. A pharmaceutical and/or cosmetic dosage form comprising a film having a uniformly dispersed composition comprising a polymer, a pharmaceutical and/or cosmetic active and a solvent, said film being formed by depositing a wet film of said composition onto a substrate

surface and controllably drying the wet film from the side contacting the substrate to prevent self-aggregation and achieve compositional uniformity.

57. A pharmaceutical and/or cosmetic dosage form comprising a polymeric film having no more than a 10% variance of a pharmaceutical and/or cosmetic active per unit area.

58. A pharmaceutical composition in the form of a film for enteral or topical administration, comprising a composition having a uniformly distributed combination of a polymer, a polar solvent, and a pharmaceutical active, said composition in its dried film form maintaining the uniform distribution of components through the application of controlled bottom drying of the film.

59. The pharmaceutical composition of claim 58 in unit dosage form sealed in a pouch.

60. A pharmaceutical dispenser comprising individual unit dosage forms of the pharmaceutical composition of claim 58.

61. The dispenser of claim 60 wherein said individual unit dosage forms are in a roll or stacked in a dispenser.

62. The pharmaceutical composition of claim 58, further including simethicone.

63. The pharmaceutical and/or cosmetic dosage form of claim 56 or 57, further including simethicone.

64. The film product of claim 1, further including simethicone.

65. An edible water-soluble delivery system in the form of a film composition comprising a water-soluble polymer and simethicone.

66. The pharmaceutical composition of claim 58, wherein the pharmaceutical composition is essentially free of a surfactant.

67. The pharmaceutical and/or cosmetic dosage form of claims 56 or 57, wherein the pharmaceutical and/or cosmetic dosage form is essentially free of a surfactant.

68. The film product of claim 1, wherein the film product is essentially free of a surfactant.

69. The pharmaceutical composition of claims 58 or 66, wherein the pharmaceutical composition is essentially free of a plasticizer.

70. The pharmaceutical and/or cosmetic dosage form of claims 56, 57 or 67, wherein the pharmaceutical and/or cosmetic dosage form is essentially free of a plasticizer.

71. The film product of claims 1 or 68, wherein the film product is essentially free of a plasticizer.

72. The pharmaceutical composition of claims 58, 66 or 69, wherein the pharmaceutical composition is essentially free of a polyalcohol.

73. The pharmaceutical and/or cosmetic dosage form of claims 56, 57, 67 or 70, wherein the pharmaceutical and/or cosmetic dosage form is essentially free of a polyalcohol.

74. The film product of claims 1, 68 or 71, wherein the film product is essentially free of a polyalcohol.

75. An edible water-soluble delivery system in the form of a film composition comprising:

a water-soluble polymer comprising hydroxypropylmethyl cellulose, hydroxypropyl cellulose, and combinations thereof; and

an active component selected from the group consisting of cosmetic agents, pharmaceutical agents, bioactive agents and combinations thereof;

wherein the delivery system is essentially free of plasticizers, surfactants and polyalcohols.

76. The edible water-soluble delivery system of claim 75, wherein said active component is present in amounts of up to about 0.1% to about 60% by weight of the total delivery system.

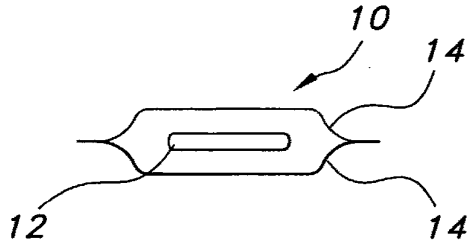

FIG. 1

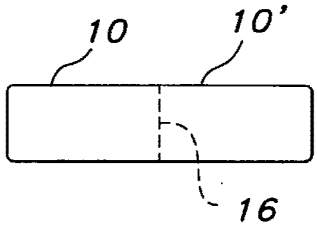

FIG. 2

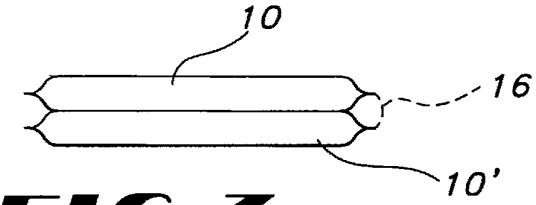

FIG. 3

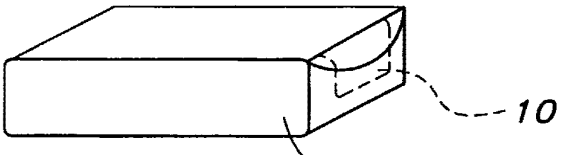

FIG. 4

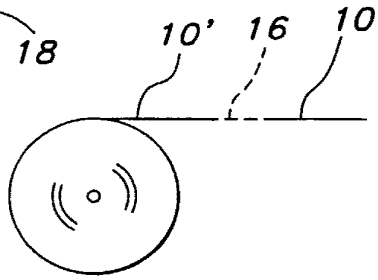

FIG. 5

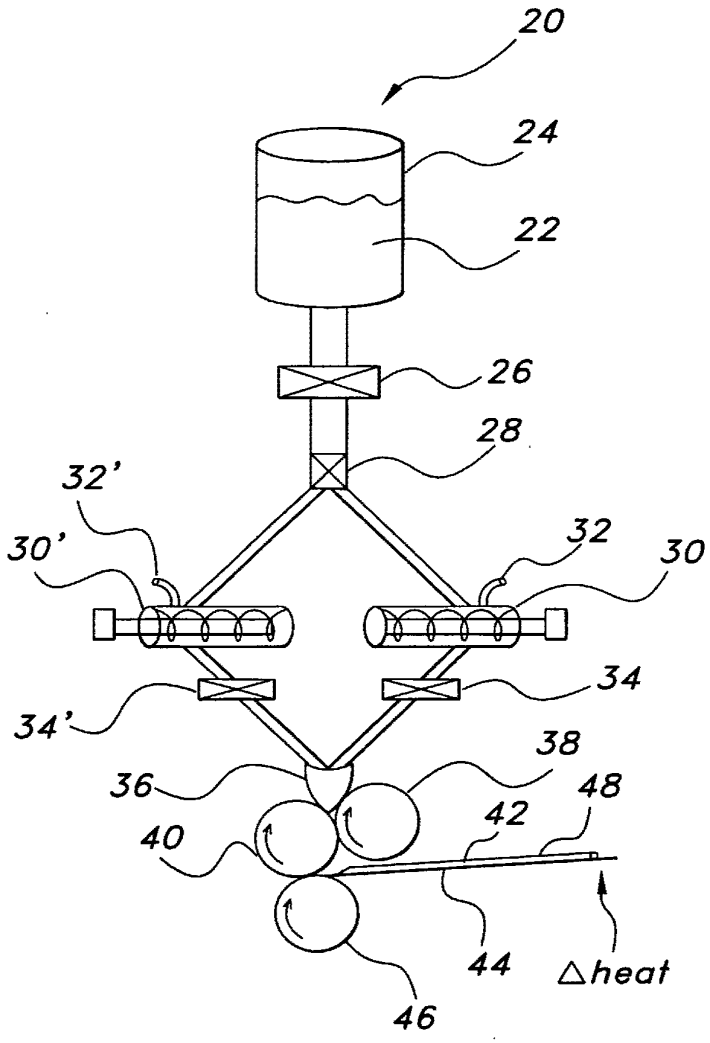

FIG. 6

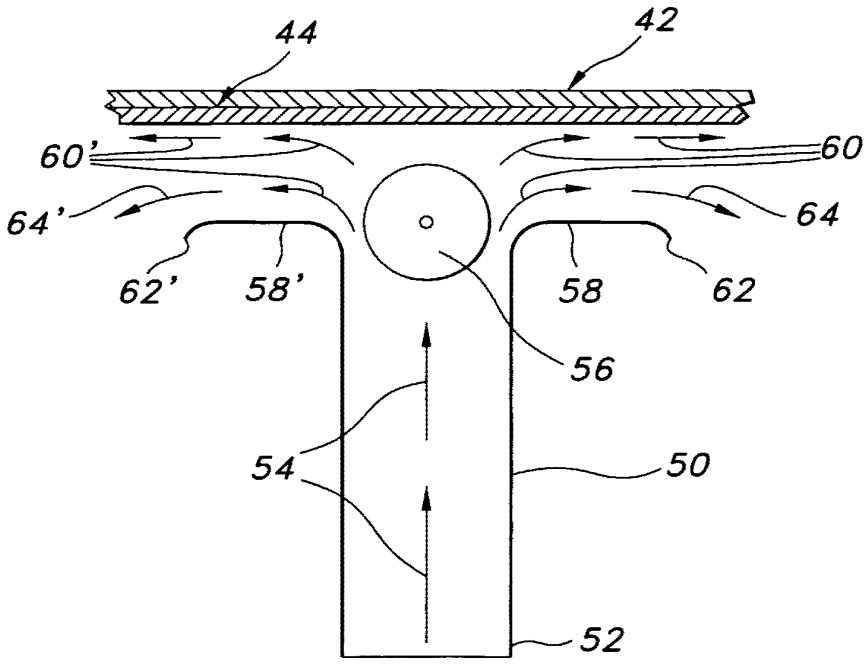

FIG. 7

INTERNATIONAL SEARCH REPORT

Internati pplication No
PCT/US 02/32575

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/70 A61K9/00

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 7 A61K A61P

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, BIOSIS, EMBASE, FSTA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 01 91721 A (STALEY MFG CO A E) 6 December 2001 (2001-12-06) example 8	1-76
X	US 6 284 264 B1 (ZERBE HORST GEORG ET AL) 4 September 2001 (2001-09-04) cited in the application column 4, line 7-11 example 1	1-76
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-/--

[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

"E" earlier document but published on or after the international filing date

"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)

"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

"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
30 January 2003	06/02/2003

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	Skjöldebrand, C

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Interna Application No
PCT/US 02/32575

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 4 849 246 A (SCHMIDT WOLFGANG) 18 July 1989 (1989-07-18) cited in the application the whole document ---	1-76
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A	US 4 136 145 A (FUCHS PETER ET AL) 23 January 1979 (1979-01-23) cited in the application the whole document ---	1-76
A	US 4 631 837 A (MAGOON RICHARD E) 30 December 1986 (1986-12-30) cited in the application the whole document -----	1-76

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 02/32575

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.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 32, 44 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. [X] Claims Nos.: 1-75 (in part)
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:

see FURTHER INFORMATION sheet PCT/ISA/210

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 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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-75 (in part)

There is an abundancy of independent claims with (partly) overlapping subject-matter. The current set of claims therefore lack clarity and conciseness (Art. 6 PCT).
The following independent claims in the respective categories were identified:
Product-by-process claims 1, 37, 47, 48, 49, 50.
Process/method claims 23, 33, 44, 51, 52, 53, 54,
Method of administration claims 32, 45
Product claims 56, 57 (pharm./cosmetic dosage form) 58 (pharm. composition), 65, 75 (delivery system).

In view of the large number of independent claims presently on file, it is difficult, if not impossible, to determine the matter for which protection is sought, the present set of claims fails to comply with the clarity and conciseness requirements of Article 6 PCT (see also Rule 6.1(a) PCT) to such an extent that a meaningful search for all these claims is impossible.

Although each respective category of independent claims contain somewhat different technical features, they appear to relate to the same invention. The following features seems however common to all the process claims:
A process for the production of a film with a uniform distribution of components, comprising:
a) combining a polymer with a polar solvent to form a matrix with a uniform distribution of said components
b)forming a film of the matrix
c) providing a surface having top and bottom sides
d) feeding the film to the surface
e) drying the film by applying heat to the bottom side of said surface

The feature "drying the film in a controlled manner" in some independent claims is vague and unclear and comprise basically all ways of drying. Consequently, the search has been carried out for the technical features a)-e) common to all independent process claims, as well as products formed by this process and a method of administering the product.

Moreover, the terms "polymer" and a "polar solvent" are so broad that they relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds used in the process claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the polymers in the present claim 15 and 16 and to the polar solvents used in the examples (water, ethanol).

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Moreover, the independent process claims relate to subject-matter defined by reference to a desirable characteristic or property, namely the uniform distribution of the components in the film. An attempt is made to define the process by reference to a result to be achieved. Said claims therefore lack clarity (Article 6 PCT). The claims should be drafted in such a way that the essential technical features necessary to achieve this desirable property are described.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat pplication No
PCT/US 02/32575

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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Application Number	12107389
Filing Date	2008-04-22
First Named Inventor	Robert K. Yang
Art Unit	1794
Examiner Name	
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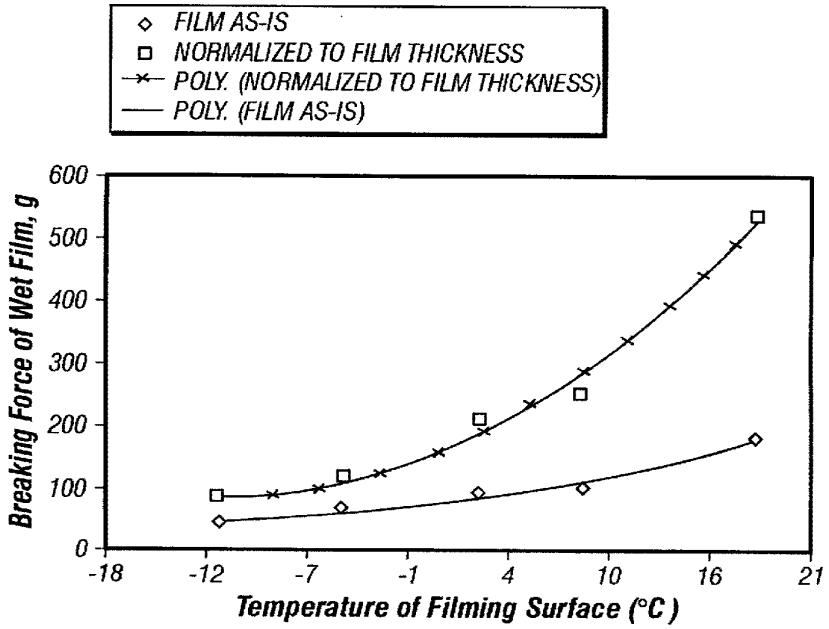
(54) Title: MODIFIED STARCH AS A REPLACEMENT FOR GELATIN IN SOFT GEL FILMS AND CAPSULES



(57) Abstract: Film-forming compositions are disclosed that can comprise, on a dry solid basis, 25 to 75 percent by weight of certain starch derivatives having a DE less than about 1,25 to 75 % plasticizer, and 0.1 to 15 % hydrocolloid gum. The starch derivatives can be chemically modified starches which range in molecular weight from 100,000 to 2,000,000. These starch-based systems can completely replace gelatin in edible film-forming applications such as soft and hard gel capsules.

WO 01/91721 A2

MODIFIED STARCH AS A REPLACEMENT FOR GELATIN IN SOFT GEL FILMS AND CAPSULES

BACKGROUND OF THE INVENTION

This invention relates to starch compositions useful in forming flexible films. More particularly, it relates to film-forming compositions containing certain modified starches.

Gelatin is a protein that forms thermo-reversible films. Gel masses composed of gelatin and a plasticizer such as glycerin are formulated to be liquid above room temperature, form a film when cast on a cooled surface, and re-melt when exposed to higher temperatures again. This ability to re-tackify enables encapsulation of liquid materials in gelatin soft capsules. Films formed from plasticized gelatin set very quickly and have high wet film strength. They are also very elastic with good clarity. Plasticized gelatin also has a relatively low viscosity, even when used at high solids concentrations. In addition, when gelatin is in the presence of water at room temperature, it swells but does not go into solution until heat is applied.

In the manufacture of soft gel films and capsules, the soft gel composition must possess the properties of good wet and dry film strength, insolubility in cold water, oil, and alcohol, solubility in hot water, temperature and pressure sealability, film clarity, film flexibility, edibility, inertness to drugs or other materials to be encapsulated, and rapid setting from a hot liquid to form a gel. In the manufacture of photographic elements, the soft gel films must possess the qualities of clarity, strength, setting power, flexibility, and non-interaction with other chemicals in the photographic film.

Although gelatin is useful in soft gel applications because of its rapid gelling ability, excellent film forming properties, and ability to impart oxygen impermeability, it has the disadvantages of high cost, limited availability, non-kosher status for food products and, at times, batch property variations. Because of these shortcomings, those industries where the need for gelatin is greatest have long sought means for replacing gelatin.

A useful gelatin replacer must be compatible with common plasticizers and fill materials used in the industry, and must provide properties equivalent to those of the gelatin which it is replacing for a particular application, e.g., film or binding strength in the pharmaceutical industry, phototransmissibility and resistance to abrasion in the photographic industry, and binding strength in the adhesive industry.

SUMMARY OF THE INVENTION

One aspect of the present invention is a film-forming composition that comprises starch material selected from the group consisting of modified starch and waxy starch; gum; and plasticizer. The modified starch or waxy starch has a dextrose equivalent (DE) of less than about 1, and preferably has no measurable DE. This composition can be, but is not required to be, 100% gelatin-free. Thus, the composition can be used as a gelatin replacement, or as an extender in gelatin formulations.

The composition typically will be prepared with water, and have a solids concentration of about 30-70% by weight. The solids in the composition preferably comprise 25-75% starch material, 25-75% plasticizer, and 0.1-15% gum. In certain preferred embodiments of the invention, the weight ratio of gum to starch is from about 0.1:1 to about 1:1, and the weight ratio of starch and gum to plasticizer is from about 1:0.8 to about 1:3.

The starch material preferably comprises starch which has been chemically modified with a monoreactive moiety to a degree of substitution of least about 0.015. It is also preferred that the starch material has an average molecular weight between about 100,000-2,000,000. In a particularly preferred embodiment, the starch material is selected from the group consisting of ether and ester derivatives of starch, such as hydroxypropyl, hydroxyethyl, succinate, and octenyl succinate starch. One specific embodiment of the invention comprises hydroxypropylated potato starch having a degree of substitution of about 0.015-0.30 and a molecular weight of about 100,000-2,000,000.

The gum preferably is selected from the group consisting of carrageenan, locust bean, xanthan, gellan, agar, alginates, guar, gum arabic, and pectin. A combination of kappa carrageenan and iota carrageenan, most preferably in a weight ratio of about 1:1, is especially preferred. The plasticizer preferably comprises at least one polyol, such as glycerol, sorbitol, maltitol, or a mixture of one or more of these. The composition of the present invention can optionally also comprise at least one monovalent or divalent cation, such as sodium, potassium, and calcium salts, or mixtures thereof.

Another aspect of the invention is an edible film that comprises the above-described starch-based composition, usually with much of the water removed. Yet another aspect of the invention is a soft gel capsule that comprises a sealed capsule wall and a first substance that is encapsulated by the sealed capsule wall. The capsule wall comprises the above-described starch-based composition. In one embodiment of the invention, the film or the capsule wall consists essentially of the combination of starch material, gum, and plasticizer.

The first substance encapsulated by the capsule wall can be any of a variety of materials which have been encapsulated by gelatin in the past. Many such substances are edible, including drugs, vitamins, nutritional supplements, and pre-measured food ingredients such as flavorings. It can also comprise, for example, photographic or dye solutions.

Another aspect of the invention is a method of encapsulating a first substance. This method comprises the steps of: providing a first substance and an edible film as described above; and encapsulating the first substance in the film. Preferably, the film used in this method has been formed on a surface having a temperature of at least about 38°C (100°F).

One object of this invention to provide an economical means for replacing gelatin in compositions utilized in the production of soft gel for food, pharmaceutical, and industrial applications. It is a further object of this invention to provide starch-based materials which are compatible with the existing application equipment used for manufacture of the various products which are primarily comprised of gelatin films.

The starch-based systems of the present invention, when incorporated as a replacement for gelatin in aqueous solutions, display properties superior to those of their parent base starch. More precisely, modified starches that have been chemically modified with monoreactive moieties to a degree of substitution of at least 0.015 DS, and degraded to molecular weights between 100,000 and 2,000,000, or, alternatively, waxy starches, when combined with gum and plasticizing agents, are a highly functional replacement for gelatin in soft gel film forming applications. The presence of gum increases the rate of film formation and enhances film strength.

In compositions of the present invention, the starch and gum preferably are mixed with plasticizers at ratios ranging from about 1 part starch and gum to about 0.8-3 parts plasticizer. The total solids in the composition preferably range from about 30 to 70% weight. Edible films are prepared by blending together the starch, gum, plasticizer, and water, and heating the mixture to a temperature and for a time sufficient to gelatinize the starch fully, (e.g., 80-100 °C for 10-60 min). A vacuum can be used either during or after cooking to remove entrained air and improve film properties. Additional materials may be added to the mixture of starch and plasticizer in order to impart improved functionality. Furthermore, properties of this system can be modified by the inclusion of various mono and divalent cations, including but not limited to sodium, potassium, and calcium. The mixture is then sheeted, while hot, to form a thin film. This film can be formed into soft gel capsules, encapsulating pharmaceutical, nutritional, photographic, or other materials, using well-known techniques.

The modified starch-based compositions of the present invention provide an acceptable balance of critical variables including mass viscosity and pot life, film rate, wet film strength, dry film strength and flexibility, and thermo-reversibility.

In one embodiment of the invention, wet film strength is significantly improved by increasing the temperature of the surface on which the film is formed. It is preferred in the present invention to use film-forming surface temperatures of about 38°C (100°F) or greater. Commercial capsule filming drum temperatures are often set around 10°C (50°F) for gelatin filming, but can easily be adjusted to 38-43°C (100-110°F). Breaking strengths can be increased by as much as 500% by increasing surface temperature from 12-66°C (53°F to 150°F). Films cast at 41°C (105°F) can have as much as twice the breaking strength films cast on 12°C (53°F) surfaces.

In one particularly preferred embodiment, the gum component of the composition consists essentially of 50% kappa carrageenan and 50% iota carrageenan. This combination can increase film strength by as much as 50% over films formed with 100% kappa carrageenan as the gum component, increase film elasticity, reduce the viscosity of the hot mass, lower the minimum temperature at which the gelled mass can be handled in liquid form, and lower the gel-setting temperature of the mass. This composition also broadens the temperature range over which the mass gels, which can improve the ease of film sealing.

The present invention has a number of benefits. One advantage of the invention is that it is a simple, cost-effective, dependable, intrinsically safe, Kosher, and efficient means for replacing the gelatin used in soft gel capsule compositions.

Another advantage of the invention is that the preparation of the starch-based compositions can be carried out by ordinary means with conventional manufacturing apparatus. The resulting compositions can be utilized in any commercial process requiring gelatin and to which conventional coating and drying methods are adaptable. Examples of end-product uses for the compositions of the present invention include encapsulated bath beads, paint balls, and pharmaceuticals. Therefore, the present invention provides a novel, efficient means for replacing gelatin in these and other applications.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a graph showing the effect of the temperature of the surface on which a film is formed on the strength of that film.

Figure 2 is a graph showing the effect of temperature on flow and gelation for compositions containing different types of carrageenan.

Figure 3 is a graph showing the effect of mass solids percentage on the flowability of compositions containing different types of carrageenan.

DETAILED DESCRIPTION OF SPECIFIC EMBODIMENTS

Examples of modified starches that can be used in the present invention include non-retrograding starches derived by chemical modification of starch from any plant source, including corn, waxy maize, potato, sweet potato, wheat, rice, sago, tapioca, sorghum, high amylose corn, and the like. The particular starch chosen will depend on its performance, availability, and cost. The starch should have a DE less than about 1, and preferably has no measurable DE (using the Lane-Eynon method). Among the useful modified starches are the common ether and ester derivatives of starch, including but not limited to hydroxypropyl, hydroxyethyl, succinate, and octenyl succinate starch derivatives. Also included among the modified starches suitable for use in the practice of this invention are the thermally converted, fluidity or thin boiling type products derived from the aforementioned types of chemically modified starches. Such materials may be of lower molecular weight, prepared by heating the modified starch alone or by subjecting the starch to a hydrolytic acid and/or heat treatment, or by any other known method designed for the thermal conversion of the starch, such as enzymic heat treatment.

Preferred modified starches are the hydroxypropyl derivatives of potato starch having a degree of substitution from 0.015-0.30 ds and a molecular weight of from 100,000 to 2,000,000. In the case of waxy starches of corn, potato, etc., the branches of the amylopectin replace the function of the ether or ester substituents; these starches are functional in the present invention without additional chemical modification, although their properties are not impaired by additional modification, and are enhanced by molecular weight reduction.

Suitable plasticizers include, but are not limited to, glycerol, sorbitol, and maltitol. Suitable hydrocolloid gums include carrageenan, locust bean gum, xanthan gum, gellan gum, agar, alginates, guar gum, gum arabic, and pectin.

The properties of the composition can be enhanced by the addition of certain cations, including but not limited to sodium, potassium, and calcium. The presence of these cations, in combination with certain gums, generally enhances viscoelastic properties and gel strength.

A variety of optional ingredients may be incorporated into the starch compositions of this invention, before, during, or after cooking the starch. Among the suitable additives which may be utilized are preservatives, colorants, flavoring agents, hardeners, antifoggers, sensitizers, and spreading agents. The inclusion of such additives has no adverse effect upon the properties exhibited by the novel starch-based compositions of the present invention.

A composition of the present invention is formed by combining the dry solids (i.e., the modified starch or waxy starch, gum, and plasticizer, plus any other additives), slurrying in water, and heating at a temperature and for a time sufficient to gelatinize the starch. Optionally, this can take place under a vacuum. Films can be formed from these starch-based compositions by any conventional method designed to solubilize and deposit a continuous coating or layer of the solution onto a substrate or mold of any form. Among the suitable coating techniques are spraying, dipping, air knife, trailing blade, reverse and direct roll coaters, etc. A film, such as an overcoating or capsule shell, may then be formed by drying the coated solution to a desired moisture content, using any means suitable for the particular purpose. Suitable conventional means include warm or cold air impingement, low humidity chamber or oven drying, etc. For example, in the pharmaceutical industry, soft gel capsules are prepared by casting a film of the gelatin solution and then continuously passing two ribbons of the film between two opposing rollers, each of which is equipped with an internal vacuum that draws in the film through half capsule wells engraved in its surface. The capsule contents are deposited between the shell halves as they are formed and sealed. The process is continuous, ending with the filled capsules being automatically conveyed to and through a drying unit that partially dries the capsule. Drying is completed in warm air tunnels.

The films of the present invention can be re-melted, and two or more of these re-melted films can be joined to form a seal.

The invention is particularly efficacious in the soft gel capsule manufacturing process that calls for film-forming materials, but it is not limited thereto. The characteristics exhibited by the present, novel starch formulations, particularly their ability to serve as a total replacement for gelatin, permit them to be used in a wide range of applications.

Although the emphasis has been placed on describing this invention in connection with film-forming gelatin-free compositions, compositions of the present invention can also be utilized as extenders in gelatin compositions such as creams, emulsions, binders, adhesives, etc.

Further compositions of the present invention can be used in the replacement of gelatin in hard shell capsule manufacturing.

EXAMPLES

The invention will be further illustrated by, but is not intended to be limited to, the following examples.

Compositions were prepared containing the component amounts given in Examples 1-7 on a dry solids basis. Starch molecular weights were measured by gel permeation chromatography and weight averaged. In Examples 1-7, the starch, plasticizer, and gum, if used, were mixed with sufficient deionized water (except where indicated) to give a total slurry mass of 35 g. The components were mixed together in the cup of a Rapid Visco Analyzer (Model RVA-4D, Foss Food Technology, Eden Prairie, MN) (hereafter referred to as "RVA"), and heated, using 160 rpm stirring, to 98°C over 4.5 minutes. The mixture was held at 98°C, with continued stirring, for 6.5 minutes, then transferred to a chilled surface and drawn into a film of 0.5 mm thickness for film testing. A second paste of the same composition was cooked in the same way and then transferred into a pre-heated glass jar, tightly capped, and placed into an oven for pot life evaluations.

In particular, in Examples 1-7, the film samples were prepared by casting a layer of the test solution at about 82°C (180°F) onto a Teflon-coated piece of glass (approximately 22.9 x 33 cm (9 in x 13 in)). The bottom of the glass was in contact with circulating cold water so that the surface temperature of the glass was 52°C. The film was formed by pouring the hot paste onto the Teflon surface and then quickly drawing the paste across the glass using a Bird Applicator or similar device, the gap width of which could be adjusted to control film thickness. Wet film thicknesses were typically 0.5-0.8 mm. The films were cast, dried, and aged in a room controlled to 21°C (70°F) and 25-30% relative humidity.

The viscosity of the starch mixture was measured by the RVA instrument, which records viscosity throughout the cook.

Pot life was evaluated by transferring the hot paste into preheated glass jars with screw lids, and placing these in a 82°C (180°F) oven. The fluidity of the mass was evaluated after 2 hours by tipping the jars upside down and assigning a flow rating of 0-5. A mass that flowed with the ease of water was given a rating of 5; a mass which did not flow at all was given a rating of 0. The oven temperature was then lowered by 10°C and the samples allowed to equilibrate for 2 hours, and then their flow properties re-assessed. The oven was lowered in 5.6°C (10 °F) increments until all samples had a flow rating of zero – that is, they had all gelled.

Thermo-reversibility was assessed by reheating the pot life samples, described above, in 5.6°C (10 °F) increments, allowing them to equilibrate at each temperature, and then assigning a flow rating using the same criteria as for pot life.

The films were evaluated for rate of filming using a Gardco Electronic Multicycle Circular Drying Time Recorder, and following test method procedure ASTM D 5895. The recorder was placed above the wet film, and a stylus was lowered onto the surface of the film and allowed to rotate for a defined time of 10 minutes. Three points were determined from this test: tack free, dry hard, and dry through. Tack free is defined as the point in the path made by the stylus on the film where the continuous track ends and a discontinuous track or tear begins. Dry hard is the point in the path where the stylus no longer tears the film, and only leaves a visible trace. Dry through is reached when the stylus no longer leaves any visible track on the film.

The tensile strength of the wet film was measured using a Stable Microsystems TA-XT2 Texture Analyzer. To do this, 1.3 cm x 20.3 cm (0.5 in x 8 in) strips were cut from the wet film 5 minutes after it was cast and these were loaded onto the Texture Analyzer. The tensile test was started 15 minutes after the film was cast.

Film appearance (color and clarity) was evaluated on the basis of visual observation.

Example 1

5.2 g potato starch, substituted with 3 wt % hydroxypropyl groups and of 600,000 molecular weight

0.75 g kappa carrageenan

9.7 g Sorbitol Special (obtained from SPI Polyols, New Castle, Delaware)

Example 2

8.4 g potato starch, substituted with 0.5% hydroxypropyl groups and of 600,000 molecular weight

11.8 g Sorbitol Special

Example 3

8.4 g potato starch, substituted with 3.0% hydroxypropyl groups and of 600,000 molecular weight

11.8 g Sorbitol Special

0.5 mm thickness.

Example 4

5.2 g potato starch, substituted with 3 wt % hydroxypropyl groups and of 600,000 molecular weight

0.75 g gellan

9.7 g sorbitol

0.5 mm thickness.

Example 5

5.2 g waxy corn starch of 800,000 molecular weight

0.75 g kappa carrageenan

9.7 g sorbitol

Example 6

5.2 g potato starch, substituted with 3 wt % hydroxypropyl groups and of 600,000 molecular weight

0.75 g kappa carrageenan

9.7 g glycerine

Example 7

5.2 g potato starch, substituted with 3 wt % hydroxypropyl groups and of 600,000 molecular weight

0.75 g kappa carrageenan

9.7 g Sorbitol Special

Sufficient 1% NaCl to bring to 35 g total mass.

The physical properties of the hot starch/plasticizer pastes for Examples 1-7, and the resulting films, are listed below in Table 1.

Table 1

Example number	Peak viscosity during cook, cps	Hot paste final visc, cps, 98°C	Time until tack free, sec	Time until dry hard, sec	Wet film tensile strength, g force	Pot life rating @ 82°C (180°F)	Minimum flowable temp, °C	Re-softening temp, °C
1	18000	1700	<5	<10	75	3.5	71	66
2	14000	2500	65	100	*			
3	13000	1150	4020	5700	*			
4		2300	<5	<10	108	0.5	>82	>82
5	13000	2400	<5	<10	65	3.0	77	66
6	16000	1500	<5	<10	50	4.0	71	66
7	11000	1300	<5	<10	75	3.5	77	66

* Too weak to test

Example 8

A formulation was prepared having the following composition (on an as-is basis):

16% starch which had been acid-thinned to approximately 600,000 mol wt and substituted with about 4 wt % hydroxypropyl groups (approx. 10% moisture).

2.3% kappa carrageenan (approx. 9% moisture)

26% Sorbitol Special (24% moisture)

6.7% glycerine (1% moisture)

49% added water

When the moisture in the components is taken into account, the total solids of the composition was 44%. The starch to carrageenan ratio was 6.75/1, and the ratio of plasticizer to thickener (starch plus carrageenan) was 1.6/1. The plasticizer was composed of 75% Sorbitol Special and 25% glycerine. The components were mixed together and then heated to 98°C for 15 minutes (or to 92°C for 30 minutes), then poured hot onto a surface and drawn down into a film.

To control the temperature of the surface onto which films were cast, a stream of water was passed underneath and in contact with that surface. In this experiment, the water stream heated water, rather than chilled water as in the previous examples. The surface temperature was controlled by adjusting the thermostat in the water reservoir – a conventional re-circulating water bath.

To determine "minimum flow temperature" and "gel temperature", masses were cooked in an RVA, then transferred to preheated glass vials and placed in a 82°C (180°F) oven. After 2 hours equilibration, the vials were tipped and the flow of the mass observed, and a ranking assigned and recorded. The oven temperature was then reduced by 5.6°C (10°F) and the samples allowed to equilibrate for an additional 2 hours. The "minimum flow temperature" was defined as the lowest temperature at which the mass would easily flow in the vial. It was viscous but "pourable". The "gel temperature" was the highest temperature at which the mass did not flow at all. Since the samples were evaluated in 5.6°C (10°F) increments, the temperature assignments are approximate.

The kappa carrageenan used for this experiment was SKW Satiagel RPT 8/60 Kappa Carrageenan. The iota carrageenan used was FMC SD 389 PF Iota Carrageenan.

During conventional production of gelatin soft-gel capsules, the hot gelatin mass is cast onto a cooled drum (10-13°C; 50-55°F). In this experiment, the surface onto which the mass was cast was heated by the circulating water stream, in order to slow the rate of cooling of the

composition. Figure 1 shows the variation in wet strength of the films formed as the surface temperature varied.

Increasing the temperature of the filming surface dramatically increased wet film strength. (Wet film strength is the important strength parameter since the film must have sufficient integrity within 1-4 minutes of casting to survive an open draw and other rigors of capsule production.) At higher temperatures, the film thicknesses were lower (probably due to flow on the heated surface). When the film strengths were normalized to film thickness (g force per mm thickness), the temperature effect was especially dramatic – increasing 5 fold as the surface temperature increased from 12-66°C (53°F to 150°F). The "as-is" film strength, uncorrected for film thickness, increased 4 fold.

Film rates were not quantified, but all conditions generated films which could be lifted and handled in under a minute.

Without being bound by theory, it is possible that the higher film strength observed when the surface temperature was higher is due to larger, greater numbers and/or more perfect helices. When the films cool slowly, they have time and mobility near the gelation temperature to form larger and/or more perfect helices. A higher percentage of the carrageenan may be involved in helices compared to material that is quench-cooled.

Example 9

Experiments were performed using compositions like that of Example 8, but in which the carrageenan content was reduced by 25% and the total mass solids percentage was increased. These compositions had a mass viscosity and wet film strength similar to that exhibited by the formulation of Example 8. The composition and properties of the two soft gels are compared in Table 2 below. The two gel masses have similar viscosity/temperature profiles, and gel at similar temperatures. (As mentioned above, a flow rating of 5 is similar to water. A rating of zero indicates that the sample is gelled and there is no flow. A rating of at least 3 is preferred for handing on commercial equipment.)

Table 2

mass solids, %	% carrageenan	% starch	Flow rating 82°C	Flow rating 77°C	Flow rating 72°C	Flow rating 66°C	Breaking strength, g 12°C filming	Breaking strength, g 41°C filming
44	4.1	37	4.5	4.0	2.0	0.0	57	180
48	5.2	42	4.0	3.0	2.0	0.0	---	78

A 25% reduction in carrageenan makes the composition significantly less costly. Increased mass solids percentage reduces shrinkage and drying costs.

Example 10

Starch-based compositions were prepared containing the same ingredients as in Example 8, except iota carrageenan was used as a complete replacement for kappa carrageenan. However, films formed from such compositions had a slow film formation rate. In addition, the films formed were soft, weak, and very elastic.

Tests were then performed using a composition like that of Example 8, except that it included a combination of kappa and iota carrageenan, rather than only kappa carrageenan. This change resulted in stronger films (higher yield stress) than either of the two types of carrageenan alone. The strongest films comprised a 50/50 (weight) combination of the two. As much as 50% increase in film strength was measured with the 50/50 blend of kappa/iota compared with the kappa-only films.

The temperature at which the kappa-only gel mass became a rigid gel was high - about 160°F for the composition of Example 8 at 44% solids. The mass viscosity builds rapidly as its temperature is dropped below 82°C (180°F). This could be a problem in manufacturing operations, because the hot mass could set up in a location in manufacturing equipment that is inadvertently underheated. Further, even higher temperatures (88°C plus) are needed to re-soften the kappa-only gel for capsule sealing. Moreover, kappa carrageenan has a very sharp liquid-gel transition, whereas iota's transition is rather broad.

Because the strength of films formed from kappa/iota blends were not a mathematical combination of the two individual carrageenans, and a 50/50 combination of the two gave the strongest films, a mixed gel structure was strongly implied. Carrageenan gels by coiling portions of its carbohydrate backbone into helixes with portions of another carrageenan molecule. If the gel is composed of helixes containing one strand of kappa carrageenan and one strand of iota carrageenan, predicting the softening temperature is not straightforward.

We therefore prepared gel masses composed of either kappa carrageenan, or a 50/50 blend of kappa and iota. All other aspects of the formula were held constant (see Example 8 for the formulation details). A series of gel masses with varying total solids were prepared for each carrageenan composition. The effects on gel temperature are illustrated in Table 3 below. ("Minimum flow" and "gel temperature" are as defined above.)

Table 3

Effect of carrageenan on mass flow properties and gel temperature

% ds	approx min. flow temp, deg C		approx gel temp, deg C	
	kappa	kappa/iota	kappa	kappa/iota
42	71	66	66	60
44	74	71	71	66
45	77	71	71	66
46	82	77	71	66
47	85	77	71	66

It can be seen that replacing half of the kappa carrageenan with iota decreased the temperature at which the mass will flow, and decreased its gel temperature, by about 5.6°C (10°F) for each of the solids levels tested.

At 82°C (180°F) the two formulations had similar flow properties, but the kappa-only samples thickened rapidly with drop in temperature. Figure 2 illustrates the effect. Lower gel temperature, and more gradual gelation, should make the films made from kappa/iota mixtures easier to handle and easier to seal.

Table 3 above illustrates the importance of solids control during handling of these formulations. Figure 3 illustrates the rapid decrease in mass flowability at 77°C (170°F) as mass solids increases. The effect is especially pronounced for the kappa-only formulation. Blending iota carrageenan with kappa allows for higher solids while maintaining manageable viscosity.

Example 11

Two films that comprised the same ingredients as Example 10 were dipped in mineral oil and then were re-melted and sealed together. During capsule production, gelatin films are typically coated with oil before they are sealed. Without being bound by theory, it is believed that in the absence of the oil coating, evaporative cooling makes it difficult to seal the films (the rapid evaporation cools the films below their gel point by the time the two surfaces came together). The mineral oil appeared to suppress evaporation and the starch-based films could be readily sealed. Both films made with kappa carrageenan and with kappa/iota blends sealed readily using this technique.

The preceding description of specific embodiments of the present invention is not intended to be a complete list of every possible embodiment of the invention. Persons skilled

in this field will recognize that modifications can be made to the specific embodiments described here that would be within the scope of the present invention.

WHAT IS CLAIMED IS:

1. A film-forming composition, comprising:
starch material having a dextrose equivalent less than about 1 and selected from the group consisting of modified starch and waxy starch;
gum; and
plasticizer.

2. The composition of claim 1, wherein the composition is gelatin-free.

3. The composition of claim 1, further comprising water.

4. The composition of claim 3, wherein the composition comprises 30-70% by weight dry solids.

5. The composition of claim 4, wherein the dry solids in the composition comprise 25-75% starch material, 25-75% plasticizer, and 0.1-15% gum.

6. The composition of claim 1, wherein the weight ratio of gum to starch is from about 0.1:1 to about 1:1.

7. The composition of claim 1, wherein the weight ratio of starch and gum to plasticizer is from about 1:0.8 to about 1:3.

8. The composition of claim 1, wherein the starch material comprises starch which has been chemically modified with a monoreactive moiety to a degree of substitution of least about 0.015.

9. The composition of claim 8, wherein the starch material has an average molecular weight of about 100,000-2,000,000.

10. The composition of claim 9, wherein the starch material is selected from the group consisting of ether and ester derivatives of starch.

11. The composition of claim 10, wherein the starch material is selected from the group consisting of hydroxypropyl, hydroxyethyl, succinate, and octenyl succinate starch.

12. The composition of claim 1, wherein the starch material comprises hydroxypropylated potato starch having a degree of substitution of about 0.015-0.30 and a molecular weight of about 100,000-2,000,000.

13. The composition of claim 1, wherein the gum is selected from the group consisting of carrageenan, locust bean, xanthan, gellan, agar, alginates, guar, gum arabic, and pectin.

14. The composition of claim 13, wherein the gum comprises a combination of kappa carrageenan and iota carrageenan.

15. The composition of claim 14, wherein the weight ratio of kappa carrageenan to iota carrageenan is about 1:1.

16. The composition of claim 1, wherein the plasticizer comprises at least one polyol.

17. The composition of claim 16, wherein the plasticizer is selected from the group consisting of glycerol, sorbitol, maltitol, and mixtures thereof.

18. The composition of claim 1, further comprising at least one monovalent or divalent cation.

19. The composition of claim 18, wherein the cation is selected from the group consisting of sodium, potassium, and calcium, and mixtures thereof.

20. The composition of claim 1, wherein:
the starch material is selected from the group consisting of (a) ether and ester derivatives of starch having a molecular weight of about 100,000-2,000,000 and a degree of substitution of about 0.015-0.30;
the gum comprises a combination of kappa carrageenan and iota carrageenan; and
the plasticizer comprises at least one polyol.

21. An edible film comprising the composition of any of claims 1-20.

22. A soft gel capsule comprising a sealed capsule wall and a first substance that is encapsulated by the sealed capsule wall;
wherein the capsule wall comprises a composition according to any of claims 1-20.

23. The capsule of claim 22, wherein the capsule wall consists essentially of a composition according to any of claims 1-20.

24. The capsule of claim 22, wherein the first substance is edible.

25. The capsule of claim 21, wherein the first substance is selected from the group consisting of drugs, vitamins, nutritional supplements, and pre-measured food additives.

26. A method of encapsulating a first substance, comprising the steps of:
providing a first substance and an edible film that comprises a composition according to any of claims 1-20; and
encapsulating the first substance in the film.

27. The method of claim 26, wherein the first substance is selected from the group consisting of drugs, vitamins, nutritional supplements, and pre-measured food additives.

28. The method of claim 26, wherein the film is formed at a temperature of at least about 38°C.

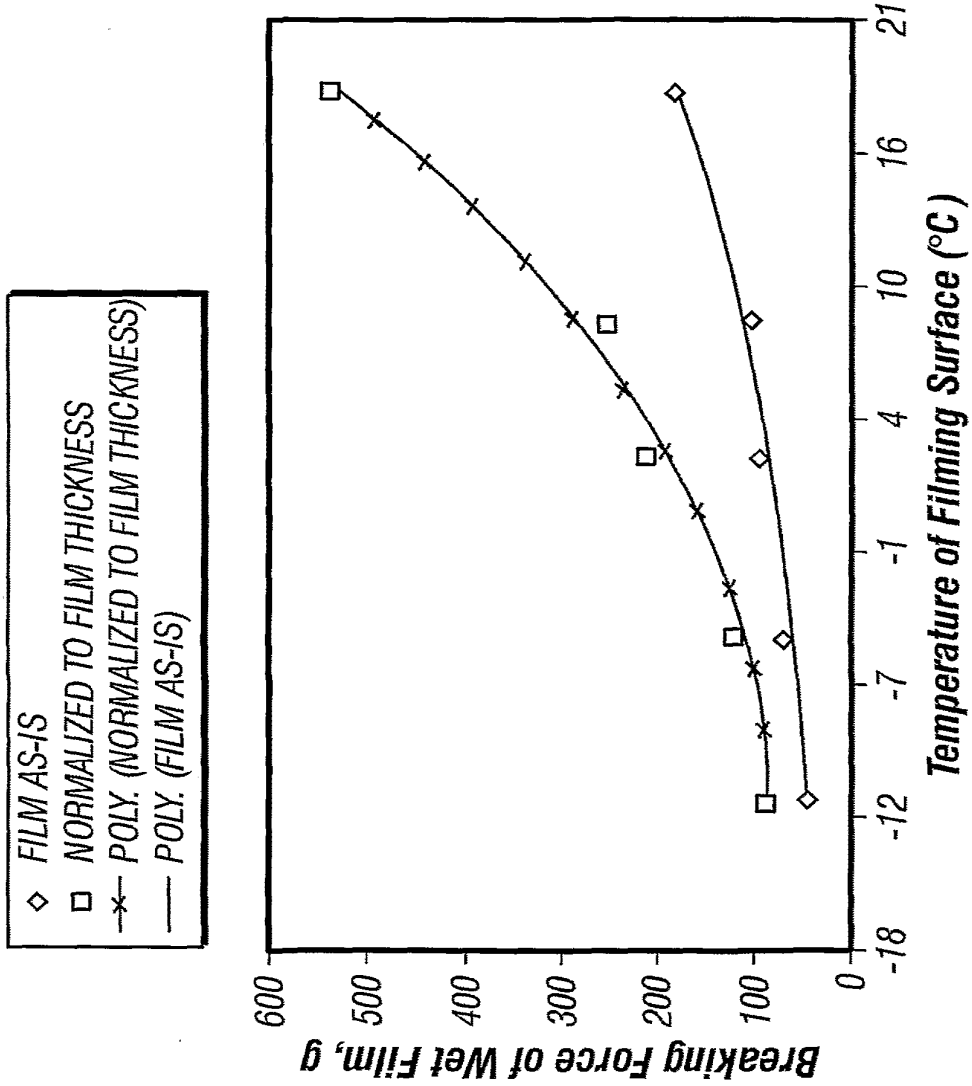


FIG. 1

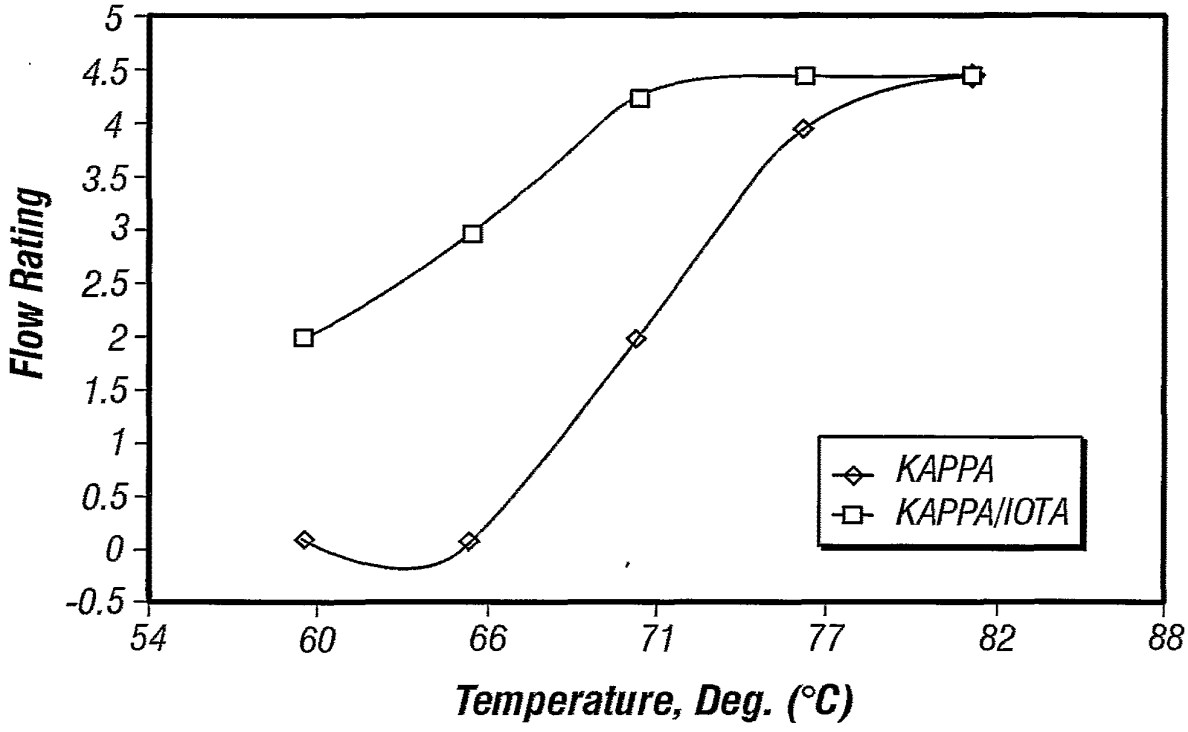


FIG. 2

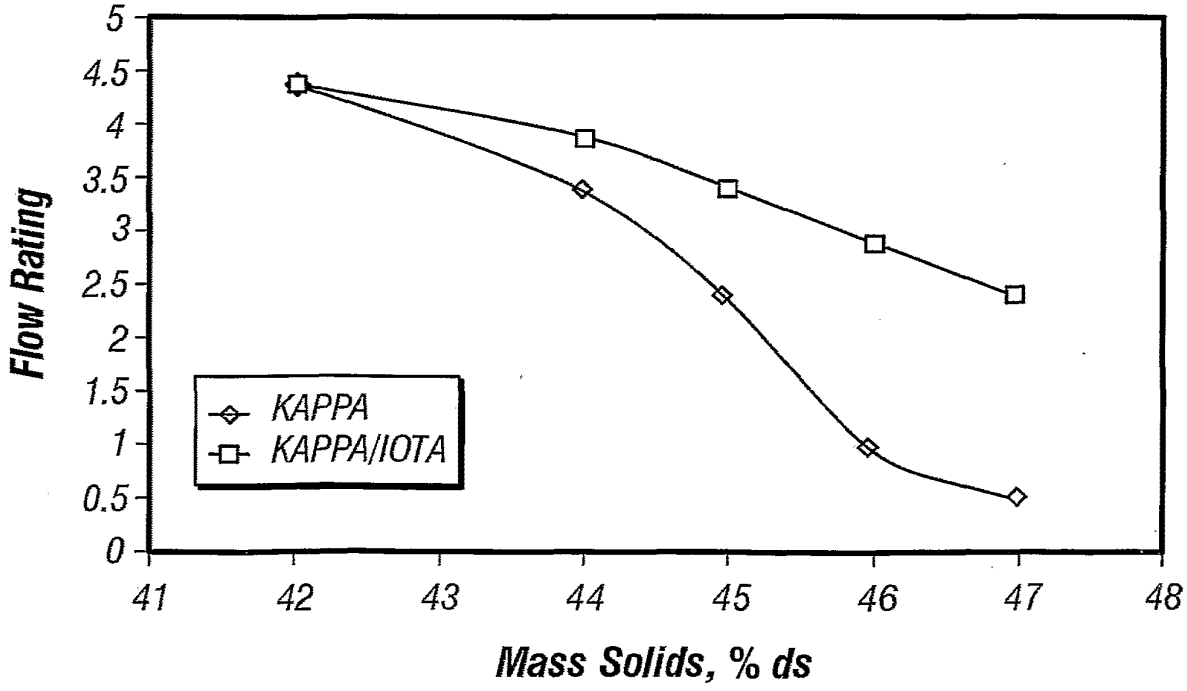


FIG. 3

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(54) Title: UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS

(57) Abstract: A thin film drug delivery composition includes (i) a flowable water-soluble film forming matrix; (ii) a particulate bioeffecting agent uniformly stationed therein; and (iii) a taste-masking agent coated or intimately associated with the particulate to provide taste-masking of the bioeffecting agent. The combined particulate and taste-masking agent have a particle size of 200 microns or less and the flowable water-soluble film forming matrix is capable of being dried without loss of uniformity in the stationing of the particulate bioeffecting agent therein. The combined particulate and taste-masking agent have a particle size of 150 microns or less, for example 100 microns or less. Moreover, the flowable water-soluble film forming matrix is formable into a dry film of less than about 380 microns in thickness, for example less than about 250 microns in thickness.

UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS

FIELD OF THE INVENTION

The present invention relates to compositions and methods for the preparation and use of a uniform rapid dissolve dosage form in the form of a film that includes a pharmaceutically active or bioeffecting agent and a taste-masking agent for masking the taste of the pharmaceutically active agent.

BACKGROUND OF RELATED TECHNOLOGY

While active ingredients such as pharmaceutical preparations may be included in a tablet or similar form to provide an accurate and consistent dose, including medicaments in such a form has several disadvantages in both the administration and preparation of the drug. Moreover, in such oral dosage forms, such as tablets or emulsions, pharmaceuticals have been coated to provide control release or taste-masking. Particle sizes of particulate pharmaceuticals are not critical in such dosage forms and generally large particle sizes, i.e., greater than 200 microns have been used.

There have been several attempts to provide an alternate dosage form, such as a film that would include a pharmaceutical active. However, such attempts have not been successful in providing a film that incorporates a drug with sufficient uniformity to provide accurate dosing.

Films that incorporate a pharmaceutically active ingredient are disclosed in expired U.S. Patent 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 specifically 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 governmental or agency standards relating to the variation of active in dosage forms. Currently, by law, 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.

Moreover, the problems of self-aggregation leading to non-uniformity of a film can result in an unpleasant tasting film when the film contains an unpleasant tasting pharmaceutical agent. Agglomerates of unpleasant tasting pharmaceutical agents may not be adequately masked by flavoring agents and sweeteners that are simply mixed into a film because the non-uniformity of the agglomerates may result in segregation of the unpleasant tasting agents from the flavoring agents and sweeteners. Fuchs merely mixes flavors and sweeteners into a film forming mix and fails to address the problem of aggregation or segregation of these materials.

Similarly, WO 00/42,992 also discloses the use of taste-modifying agents in a film dosage form. This international application also merely mixes taste-modifying agents into the film-forming mix without recognizing the problem of separation or aggregation of the taste-modifying agents from the unpleasant tasting pharmaceutical agents.

Furthermore, WO 01/70,194 discloses the use of ion exchange resins to for covalently binding pharmaceutical agents thereto. The resins have particle sizes from 20 microns to 200 microns and are described as being taste masking agents. The ion exchange resins are described as being bound with pharmaceutical agents and being mixed into consumerable films having thicknesses from 7 to 11 mils, or 180 microns to 280 microns. Such ion exchange resins, however, have limitations in the binding of pharmaceutical agents to the ion exchange resins, making the process for producing taste-masked comsumerable films complicated and expensive. Moreover, the use of ion exchange resins, which are water insoluble, limits the selection of useful pharmaceutical agents in water soluble films to only certain water soluble pharmaceutical agents that can covalently bond to the ionic resin.

Therefore, there is a need for a rapid dissolve dosage form, presented as a uniform film that addresses and corrects the problems associated with non-uniformity of a drug in film such as agglomeration or separation of particles within the film and the unpleasant tasting effects of the same. Moreover, there is a need for taste-masked, pharmaceutically active agents suitably contained within such a uniform film.

SUMMARY OF THE INVENTION

The present invention seeks to attain low adjuvant content, high taste-masked pharmaceutical active content films which have enhanced flexibility, structural integrity and uniformity. The present invention also provides for a unique method of producing the inventive compositions such that the compositional components are evenly distributed throughout the film. This process is described in detail in co-pending U.S. Patent Application No. 10/074,272, entitled "Thin Film with Non-Self-Aggregating Uniform Heterogeneity and Drug Delivery Systems Made Therefrom", the subject matter of which is herein incorporated by its entirety.

In one aspect of the present invention, a drug delivery composition includes (i) a flowable water-soluble film forming matrix; (ii) a particulate bioeffecting agent uniformly stationed therein; and (iii) a taste-masking agent coated or intimately associated with the particulate to provide taste-masking of the bioeffecting agent. The combined particulate and taste-masking agent have a particle size of 200 microns or less, and the flowable water-soluble film forming matrix is capable of being dried without loss of uniformity in the

stationing of the particulate bioeffecting agent therein. The importance of such particle sizes has not been recognized in the prior art, especially in prior art dosage forms, such as tablets and emulsions. Moreover, the importance of particle size is heightened in orally ingestible thin films, where uniformity is also of particular importance, and the prior art has failed to recognize such critically important features.

Desirably, the size of the combined particulate and taste-masking agent have a particle size of 150 microns or less, for example 100 microns or less. Moreover, the flowable water-soluble film forming matrix is formable into a dry film of less than about 380 microns in thickness, for example less than about 250 microns in thickness. Desirably, such particle sizes are contained within these dry films. In other words the dry films of the present invention desirably have smooth surfaces free of exposed agents that could impart grittiness or maldistribution of the active. Thus, in one aspect of the invention there is provided a film vehicle which contains a uniform distribution of actives, as defined herein, being suitably free of particles which accumulate on the film surface when dried.

Desirably, taste-masking agent is a thin film coating over portions of the bioeffecting agent. Useful taste-masking agents include polymeric materials. Water-soluble polymers are also useful. Desirably, the water-soluble polymer has an average molecular weight of equal to or greater than about 40,000. Furthermore, water-soluble polymers may be acrylic polymers, cellulosic polymers, and combinations thereof. Additionally, vinyl polymers, crown ethers, hydrogenated oils and waxes, and combinations thereof may also be used as taste-masking agents.

The matrix may be a cellulosic material; a gum; a protein; a starch; a glucan; and combinations thereof; such as but not limited to carboxymethyl cellulose; methyl cellulose; hydroxyl methyl cellulose; hydroxyethyl cellulose; hydroxypropyl cellulose; hydroxypropylmethyl cellulose; hydroxymethylpropyl cellulose; gum arabic; xanthan gum; tragacanth; acacia; carageenan; guar gum; locust bean gum; pectin; alginates; gelatinized, modified or unmodified starch, including tapioca starch, rice starch, corn starch, potato starch, and wheat starch; polyvinyl alcohol; polyacrylic acid; polyvinyl pyrrolidone; poly(meth)acrylate; poly(meth)copolymers; dextrin; dextran; proteins, such as, gelatin, zein, gluten, soy protein, soy protein isolate, and whey protein; whey protein isolate; casein; levin; collagen; chitin; chitosin; polydextrose and combinations thereof.

The bioeffecting agent may be present in amounts of up to about 0.1% to about 60% by weight of the total composition. Useful bioeffecting agents include, but are not limited to, antimicrobial agents, non-steroidal anti-inflammatory drugs, anti-tussives, decongestants, antihistamines, expectorants, anti-diarrheals, H_2 antagonists, proton pump inhibitors, general non-selective CNS depressants, general non-selective CNS stimulants, selective CNS functional modifiers, anti-parkinsonism drugs, narcotics, analgesics, anti-pyretics, psychopharmacological drugs and combinations thereof. The delivery vehicle composition may further include an organoleptic agent.

In another aspect of the present invention, a drug delivery vehicle includes (i) a water-soluble film matrix; and (ii) a particulate bioeffecting agent uniformly suspended within the matrix and having associated with it a taste-masking agent. The uniformity is determined by the presence of no more than a 10% by weight of drug variance throughout the matrix. Desirably, the drug variance is less than 5% by weight, less than 2% by weight, less than 1% by weight, or less than 0.5% by weight. Moreover, the particulates have a particle size of 200 microns or less. Furthermore, the film matrix desirably has a thickness of less than about 380 microns. Useful taste-masking agents include water-soluble polymers. Desirably, the water-soluble polymer has an average molecular weight of equal to or greater than about 40,000. Non-limiting water-soluble polymers include acrylic polymers, cellulosic polymers, and combinations thereof. The taste-masking agents may also include vinyl polymers, crown ethers, hydrogenated oils and waxes, and combinations thereof. The drug delivery vehicle of claim may further include an organoleptic agent with the bioeffecting agent.

In another aspect of the present invention, a drug delivery vehicle includes a dry mucoadhering film having a thickness defined by opposed surfaces. The film includes (i) a water-soluble polymer; and (ii) a pharmaceutically active particle comprising a pharmaceutically active agent coated or encapsulated with a water-soluble polymer having an average molecular weight of equal to or greater than about 25,000. Water-soluble polymers having an average molecular weight of equal to or greater than about 40,000 are also useful. Useful water-soluble polymers include of acrylic polymers, cellulosic polymers, and combinations thereof. Desirably, the pharmaceutically active particles are embedded within the film. Additionally, the film includes sections of substantially equal size and the particles are distributed in an amount that varies less than about 10% among the sections. Desirably,

the size of the particles are about 200 microns or less. Desirably, the film has a thickness of less than about 380 microns. Moreover, the drug delivery vehicle may further include an organoleptic agent with the water-soluble polymer.

In another aspect of the present invention, a drug delivery vehicle includes a dry mucoadhering film having a thickness defined by opposed surfaces. The film includes (i) a water-soluble polymer; and (ii) a pharmaceutically active particle having a pharmaceutically active agent and a taste-masking agent present in the amount of about 15-80% by weight of the particle. Desirably, the taste-masking agent is present in the amount of about 20-60% by weight of the particle. More desirably, the taste-masking agent is present in the amount of about 25-35% by weight of the particle. The pharmaceutically active particle is desirably embedded within the film, and the film includes sections of substantially equal size where the particles are distributed in an amount that varies less than about 10% among the sections. Useful sizes of the pharmaceutically active particles include particle sizes of 200 microns or less. Desirably, the film has a thickness of less than about 380 microns. The drug delivery vehicle may further include an organoleptic agent with the taste-masking agent.

In another aspect of the present invention, a drug delivery vehicle includes a dry mucoadhering film having a thickness defined by opposed surfaces. The film includes (i) a water-soluble polymer; and (ii) a pharmaceutically active particle comprising a pharmaceutically active agent and a taste-masking agent. The active particle has a particle size of less than about 200 microns. Desirably, the thickness of the film is less than about 380 microns.

In another aspect of the present invention, a drug delivery vehicle includes a dry mucoadhering film having a thickness defined by opposed surfaces. The film includes (i) a water-soluble polymer; and (ii) a pharmaceutically active particle comprising a pharmaceutically active agent and a taste-masking agent. The particle desirably has a particle size of less than about 200 microns and the taste-masking agent is present in amounts of about 15-80% by weight of the particle. A particle size of about 150 microns or less is also useful. Desirably, the particle size of the particle is about 100 microns or less. Desirably, the thickness of the film is less than about 380 microns, for example, less than about 250 microns. Furthermore, the taste-masking agent may be present in the amount of about 20-

60% by weight of the particle. Desirably, the taste-masking agent is present in the amount of about 25-35% by weight of the particle.

In another aspect of the present invention, a drug delivery vehicle includes a dry mucoadhering film having a thickness defined by opposed surfaces. The film includes (i) a water-soluble polymer; and (ii) a pharmaceutically active particle comprising a pharmaceutically active agent and an organoleptic agent. The active particle is taste-masked with a taste-masking agent. Useful organoleptic agents include flavors, sweeteners and combinations thereof.

In another aspect of the present invention, a drug delivery vehicle includes a dry mucoadhering film having a thickness defined by opposed surfaces. The film includes (i) a water-soluble polymer; and (ii) a pharmaceutically active particle comprising a pharmaceutically active agent being taste-masked with a taste-masking composition comprising a water-soluble polymer and at least one of a flavor or a sweetener.

In another aspect of the present invention, a method of preparing a thin film drug delivery vehicle is provided. The method includes the steps of (a) providing a pharmaceutically active agent / taste-masking agent complex; (b) combining the complex with a water-soluble polymer and a solvent to form a mixture with uniform distribution of the complex therein; (c) casting the mixture onto a planar carrier surface to form a thin film on the carrier surface; and (d) controllably drying the thin film to form a distribution variance of the complex having less than about 10% variance throughout any given area of the thin film. The step of providing the pharmaceutically active agent with the taste-masking agent includes a treatment for coating the taste masking agent onto portions of the pharmaceutically active agent. The drying includes applying heat the bottom of the carrier surface. Moreover, the drying may include applying microwave energy to the film. Useful methods for providing the pharmaceutically active agent with the taste-masking agent include fluidized bed coating, spray congealing coating, agglomeration or granulation coating, entrapment coating, coaccervation coating, infusion coating, spin coating, ion exchange coating the taste masking agent onto portions of the pharmaceutically active agent.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a side view of a package containing a unit dosage film of the present invention.

Figure 2 shows a top view of two adjacently coupled packages containing individual unit dosage forms of the present invention, separated by a tearable perforation.

Figure 3 shows a side view of the adjacently coupled packages of Figure 2 arranged in a stacked configuration.

Figure 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.

Figure 5 is a schematic view of a roll of coupled unit dose packages of the present invention.

Figure 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.

Figure 7 is a schematic view of an apparatus suitable for drying the films of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a pharmaceutical composition in the form of a film for external or topical administration, including a composition having a uniformly distributed combination of a polymer, a polar solvent, and a taste-masked pharmaceutically active or bioeffecting agent. The composition in its dried film form maintains the uniform distribution of components through the application of controlled bottom drying of the film.

Water-soluble polymers useful in the present invention include cellulosic materials, gums, proteins, starches, 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.

Examples of cellulosic materials include, without limitation, carboxymethyl cellulose, methyl cellulose, ethyl cellulose, hydroxylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, hydroxymethylpropyl cellulose, and combinations thereof.

Examples of water-soluble gums include gum arabic, xanthan gum, tragacanth, acacia, carageenan, guar gum, locust bean gum, pectin, alginates and combinations thereof.

Examples of other polymeric materials which may be incorporated include polyvinyl alcohol, polyacrylic acid, polyvinyl pyrrolidone, poly(meth)acrylate, poly(meth)copolymers and combinations thereof.

Useful starches include gelatinized, modified or unmodified starches. The source of the starches may vary and include pullulan, tapioca, rice, corn, potato, wheat and combinations thereof.

Useful water-soluble protein polymers include gelatin, zein, gluten, soy protein, soy protein isolate, whey protein, whey protein isolate, casein, levin, collagen and combinations thereof. Additional water-soluble polymers include dextrin, dextran and combinations thereof, as well as chitin, chitosin and combinations thereof, polydextrose and fructose oligomers.

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. 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 edible water-soluble delivery system of the present invention further include glucans, such as pullulan and elsinan. The ratio of glucan to water soluble polymer is about 40:1 to about 0.1:5. Glucans are generally desirable materials for edible film because of their high water solubility, rapid dissolution and excellent mouth-feel.

The edible water-soluble delivery system of the present invention further include an anti-foaming or defoaming agent, such as simethicone, which is a combination of a polymethylsiloxane and silicon dioxide. Simethicone acts as either an anti-foaming or defoaming agent which reduces or eliminates air from the film composition. An anti-foaming agent will aid in preventing the introduction of air into a composition, while a defoaming agent will aid in removing air from the composition.

The edible water-soluble delivery system of the present invention further include an active component selected from cosmetic agents, pharmaceutical agents, bioactive agents and combinations thereof. The active component may be present in any amount effective for the intended treatment. It is particularly desirable and an advantage of the present invention that the active component can be included in high loads. For example, the active component may be present in amounts up to about 60% by weight of the total composition and desirably in amounts of 0.01% to about 50% by weight of total composition.

The pharmaceutically or bioeffecting active components that may be incorporated into the films of the present invention include a wide variety of medicaments and pharmaceutical compositions. Examples of useful drugs include ace-inhibitors, antianginal drugs, anti-arrhythmias, anti-asthmátics, 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.

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®.

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 paroxtine hydrochloride (available as Paxil®); anti-migraines such as Imigra®, ACE-inhibitors such as enalaprilat (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®).

The popular H_2-antagonists which are contemplated for use in the present invention include cimetidine, ranitidine hydrochloride, famotidine, nizatidien, 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-ordibasic 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.

The pharmaceutically active agents employed in the present invention may be incorporated into the film compositions of the present invention in a taste-masked form. For example, particles of drug may be coated with taste-masking agents, for example polymers, oils and waxes. Additionally, organoleptic agents, such as, but not limited to sweeteners and/or flavors, may also be employed in such taste-masked compositions, including in the coating layer of the taste masking agent.

Suitable sweeteners include both natural and artificial sweeteners. Non-limiting examples of suitable sweeteners include, e.g.:

a. water-soluble sweetening agents such as monosaccharides, disaccharides and polysaccharides such as xylose, ribose, glucose (dextrose), mannose, galactose, fructose (levulose), sucrose (sugar), maltose, invert sugar (a mixture of fructose and glucose derived from sucrose), partially hydrolyzed starch, corn syrup solids, dihydrochalcones, monellin, steviosides, and glycyrrhizin;

b. water-soluble artificial sweeteners such as the soluble saccharin salts, i.e., sodium or calcium saccharin salts, cyclamate salts, the sodium, ammonium or calcium salt of 3,4-dihydro-6-methyl-1,2,3-oxathiazine-4-one-2, 2-dioxide, the potassium salt

of 3,4-dihydro-6-methyl-1,2,3-oxathiazine-4-one-2,2-dioxide (acesulfame-K), the free acid form of saccharin and the like;

c. dipeptide based sweeteners, such as L-aspartic acid derived sweeteners, such as L-aspartyl-L-phenylalanine methyl ester (aspartame), L-alpha-aspartyl-N-(2,2,4,4-tetramethyl-3-thietanyl)-D-alaninamide hydrate, methyl esters of L-aspartyl-L-phenylglycerin and L-aspartyl-L-2,5,dihydrophenylglycine, L-aspartyl-2,5-dihydro-L-phenylalanine, L-aspartyl-L-(1-cyclohexyen)-alanine, and the like;

d. water-soluble sweeteners derived from naturally occurring water-soluble sweeteners, such as a chlorinated derivatives of ordinary sugar(sucrose), known, for example, under the product description of sucralose; and

e. protein based sweeteners such as thaurnatoccous danielli(Thaurnatin I and II).

In general, an effective amount of auxiliary sweetener is utilized to provide the level of sweetness desired for a particular composition, and this amount will vary with the sweetener selected. This amount will normally be 0.01 % to about 10 % by weight of the composition. These amounts may be used to achieve a desired level of sweetness independent from the flavor level achieved from any optional flavor oils used. Of course, sweeteners need not be added to films intended for non-oral administration.

Useful flavors or flavoring agents include natural and artificial flavors. These flavorings may be chosen from synthetic flavor oils and flavoring aromatics, and/or oils, oleo resins and extracts derived from plants, leaves, flowers, fruits and so forth, and combinations thereof. Non-limiting flavor oils include: spearmint oil, cinnamon oil, peppermint oil, clove oil, bay oil, thyme oil, cedar leaf oil, oil of nutmeg, oil of sage, and oil of bitter almonds. Also useful are artificial, natural or synthetic fruit flavors such as vanilla, chocolate, coffee, cocoa and citrus oil, including lemon, orange, grape, lime and grapefruit, and fruit essences including apple, pear, peach, strawberry, raspberry, cherry, plum, pineapple, apricot and the like. These flavorings can be used individually or in combination. Commonly used flavors include mints such as peppermint, artificial vanilla, cinnamon derivatives, and various fruit flavors, whether employed individually or in combination. Flavorings such as aldehydes and esters including cinnamylacetate, cinnamaldehyde, citral, diethylacetal, dihydrocarvyl acetate, eugenyl formate, p-methylanisole, and the like may also be used. Further examples of aldehyde flavorings include, but are not limited to acetaldehyde (apple); benzaldehyde (cherry, almond); cinnamicaldehyde (cinnamon); citral, i.e., alpha citral (lemon, lime); neral,

i.e. beta citral(lemon, lime); decanal (orange, lemon); ethyl vanillin (vanilla, cream);heliotropine, i.e., piperonal (vanilla, cream); vanillin (vanilla, cream); alpha-amyl cinnamaldehyde (spicy fruity flavors); butyraldehyde (butter, cheese);valeraldehyde (butter, cheese); citronellal (modifies, many types); decanal(citrus fruits); aldehyde C-8 (citrus fruits); aldehyde C-9 (citrus fruits);aldehyde C-12 (citrus fruits); 2-ethyl butyraldehyde (berry fruits); hexenal, i.e. trans-2 (berry fruits); tolyl aldehyde (cherry, almond); veratraldehyde (vanilla);12,6-dimethyl- 5-heptenal, i.e. melonal (melon); 2 dimethyloctanal (greenfruit); and 2-dodecenal (citrus, mandarin); cherry; grape; mixtures thereof; and the like.

The amount of flavoring employed is normally a matter of preference, subject to such factors as flavor type, individual flavor, and strength desired. The amount may be varied in order to obtain the result desired in the final product. Such variations are within the capabilities of those skilled in the art without the need for undue experimentation. In general, amounts of about 0.1 to about 30 wt% are useful with the practice of the present invention.

A variety of polymeric and non-polymeric materials can be employed for taste masking pharmaceutically active agents. Non-limiting examples of polymers include acrylic polymers, cellulosic polymers or vinyl polymers. Non-limiting examples of non-polymeric materials include crown ethers, fully hydrogenated oils and waxes. Moreover, the taste masking agents may be water soluble, water insoluble or partially water soluble.

Useful non-limiting acrylic polymers include those available under the trade name Eudragit® from Röhm America, LLC, such as methacrylic acid co-polymers sold under the trade names Eudragit E®, Eudragit L®, Eudragit RD® and Eudragit S®, and polyethylacrylate-methylmethacrylate sold under the trade name, Eudragit NE®. These acrylic polymers are generally water soluble materials.

Useful non-limiting cellulosic polymers include, alkylcelluloses, such as, methyl or ethyl cellulose and, hydroxyalkylcelluloses, such as hydroxylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, hydroxymethylpropyl cellulose, and combinations thereof. Useful alkylcelluloses include those sold under the trade names Methocel E™ by Dow Chemicals. Additionally, useful ethylcelluloses are commercially available commercially available from FMC Corporation under brand name Aquacoat ECD. These acrylic polymers are generally water soluble materials.

Moreover, the pharmaceutically active agents may be sprayed and congealed with fully hydrogenated oils or waxes considered safe for human consumption and are relatively stable. Useful, but non-limiting, pharmaceutically acceptable oils include mineral oil, peanut oil, soybean oil, sunflower oil, corn oil, olive oil, hard palm oil and rapeseed oil.

Furthermore, crown ether compounds, such as cyclodextrins, are also useful for coating the pharmaceutically active agents. The pharmaceutically active agents are taste masked with crown ethers through entrapment or coaccervation methods. Useful cyclodextrins are commercially available under the trade name of Trappsol® from CTD, Inc.

Pharmaceutically active agents may be taste masked with the above-described taste-masking agents by a variety of techniques. The techniques coat the pharmaceutically active agents or portions of the pharmaceutically active agents with taste masking agents to avoid the unpleasant taste effects, such as bitterness, often associates with the pharmaceutically active agents or drugs. Useful coating techniques include, but are not limited to, fluidized bed coating, spray congealing coating, agglomeration or granulation coating, entrapment coating, coaccervation coating, infusion coating, spin coating, ion exchange coating and the like.

The fluidized bed coating method is commonly used in pharmaceutical industries for taste masking pharmaceutically active agents. Fluidized bed coaters achieve fluidization of the pharmaceutically active agents by introducing a continuous stream of process gas into a chamber. The coating material is deposited onto the suspended agent as it passes through the spray path of the coating material. The coated agents is dried. A relative low water solubility polymer is typically used to coat the active particles' surface. Minimum limits on particle sizes are about 100 to 120 microns. Smaller particle sizes are difficult to achieve due to process limitation and product loss. Water insoluble pharmaceutically active agents may be suitable coated with water soluble taste masking agents with this method.

In the spray congealing method both the pharmaceutically active agents and the coating materials are sprayed simultaneously into a chamber supplied with process gas to create a uniformly coated active. This method typically involves the coating of the actives with material that could be melted at reasonable temperatures, for example fatty materials or polymers such as certain Eudragit® polymers. The mix of materials are sprayed through a

fine nozzle and cooled through a temperature-control air stream or a cold surface. Consideration of mixture temperature is important. The melting temperature of the coating agent selected should not exceed a degradation temperature of the pharmaceutically active agent.

In the agglomeration or granulation method, the pharmaceutically active agents are mixed with the taste-masking agents and a solvent by mechanical means or by spray drying. The solvent is gradually removed by vacuum or heating, or both. Particles are then agglomerated. The agglomerated particles are not typically coated entirely with the taste masking agent and some bitterness may result accordingly. The bitterness, however, may be further reduced by incorporating such coated particles in the films of the present invention.

In typical entrapment coating methods, certain compounds having specific properties that can trap pharmaceutically active agents into its molecule cages must first be selected. Compounds, like certain specifically made starches and crown ether type molecules, such as cyclodextrins and zeolites, are useful with this method. The compounds and the agents are entrapped by ionic attraction. The entrapped agents are then precipitated from solution.

The coaccervation coating method uses two polymers with opposite charges in solution. When the solution is neutralized an insoluble matrix will precipitate from solution and trap the pharmaceutically active agents therein. Examples include interactions of gum arabic and gelatin solutions and interactions of cyclodextrins and protein solutions.

In the infusion method pharmaceutically active agents and flavors or sweeteners are dissolved and infused into a polymer matrix to form a dry powder. In spin coating methods, pharmaceutically active agents are combined with sugars or fats and spun into coated particles. Details of the method are disclosed in U.S. Patent No. 5,028,632, the contents of which is incorporated herein by reference. In ion exchange coating, ionic bonding of pharmaceutically active agents to ion exchange resins masks the tastes of the agents.

Extrusion and spheronization methods may also be used of taste-masking pharmaceutically active particulates. Ratios of active(s) and polymer(s) (such as, starch, cellulose, gum and/or combinations thereof) are first mixed and thicken by adding a small amount of water. The thickened mixture is then extruded through a single or double nozzle

screw. Small spherical particles are formed by a Marumerization® process. Desirable particle sizes are obtained through process control and particulate sieving.

Lyophilization (Freeze-Drying) methods may also be used with the practice of the present invention A combination of polymer(s) (such as, starch, gum, cellulose and/or combinations thereof) with active(s) are mixed and dissolved (or dispersed) in aqueous medium. This mixture is then freeze-dried on a pre-form substrate. Desirable particles sizes can be obtained by process control and product sieving.

In some instances, taste-masking may amount to the addition of two components together, neither of which are particularly pleasing to the taste, but which, due to their chemical makeup, counteract each other or allow for a third substance or more of one of the substances to be added without a concomitant reduction in pleasantness of the taste.

The edible water-soluble delivery system of the present invention further includes one or more members selected from antifoaming agents, plasticizing agents, surfactants, emulsifying agents, thickening agents, binding agents, cooling agents, saliva-stimulating agents, sweetening agents, antimicrobial agents, antigens and combinations thereof.

In one aspect of the present invention, a drug delivery composition includes (i) a flowable water-soluble film forming matrix; (ii) a particulate bioeffecting agent uniformly stationed therein; and (iii) a taste-masking agent coated or intimately associated with the particulate to provide taste-masking of the bioeffecting agent. The combined particulate and taste-masking agent have a particle size of 200 microns or less, and the flowable water-soluble film forming matrix is capable of being dried without loss of uniformity in the stationing of the particulate bioeffecting agent therein.

Desirably, the size of the combined particulate and taste-masking agent have 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. Furthermore, the flowable

water-soluble film forming matrix is formable into a dry film of less than about 380 microns in thickness, for example less than about 250 microns in thickness.

Desirably, taste-masking agent is a thin film coating over portions of the bioeffecting agent. Useful taste-masking agents include polymeric materials. Water-soluble polymers are also useful. Desirably, the water-soluble polymers have an average molecular weight of equal to or greater than about 40,000. Furthermore, water-soluble polymer may be acrylic polymers, cellulosic polymers, and combinations thereof. Additionally, vinyl polymers, crown ethers, hydrogenated oils and waxes, and combinations thereof may also be used as taste-masking agents.

The matrix may be a cellulosic material; a gum; a protein; a starch; a glucan; and combinations thereof; such as but not limited to carboxymethyl cellulose; methyl cellulose; ethyl cellulose; hydroxyl methyl cellulose; hydroxyethyl cellulose; hydroxypropyl cellulose; hydroxypropylmethyl cellulose; hydroxymethylpropyl cellulose; gum arabic; xanthan gum; tragacanth; acacia; carageenan; guar gum; locust bean gum; pectin; alginates; gelatinized, modified or unmodified starch, including tapioca starch, rice starch, corn starch, potato starch, and wheat starch; polyvinyl alcohol; polyacrylic acid; polyvinyl pyrrolidone; poly(meth)acrylate; poly(meth)copolymers; dextrin; dextran; proteins, such as, gelatin, zein, gluten, soy protein, soy protein isolate, and whey protein; whey protein isolate; casein; levin; collagen; chitin; chitosin; polydextrose and combinations thereof.

The bioeffecting agent may be present in amounts of up to about 0.1% to about 60% by weight of the total composition. Useful bioeffecting agents include, but are not limited to, antimicrobial agents, non-steroidal anti-inflammatory drugs, anti-tussives, decongestants, antihistamines, expectorants, anti-diarrheals, H_2 antagonists, proton pump inhibitors, general non-selective CNS depressants, general non-selective CNS stimulants, selective CNS functional modifiers, anti-parkinsonism drugs, narcotics, analgesics, erectile dysfunction therapies, anti-pyretics, psychopharmacological drugs and combinations thereof. The delivery vehicle composition may further include an organoleptic agent.

In another aspect of the present invention, a drug delivery vehicle includes (i) a water-soluble film matrix; and (ii) a particulate bioeffecting agent uniformly suspended within the matrix and having associated with it a taste-masking agent. The uniformity is determined by

the presence of no more than a 10% by weight of drug variance throughout the matrix. Desirably, the drug variance is less than 5% by weight, less than 2% by weight, less than 1% by weight, or less than 0.5% by weight. Moreover, the particulates have a particle size of 200 microns or less. Furthermore, the film matrix desirably has a thickness of less than about 380 microns.

Useful taste-masking agents include water-soluble polymers. Desirably, the water-soluble polymer has an average molecular weight of equal to or greater than about 40,000. Non-limiting water-soluble polymers include acrylic polymers, cellulosic polymers, and combinations thereof. The taste-masking agents may also include vinyl polymers, crown ethers, hydrogenated oils and waxes, and combinations thereof. The drug delivery vehicle of claim may further include an organoleptic agent with the bioeffecting agent.

In another aspect of the present invention, a drug delivery vehicle includes a dry mucoadhering film having a thickness defined by opposed surfaces. The film includes (i) a water-soluble polymer; and (ii) a pharmaceutically active particle comprising a pharmaceutically active agent coated or encapsulated with a water-soluble polymer having an average molecular weight of equal to or greater than about 25,000. Water-soluble polymers having an average molecular weight of equal to or greater than about 40,000 are also useful. Useful water-soluble polymers include of acrylic polymers, cellulosic polymers, and combinations thereof. Desirably, the pharmaceutically active particles are embedded within the film. Additionally, the film includes sections of substantially equal size and the particles are distributed in an amount that varies less than about 10% among the sections. Desirably, the size of the particles are about 200 microns or less. Desirably, the film has a thickness of less than about 380 microns. Moreover, the drug delivery vehicle may further include an organoleptic agent with the water-soluble polymer.

In another aspect of the present invention, a drug delivery vehicle includes a dry mucoadhering film having a thickness defined by opposed surfaces. The film includes (i) a water-soluble polymer; and (ii) a pharmaceutically active particle having a pharmaceutically active agent and a taste-masking agent present in the amount of about 15-80% by weight of the particle. Desirably, the taste-masking agent is present in the amount of about 20-60% by weight of the particle. More desirably, the taste-masking agent is present in the amount of about 25-35% by weight of the particle. The pharmaceutically active particle is desirably

embedded within the film, and the film includes sections of substantially equal size where the particles are distributed in an amount that varies less than about 10% among the sections. Useful sizes of the pharmaceutically active particles include particle sizes of 200 microns or less. Desirably, the film has a thickness of less than about 380 microns. The drug delivery vehicle may further include an organoleptic agent with the taste-masking agent.

In another aspect of the present invention, a drug delivery vehicle includes a dry mucoadhering film having a thickness defined by opposed surfaces. The film includes (i) a water-soluble polymer; and (ii) a pharmaceutically active particle comprising a pharmaceutically active agent and a taste-masking agent. The active particle has a particle size of less than about 200 microns. Desirably, the thickness of the film is less than about 380 microns.

In another aspect of the present invention, a drug delivery vehicle includes a dry mucoadhering film having a thickness defined by opposed surfaces. The film includes (i) a water-soluble polymer; and (ii) a pharmaceutically active particle comprising a pharmaceutically active agent and a taste-masking agent. The particle desirably has a particle size of less than about 200 microns and the taste-masking agent is present in amounts of about 15-80% by weight of the particle. A particle size of about 150 microns or less is also useful. Desirably, the particle size of the particle is about 100 microns or less. Desirably, the thickness of the film is less than about 380 microns, for example, less than about 250 microns. Furthermore, the taste-masking agent may be present in the amount of about 20-60% by weight of the particle. Desirably, the taste-masking agent is present in the amount of about 25-35% by weight of the particle.

In another aspect of the present invention, a drug delivery vehicle includes a dry mucoadhering film having a thickness defined by opposed surfaces. The film includes (i) a water-soluble polymer; and (ii) a pharmaceutically active particle comprising a pharmaceutically active agent and an organoleptic agent. The active particle is taste-masked with a taste-masking agent. Useful organoleptic agents include flavors, sweeteners and combinations thereof.

In another aspect of the present invention, a drug delivery vehicle includes a dry mucoadhering film having a thickness defined by opposed surfaces. The film includes (i) a

water-soluble polymer; and (ii) a pharmaceutically active particle comprising a pharmaceutically active agent being taste-masked with a taste-masking composition comprising a water-soluble polymer and at least one of a flavor or a sweetener.

In another aspect of the present invention, a method of preparing a thin film drug delivery vehicle is provided. The method includes the steps of (a) providing a pharmaceutically active agent / taste-masking agent complex; (b) combining the complex with a water-soluble polymer and a solvent to form a mixture with uniform distribution of the complex therein; (c) casting the mixture onto a planar carrier surface to form a thin film on the carrier surface; and (d) controllably drying the thin film to form a distribution variance of the complex having less than about 10% variance throughout any given area of the thin film. The step of providing the pharmaceutically active agent with the taste-masking agent includes a treatment for coating the taste masking agent onto portions of the pharmaceutically active agent.

The drying includes applying heat to the bottom of the carrier surface. Moreover, the drying may include applying microwave energy to the film. Such microwave drying is useful because drying initiates in the middle portions of the film. The present invention, however, is not limited to these drying methods. Any drying method may suitably be used as long as the drying does not initiate at the top surface of the casted mixture. Such top surface drying does not typically provide desirable film uniformity.

Useful methods for providing the pharmaceutically active agent with the taste-masking agent include fluidized bed coating, spray congealing coating, agglomeration or granulation coating, entrapment coating, coaccervation coating, infusion coating, spin coating, ion exchange coating the taste masking agent onto portions of the pharmaceutically active agent.

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, ophthalmological, 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 Figure 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 Figure 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 Figure 5 or stacked as shown in Figure 3 and sold in a dispenser 18 as shown in Figure 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.

Rheology and Films Properties

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. Patent 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_l) 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:

$$V_o = (2gr^r)(\rho_p - \rho_l)/9\mu$$

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:

$$v/V_o = 1/(1 + \kappa\varphi)$$

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

$$\mu/\mu_o = 1 + 2.5\varphi + C_1\varphi^2 + C_2\varphi^3 + ...$$

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., <500μm. 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 $10 - 10^5$ 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.

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 ("cps" or "centipoise") 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.

Film Component Mixing:

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 pre-mix 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 pre-mix 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.

Figure 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 Figure 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.

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.

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

While the proper viscosity, uniformity in mixture and stable suspension of particles, and casting method are important in the initial steps of forming the 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. 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. 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 ½ minute to about the first 4 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.

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.

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 0.1mils to about 10mils. 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.

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, 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.

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 Figure 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 Figure 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.

It has also been unexpectedly discovered that high temperature fat materials, e.g. M.P. 55°C or greater, can be used to encapsulate dry particles before or after enteric coating. The drying process temperatures are sufficiently rapid and low, and evaporative cooling effect as a result of water vapor loss is sufficiently high enough, that the fat does not appreciably melt.

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.

The following non-limiting examples are intended to further illustrate the present invention.

EXAMPLES

Preparation Of Taste-Masked Pharmaceutically Active Agents:

The following drugs were coated with taste masking components and were used in the films of the present invention.

a. Fluidized Bed Coating: A taste-masked particle was prepared having a core material of northindrone (Norlutin®). Northindrone was first sieved through a 60 mesh screen having a 250 micron sieve opening. The resulting particles, i.e., having particles sizes of less than 250 microns, were then coated by the fluidized bed coating procedure in a Verse Glatt Fluidized Bed using a Wurster Column. Accordingly, a 625 grams of 5 % methylcellulose and 0.5 % Acesulfame® K (a non-caloric sweetener) solution was prepared. The solution was then applied onto 500 grams of the sieved northindrone powder at an air pressure of 40 psi through a Gustav Schlick nozzle model 941. The fluidized bed temperature was heated and maintained at 115°F during the spraying process. At the end of coating, the resulting particles were further dried therein for 3 minutes. A total of 530 grams taste masked northindrone was obtained.

b. Agglomeration Process: A sweetener solution of 94 grams of 2.5 % sodium saccharin and 2.5 % Acesulfame® K was prepared. A dry blend of 60 grams of hydroxypropylmethyl cellulose and 40 grams of silica dioxide with 20 grams polythiazide (Renese®) was made. The sweetener solution was then sprayed a little at a time onto the dry blend powder during low-shear mixing. The dry powder was, at this point, being agglomerated through the granulation/absorption process. The wet mixture was then dried in a convection oven at 105°F for 17 hours. The resulting dried product was ground in a Fitz Hammer Mill grinder and sieved through a 100 mesh screen having a 149 micron sieve opening.

c. Pelletization Process: The following product was made using a model RV02 Mix Pelletizer (made by Eirich Machines Ltd.) at maximum mixing speed. A small of crashed ice was added, slowly through a funnel, to the 40 grams Loratidine®, 40 grams Aspartame®, 10 grams hydroxypropyl cellulose and 5 grams gum arabic powder mix in the mixer while mixing at low settings of both pan rotation and mixing motor. It took 1 to 2 minutes to add the ice. Once the ice addition was completed, both the pan and the rotor mix were turned to high speed to form spherical particles. The end point was determined by examining the particles using a low power microscope. When the end point is not reached after 2 minutes of intense mixing, additional 1 to 2 minutes mixing with or without adding more ice is tried. This procedure is repeated until the end point is reach, i.e., the spherical particles are formed. The wet samples obtained were dried in a tray dryer at 55°C for about 5 hours. The resulting particles size ranged from 20 to 200 mesh. The particles were then sieved to obtain the desired particle size.

d. Infusion Method: A dry blend of 3.7 grams of Sucralose®, 10 grams fluoxetine HCl (Prozac®), and 1.25 grams polyvinylpyrrolidone were mixed uniformly. Water of 5.0 grams and 2.74 grams of propylene glycol were then added to the mixture and mixed thoroughly. To this mixture, 22 grams of hydroxypropylmethyl cellulose was added and blended under a high shear Stephan Mixer for at least 3 minutes. The resulting particles were sieved through a 100 mesh screen and were ready to be used in film matrix solution.

e. Triglyceride Reduction Formula™ microspheres from Southwest Research Institute were coated with ethylcellulose by a spinning and congealing particle producing process. The coated particles had a particle size of less than 100 microns. The polymer condensed on the drug particles thereby imparting a taste-masked pharmaceutically active agent.

f. Tamoxifen was produced by spray coating 50 to 100 micron sized particles of Eudragit® E100 (cationic methacrylate with dimethylamino ethyl ammonium groups). During fluidized coating, coated particles were isolated using a fractional separation device which insured particles having a size of less than 150 microns. The estimated level of coating was about 15%. The polymer condensed on the drug particles thereby imparting a taste-masked pharmaceutically active agent.

g. Torsemide was coated by a critical fluid process by dissolving torsemide in polyethylene glycol (400 molecular weight) which was added to a flowing stream of supercritical CO_2 by using a sonic spray nozzle. The resulting droplet size was controlled to produce approximated 150 micron sized spherical particles. The particles were then moved to an apparatus used for spraying a polymer coating. The polymer condensed on the drug particles thereby imparting a taste-masked pharmaceutically active agent. The polymer coating used was Eudragit® E100 dissolved in ethanol at 15% solids. The coated product was isolated by lowering the pressure and removal of the CO2 and the ethanol.

h. Felodipine was coated via an emulsion solvent evaporation method using acrylate methacrylate copolymers (Eudragit® RL or Eudragit® PO and Eudragit® RS or Eudragit® PO) as the coating materials. The mean sphere diameter was 12 microns with a drug loading of about 50%.

i. Digoxin was coated with Trappsol® cyclodextrin. A 50% (wt/vol) solution of chemically modified cyclodextrin was produced by mixing it with water at room temperature. A finely ground digoxtin (less than 15 microns) was suspended in the solution with mild stirring. The mix was stirred for 60 minutes and any undissolved drug was removed by

centrifugation through a 0.45 micron sized membrane. Spray drying of the solution yielded a dry powder with a 10% drug loading.

Preparation Of The Film Forming Composition:

A film-forming composition, Composition A in Table 1, was prepared and mixed under vacuum to remove air bubbles. In further detail, a polymer mix of hydroxypropylmethyl cellulose (Methocel™ E15), polyvinylpyrrolidone and starch and xanthan were added to water with stirring over a short period of time of about 15 minutes. The stirring was set at 350 to 1500 rpm using an axial impeller. Stirring continued for another 45 minutes after combining the components to form a viscous, uniform mix.

To this viscous mix plasticizer (propylene glycol), flavor, antifoam and sweetener were sequentially added. The mixture was stirred for an additional 10 minutes at 500 rpm before the addition of a taste-masked drug.

TABLE 1

Film Forming Polymer Composition	Composition
Ingredient	**A**
Hydroxypropylmethyl cellulose	8.5
Polyvinylpyrrolidone	5.5
Starch	5.5
Sweetener	2.4
Flavor (Mint Mix)	3.3
Xanthan Gum	0.3
Plasticizer	3.4
Antifoam agent	0.8
Water	70.4
Total:	100

A taste-masked drug was added to the mixture in about a 5 minute time period. After the addition of the drug the mixture was placed under a vacuum from about 0.1 to about 0.7 torr for about 45 minutes.

Film Compositions With Taste-Masked Pharmaceutically Active Agents:

After removing the vacuum, the product mix was added to a coating pan and filmed using a three-roll coater. The suspension was coated at 250 microns onto siliconized paper

substrate and moved through a drying oven heated at 90°C. The composition was dried in accordance with the process set forth in co-pending U.S. Application No. 10/074,272.

The dried product was examined for physical appearance, dissolution in the mouth and bitterness.

The resultant uncut films of inventive composition A with the above-described taste-masked drugs exhibited uniformity in content particularly with respect to the tasted-masked drugs, as well as unit doses of ¾" by 1" by 5-6 mils cut therefrom. The inventive compositions also were observed to have a smooth surface, absent of air bubbles. The films had minimal taste when ingested. All films dissolved in the mouth in less than 15 seconds.

The film produced with the less than 100 micron sized taste-masked triglyceride had a loading of 20 mg per 25 mm^2 piece of film. The film produced with the less than 150 micron sized taste-masked tamoxifen had a loading of 10 mg per 20 mm^2 of film (assuming 85% active). The film produced with the less than 150 micron sized taste-masked torsemide had a loading of 10 mg per 25 mm^2 of film (assuming 90% active). The film produced with the taste-masked digoxin had a loading of 0.5 mg per 15 mm^2 of film (assuming 90% active).

Film Compositions Free of Surfactants and/or Plasticizers

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-forming 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 2

Ingredient	(parts by wt.) B
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 3

Ingredient	(parts by wt.) C
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 4

Ingredient	(parts by wt.) D
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 Dave
[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.

While there have been described what are presently believed to be the certain desirable 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 drug delivery composition comprising:

(i) a flowable water-soluble film forming matrix;

(ii) a particulate bioeffecting agent uniformly stationed therein; and

(iii) a taste-masking agent coated or intimately associated with said particulate to provide taste-masking of the bioeffecting agent;

wherein the combined particulate and taste-masking agent have a particle size of 200 microns or less and said flowable water-soluble film forming matrix is capable of being dried without loss of uniformity in the stationing of said particulate bioeffecting agent therein.

2. The drug delivery composition of claim 1, wherein the size of said combined particulate and taste-masking agent have a particle size of 150 microns or less.

3. The drug delivery composition of claim 1, wherein the size of said combined particulate and taste-masking agent have a particle size of 100 microns or less.

4. The drug delivery composition of claim 1, wherein said flowable water-soluble film forming matrix is formable into a dry film of less than about 380 microns in thickness.

5. The drug delivery composition of claim 1, wherein said flowable water-soluble film forming matrix is formable into a dry film of less than about 250 microns in thickness.

6. The drug delivery composition of claim 1, wherein said taste-masking agent is a thin film coating over portions of said bioeffecting agent.

7. The drug delivery composition of claim 1, wherein said taste-masking agent is a polymer.

8. The drug delivery composition of claim 7, wherein said taste-masking agent is a water-soluble polymer.

9. The drug delivery composition of claim 8, wherein said water-soluble polymer has an average molecular weight of equal to or greater than about 40,000.

10. The drug delivery composition of claim 8, wherein said water-soluble polymer is selected from the group consisting of acrylic polymers, cellulosic polymers, and combinations thereof.

11. The drug delivery composition of claim 1, wherein said taste-masking agent is selected from the group consisting of acrylic polymers, cellulosic polymers, vinyl polymers, crown ethers, hydrogenated oils and waxes, and combinations thereof.

12. The drug delivery composition of claim 1, wherein said matrix is a cellulosic material, a gum, a protein, a starch, a glucan, and combinations thereof.

13. The delivery vehicle composition of claim 1, wherein said matrix is selected from the group consisting of carboxymethyl cellulose, methyl cellulose, ethyl cellulose, hydroxyl methyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, hydroxymethylpropyl cellulose, and combinations thereof.

14. The delivery vehicle composition of claim 1, wherein said matrix is selected from the group consisting of gum arabic, xanthan gum, tragacanth, acacia, carageenan, guar gum, locust bean gum, pectin, alginates and combinations thereof.

15. The delivery vehicle composition of claim 1, wherein said matrix is a starch selected from the group consisting of tapioca, rice, corn, potato, wheat and combinations thereof.

16. The delivery vehicle composition of claim 15, wherein said starch is gelatinized, modified or unmodified.

17. The delivery vehicle composition of claim 1, wherein said matrix is selected from the group consisting of polyvinyl alcohol, polyacrylic acid, polyvinyl pyrrolidone, poly(meth)acrylate, poly(meth)copolymers and combinations thereof.

18. The delivery vehicle composition of claim 1, wherein said matrix is a protein selected from the group consisting of gelatin, zein, gluten, soy protein, soy protein isolate, whey protein, whey protein isolate, casein, levin, collagen and combinations thereof.

19. The delivery vehicle composition of claim 1, wherein said matrix is selected from the group consisting of dextrin, dextran and combinations thereof.

20. The delivery vehicle composition of claim 1, wherein said matrix is selected from the group consisting of chitin, chitosin or combinations thereof.

21. The delivery vehicle composition of claim 1, wherein said matrix is polydextrose, fructose oligomers, or combinations thereof.

22. The delivery vehicle composition of claim 1, wherein said bioeffecting agent is present in amounts of up to about 0.1% to about 60% by weight of the total composition.

23. The delivery vehicle composition of claim 1, wherein said bioeffecting agent is selected from the group consisting of antimicrobial agents, non-steroidal anti-inflammatory drugs, anti-tussives, decongestants, antihistamines, expectorants, anti-diarrheals, H_2 antagonists, proton pump inhibitors, general non-selective CNS depressants, general non-selective CNS stimulants, selective CNS functional modifiers, anti-parkinsonism drugs, narcotics, analgesics, erectile dysfunction therapies, anti-pyretics, psychopharmacological drugs and combinations thereof.

24. The delivery vehicle composition of claim 1, further including organoleptic agent.

25. A drug delivery vehicle comprising:

(i) a water-soluble film matrix; and

(ii) a particulate bioeffecting agent uniformly suspended within said matrix and having associated with it a taste-masking agent;

wherein the uniformity is determined by the presence of no more than a 10% by weight of drug variance throughout said matrix.

26. The drug delivery vehicle of claim 25, wherein said drug variance is less than 5% by weight.

27. The drug delivery vehicle of claim 25, wherein said drug variance is less than 2% by weight.

28. The drug delivery vehicle of claim 25, wherein said drug variance is less than 1% by weight.

29. The drug delivery vehicle of claim 25, wherein said drug variance is less than 0.5% by weight.

30. The drug delivery vehicle of claim 25, wherein the size of particulate has a particle size of 200 microns or less.

31. The drug delivery vehicle of claim 25, wherein said film matrix has a thickness of less than about 380 microns.

32. The drug delivery vehicle of claim 1, wherein said taste-masking agent is a water-soluble polymer.

33. The drug delivery vehicle of claim 32, wherein said water-soluble polymer has an average molecular weight of equal to or greater than about 40,000.

34. The drug delivery vehicle of claim 32, wherein said water-soluble polymer is selected from the group consisting of acrylic polymers, cellulosic polymers, and combinations thereof.

35. The drug delivery vehicle of claim 25, wherein said taste-masking agent is selected from the group consisting of acrylic polymers, cellulosic polymers, vinyl polymers, crown ethers, hydrogenated oils and waxes, and combinations thereof.

36. The drug delivery vehicle of claim 25, further including organoleptic agent with said bioeffecting agent.

37. A drug delivery vehicle comprising:

a dry mucoadhering film having a thickness defined by opposed surfaces; said film comprising:

(i) a water-soluble polymer; and

(ii) a pharmaceutically active particle comprising a pharmaceutically active agent coated or encapsulated with a water-soluble polymer having an average molecular weight of equal to or greater than about 25,000.

38. The drug delivery vehicle of claim 37, wherein said water-soluble polymer has an average molecular weight of equal to or greater than about 40,000.

39. The drug delivery vehicle of claim 37, wherein said water-soluble polymer is selected from the group consisting of acrylic polymers, cellulosic polymers, and combinations thereof.

40. The drug delivery vehicle of claim 37, wherein said pharmaceutically active particle are embedded within said film and further wherein said film includes sections of substantially equal size and said particles are distributed in an amount that varies less than about 10% among said sections.

41. The drug delivery vehicle of claim 37, wherein the size of said particle is about 200 microns or less.

42. The drug delivery vehicle of claim 37, wherein said film has a thickness of less than about 380 microns.

43. The drug delivery vehicle of claim 25, further including organoleptic agent with said water-soluble polymer.

44. A drug delivery vehicle comprising:

a dry mucoadhering film having a thickness defined by opposed surfaces; said film comprising:

(i) a water-soluble polymer; and

(ii) a pharmaceutically active particle comprising a pharmaceutically active agent and a taste-masking agent present in the amount of about 15-80% by weight of the particle.

45. The drug delivery vehicle of claim 44, wherein said taste-masking agent is present in the amount of about 20-60% by weight of the particle.

46. The drug delivery vehicle of claim 44, wherein said taste-masking agent is present in the amount of about 25-35% by weight of the particle.

47. The drug delivery vehicle of claim 44, wherein said pharmaceutically active particle is embedded within said film and further wherein said film includes sections of substantially equal size and said particles are distributed in an amount that varies less than about 10% among said sections.

48. The drug delivery vehicle of claim 44, wherein the size of said pharmaceutically active particle has a particle size of 200 microns or less.

49. The drug delivery vehicle of claim 44, wherein said film has a thickness of less than about 380 microns.

50. The drug delivery vehicle of claim 44, further including an organoleptic agent with said taste-masking agent.

51. A drug delivery vehicle comprising:

a dry mucoadhering film having a thickness defined by opposed surfaces; said film comprising:

(i) a water-soluble polymer;

(ii) a pharmaceutically active particle comprising a pharmaceutically active agent and a taste-masking agent;

wherein said active particle having a particle size of less than about 200 microns.

52. The delivery vehicle of claim 51, wherein said thickness of said film is less than about 380 microns.

53. A drug delivery vehicle comprising:

a dry mucoadhering film having a thickness defined by opposed surfaces; said film comprising:

(i) a water-soluble polymer;

(ii) a pharmaceutically active particle comprising a pharmaceutically active agent; and a taste-masking agent;

wherein said particle having a particle size of less than about 200 microns and said taste-masking agent being present in amounts of about 15-80% by weight of the particle.

54. The drug delivery vehicle of claim 53, wherein the particle size of said particle is about 150 microns or less.

55. The drug delivery vehicle of claim 53, wherein the particle size of said particle is about 100 microns or less.

56. The delivery vehicle of claim 53, wherein said thickness of said film is less than about 380 microns.

57. The delivery vehicle of claim 53, wherein said thickness of said film is less than about 250 microns.

58. The drug delivery vehicle of claim 53, wherein said taste-masking agent is present in the amount of about 20-60% by weight of the particle

59. The drug delivery vehicle of claim 53, wherein said taste-masking agent is present in the amount of about 25-35% by weight of the particle

60. A drug delivery vehicle comprising:

a dry mucoadhering film having a thickness defined by opposed surfaces; said film comprising:

(i) a water-soluble polymer; and

(ii) a pharmaceutically active particle comprising a pharmaceutically active agent and an organoleptic agent; said active particle being taste-masked with a taste-masking agent.

61. The delivery vehicle of claim 60, wherein said organoleptic agent is selected from the group consisting of flavors, sweeteners and combinations thereof.

62. A drug delivery vehicle comprising:

a dry mucoadhering film having a thickness defined by opposed surfaces; said film comprising:

(i) a water-soluble polymer; and

(ii) a pharmaceutically active particle comprising a pharmaceutically active agent being taste-masked with a taste-masking composition comprising a water-soluble polymer and at least one of a flavor or a sweetener.

63. A method of preparing a thin film drug delivery vehicle comprising:

(a) providing a pharmaceutically active agent / taste-masking agent complex;

(b) combining said complex with a water-soluble polymer and a solvent to form a mixture with uniform distribution of said complex therein;

(c) casting said mixture onto a planar carrier surface to form a thin film on said carrier surface; and

(d) controllably drying said thin film to form a distribution variance of said complex having less than about 10% variance throughout any given area of said thin film.

64. The method of claim 63, wherein said providing said pharmaceutically active agent with said taste-masking agent includes a treatment for coating said taste masking agent onto portions of said pharmaceutically active agent.

65. The method of claim 64, wherein said treatment for coating said taste masking agent onto said portions of said pharmaceutically active agent. is selected from the group consisting of acrylic polymers, cellulosic polymers, vinyl polymers, crown ethers and oils.

66. The method of claim 63, wherein said drying includes applying heat to the bottom of said carrier surface.

67. The method of claim 63, wherein said drying includes applying microwave energy to said film.

68. The method of claim 63, wherein said pharmaceutically active agent comprises particles that are less than about 300 microns.

69. The method of claim 63, wherein said pharmaceutically active agent comprises particles that are less than about 250 microns.

70. The method of claim 63, wherein said providing said pharmaceutically active agent with said taste-masking agent is selected from the group consisting of fluidized bed coating, spray congealing coating, agglomeration or granulation coating, entrapment coating, coaccervation coating, infusion coating, spin coating, ion exchange coating said taste masking agent onto portions of said pharmaceutically active agent.

71. The drug delivery composition of claim 1, wherein said combined particulate and taste-masking agent have a shape selected from the group consisting of spherically shaped particles, ellipsoidally shaped particles, irregularly shaped particles, and combinations thereof.

72. The drug delivery of claim 25, wherein said particulates have a shape selected from the group consisting of spherically shaped particles, ellipsoidally shaped particles, irregularly shaped particles, and combinations thereof.

73. The drug delivery vehicle of claim 37, wherein said particle has a shape selected from the group consisting of spherically shaped particles, ellipsoidally shaped particles, irregularly shaped particles, and combinations thereof.

74. The drug delivery composition of claim 1, wherein the composition is essentially free of a surfactant.

75. The drug delivery composition of claims 1 or 74, wherein the composition is essentially free of a plasticizer.

76. The drug delivery composition of claims 1, 74 or 75, wherein the composition is essentially free of a polyalcohol.

77. The drug delivery vehicle of claims 25, 37, 44, 51, 53, 60 or 62, wherein the vehicle is essentially free of a surfactant.

78. The drug delivery vehicle of claims 25, 37, 44, 51, 53, 60, 62 or 77, wherein the vehicle is essentially free of a plasticizer.

79. The drug delivery vehicle of claims 25, 37, 44, 51, 53, 60, 62, 77 or 78, wherein the vehicle is essentially free of a polyalcohol.

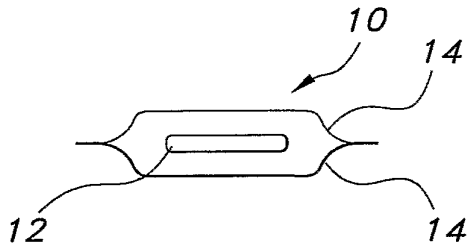

FIG. 1

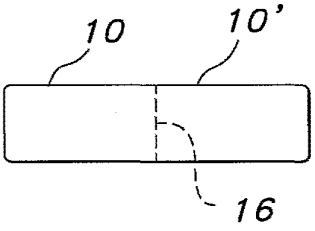

FIG. 2

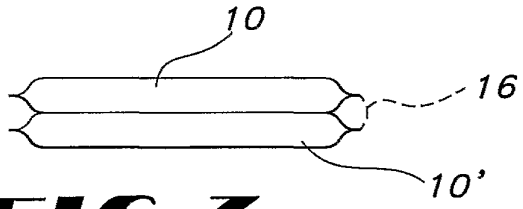

FIG. 3

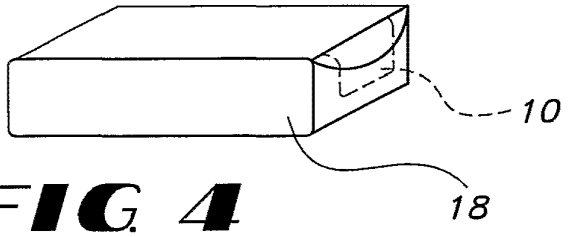

FIG. 4

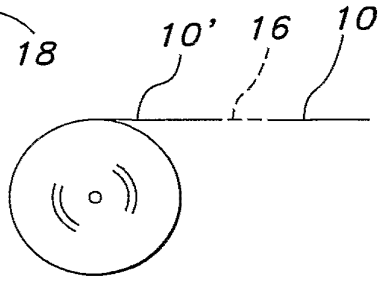

FIG. 5

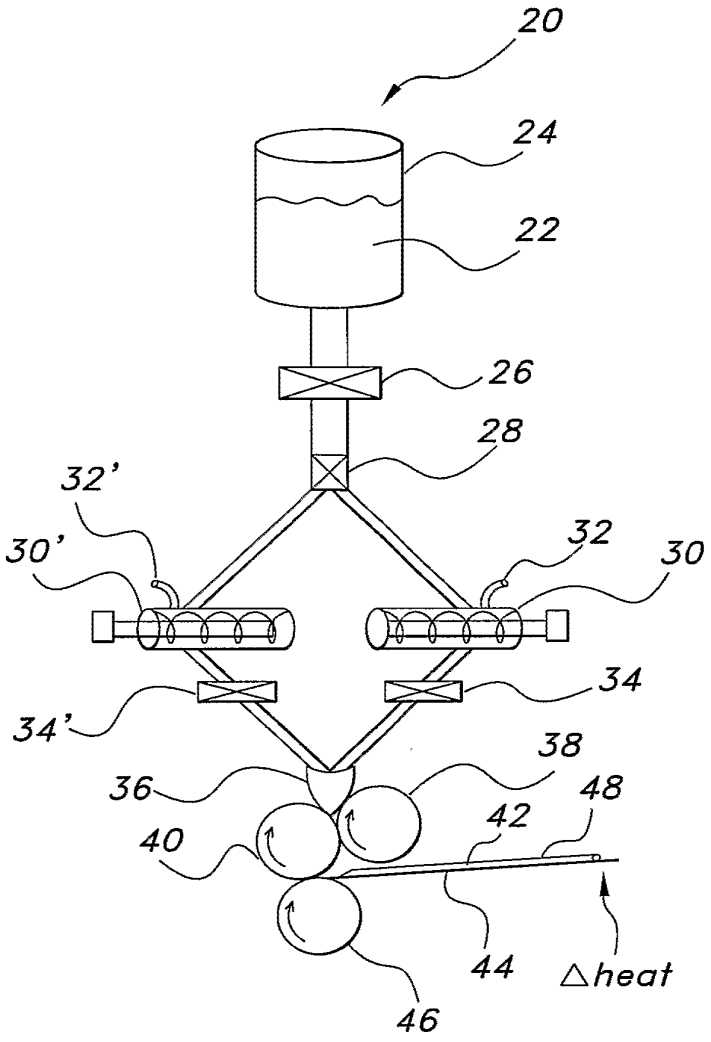

FIG. 6

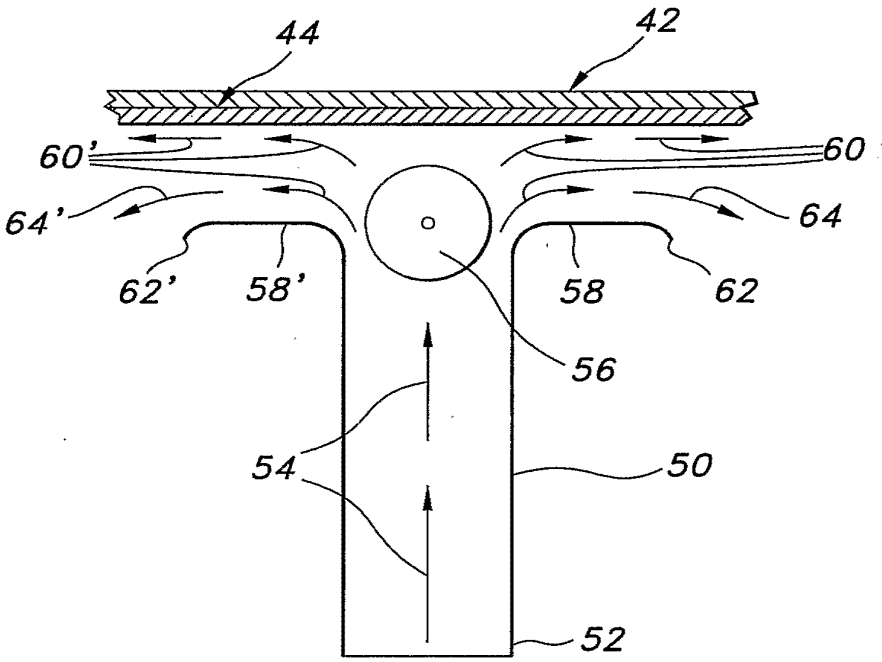

FIG. 7

INTERNATIONAL SEARCH REPORT

Inter ıal Application No
PCT/US 02/32594

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/70 A61K9/00 A61K9/16

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 7 A61K A61P

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, FSTA, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 42992 A (LAVIPHARM LAB INC) 27 July 2000 (2000-07-27) cited in the application page 8, line 10,11 page 19, line 17 -page 20, line 12 claims 2,25	1-79
X	WO 01 70194 A (WARNER LAMBERT CO) 27 September 2001 (2001-09-27) cited in the application abstract page 7, line 19-21 page 10, line 7,8 figure 2	1-79

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[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

"E" earlier document but published on or after the international filing date

"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)

"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

"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
30 January 2003	06/02/2003

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	Skjöldebrand, C

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 4 136 145 A (FUCHS PETER ET AL) 23 January 1979 (1979-01-23) cited in the application the whole document	1-62, 71-79
X	EP 0 241 178 A (ROHTO PHARMA) 14 October 1987 (1987-10-14) abstract claims 3,4 column 5, line 31-33	1-62, 71-79
X	US 2001/006677 A1 (ROBINSON JOSEPH R ET AL) 5 July 2001 (2001-07-05) abstract claims paragraph '0051!	1-62, 71-79
A	US 5 028 632 A (FUISZ RICHARD C) 2 July 1991 (1991-07-02) cited in the application the whole document	1-79
A	US 4 631 837 A (MAGOON RICHARD E) 30 December 1986 (1986-12-30) cited in the application the whole document	1-79
A	US 6 153 210 A (SPACCIAPOLI PETER ET AL) 28 November 2000 (2000-11-28) abstract; example 1	1-79
A	US 5 567 431 A (VERT MICHEL ET AL) 22 October 1996 (1996-10-22) abstract; example 2	1-79

INTERNATIONAL SEARCH REPORT

national application No.
PCT/US 02/32594

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. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-79 (in part)
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:
see FURTHER INFORMATION sheet PCT/ISA/210

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 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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-79 (in part)

There is an abundance of independent product claims with (partly) overlapping subject-matter. The current set of claims therefore lacks clarity and conciseness (Art. 6 PCT).

Independent product claims 1, 25, 37, 44, 51, 53, 60, 62 appear to relate to the same invention. Said claims however contain somewhat differing technical features. The following features seems however common to all these drug delivery devices: a water soluble film, a particulate bioactive agent associated with a taste masking agent. In view of the large number independent product claims presently on file, it is difficult, if not impossible, to determine the matter for which protection is sought, the present set of product claims 1-62 and 71- fails to comply with the clarity and conciseness requirements of Article 6 PCT (see also Rule 6.1(a) PCT) to such an extent that a meaningful search for all these claims is impossible. Consequently, the search has been carried out for those parts of the said product claims which do appear to be clear and concise, namely the technical features common to all independent product claims, namely: a water soluble film, a particulate bioactive agent associated with a taste masking agent.

Moreover, independent product claims 1, 25 and method claim 63 relate to subject-matter defined by reference to a desirable characteristic or property, namely the uniform distribution of the active agent in the film. An attempt is made to define the product/method by reference to a result to be achieved. Said claims therefore lack clarity (Article 6 PCT). The claims should be drafted in such a way that the essential technical features necessary to achieve this desirable property are described. As the unifom distribution of the drug is not mentioned in independent product claims 37, 44, 51, 53, 60 and 62, this feature appears to be optional, and the search was performed for devices as described above.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

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Inte al Application No
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Electronic Acknowledgement Receipt

EFS ID:	3718026
Application Number:	12107389
International Application Number:	
Confirmation Number:	9641
Title of Invention:	POLYETHYLENE OXIDE-BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM
First Named Inventor/Applicant Name:	Robert K. Yang
Customer Number:	23869
Filer:	Jon Anthony Chiodo/Barbara Thomas
Filer Authorized By:	Jon Anthony Chiodo
Attorney Docket Number:	1199-26 DIV
Receipt Date:	01-AUG-2008
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Time Stamp:	16:03:15
Application Type:	Utility under 35 USC 111(a)

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File Listing:

Document Number	Document Description	File Name	File Size(Bytes) /Message Digest	Multi Part /.zip	Pages (if appl.)
1	Information Disclosure Statement (IDS) Filed	1199-26_DIV_IDS_Part_1.pdf	13336747 fa39aae79fc0c993ff7dca48a466272a8915d6f0	no	9

Warnings:	
Information:	

2	Foreign Reference	DE19646392.pdf	285033 79632166b5455d1fc98fe18af2b72bedc94e2551	no	4
Warnings:					
Information:					
3	Foreign Reference	WO00170194A1.pdf	1700341 fed801bd8631b35546050b039283c5dfa5b853ee	no	41
Warnings:					
Information:					
4	Foreign Reference	WO09731621A1.pdf	1402725 8eedf8ba5a1345478dc28b142db7f88dd42bdd58	no	35
Warnings:					
Information:					
5	Foreign Reference	WO2005102287.pdf	2171625 c45129d979c558dbc4b349e80cced3497af6a88f	no	56
Warnings:					
Information:					
6	Foreign Reference	EP00598606A1.pdf	757025 df12c2c2c1dd57028f8f24397652ea9c20e15ed7	no	15
Warnings:					
Information:					
7	Foreign Reference	EP01110546A1.pdf	258701 89be4f073ba87b8a60de50db9104a365e798d797	no	15
Warnings:					
Information:					
8	Foreign Reference	WO03030882A1.pdf	3468456 8f85202ab23b4d8297ed315e6b4c3ecad7deae2a	no	77
Warnings:					
Information:					
9	NPL Documents	Article-Polyethylenglykole.pdf	95950 2ca2cf9dacb941aa3594d37057afad88a897dbbd	no	2
Warnings:					
Information:					
10	NPL Documents	Article-Repka-Bioadhesive.pdf	821731 83f1a5cfe7cc8dbdef7937a303dee6980ac283ca	no	12
Warnings:					
Information:					

11	NPL Documents	Article-Repka-Vitamin_E.pdf	529225 cbb6e7065d42c273f2c0706006a3f51c6b64dc37	no	8
Warnings:					
Information:					
12	Information Disclosure Statement (IDS) Filed	1199-26_DIV_IDS_Part_2.pdf	12760234 1bc934db75ee008ba195ad70978c568c7135f16d	no	8
Warnings:					
Information:					
13	Foreign Reference	WO00191721A2.pdf	1004879 9eae9da5b736c32af0a45ce1c350f2b0616efd37	no	21
Warnings:					
Information:					
14	Foreign Reference	WO03030883A1.pdf	3495280 5baea410922b241f8f9c793740402dad01a255e8	no	66
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PTO/SB/08a (03-08)
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	12107389
Filing Date	2008-04-22
First Named Inventor	Robert K. Yang
Art Unit	1794
Examiner Name	
Attorney Docket Number	1199-26 DIV

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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	6284264		2001-09-04	Zerbe et al.	
	2	5047244		1991-09-10	Sanvordeker et al	
	3	5064717		1991-11-12	Suzuki et al	
	4	5089307		1992-02-18	Ninomiya et al	
	5	5158825		1992-10-27	Altwirth	
	6	5166233		1992-11-24	Kuroya et al	
	7	5186938		1993-02-16	Sablotsky et al	
	8	5229164		1993-07-20	Pins et al	

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	9	5234957		1993-08-10	Mantelle	
	10	5271940		1993-12-21	Cleary et al	
	11	5272191		1993-12-21	Ibrahim et al	
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	18	5462749		1995-10-31	Rencher	
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	Attorney Docket Number	1199-26 DIV

	20	5518902		1996-05-21	Ozaki et al	
	21	5567431		1996-10-22	Vert et al	
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	Art Unit	1794
	Examiner Name	
	Attorney Docket Number	1199-26 DIV

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	1	2432925	DE	C3	1976-01-22	Schering AG		☐
	2	2449865	DE	B2	1976-04-29	Schering AG Berlin and Bergkamen		☐
	3	3630603	DE	C2	1988-03-10	Desitin Arzneimittel GmbH		☐

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	Filing Date	2008-04-22
	First Named Inventor	Robert K. Yang
	Art Unit	1794
	Examiner Name	
	Attorney Docket Number	1199-26 DIV

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	5	0219762	EP	A1	1987-04-29	Desitin Arzneimittel GmbH		☐
	6	0241178	EP	B1	1987-10-14	Rohto Pharmaceutical Co., Ltd.		☐
	7	0250187	EP	B1	1987-12-23	Johnson & Johnson Consumer Products, Inc.		☐
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	12	0514691	EP	B1	1992-11-25	Euroresearch S.r.L.		☐
	13	1110546	EP	A1	2001-06-27	Johnson & Johnson Consumer Companies, Inc.		☐
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	18	0018365	WO		2000-04-06	Warner-Lambert Company		☐
	19	0042992	WO		2000-07-27	Lavipharm Laboratories, Inc.		☐

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	Attorney Docket Number	1199-26 DIV

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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).

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☐ 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	/Jon A. CHIODO, Reg. No. 52,739/	Date (YYYY-MM-DD)	2008-08-01
Name/Print	Jon A. Chiodo	Registration Number	52739

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(51) Int. Cl. 2: A 61 K 9-70

(19) BUNDESREPUBLIK DEUTSCHLAND

DEUTSCHES PATENTAMT

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(32) (33) (31) —

(54) Bezeichnung: Arzneimittelwirkstoffträger in Folienform mit inkorporiertem Wirkstoff

(71) Anmelder: Schering AG, 1000 Berlin und 4619 Bergkamen

(72) Erfinder: Fuchs, Peter, Dr.; Hilmann, Jürgen; 1000 Berlin

DT 24 32 925 A1

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SCHERING AG
Patentabteilung

2432925

4. Juli 1974

Arzneimittelwirkstoffträger in Folienform mit inkorporiertem Wirkstoff

Die Erfindung betrifft Arzneimittelwirkstoffträger in Folienform mit inkorporiertem Wirkstoff zur inneren und äußeren Anwendung.

Aus der belgischen Patentschrift sind Papierfolien bekannt, die mit Wirkstoff beschichtet zur oralen Anwendung geeignet sind. Die Folien bestehen aus in Wasser unlöslichen Cellulosefasern und einem wasserlöslichen Bindemittel. Als wasserlösliches Bindemittel wird vorzugsweise Carboxymethylcellulose-Natrium verwendet. Der Wirkstoff wird durch Auftropfen des gelösten Wirkstoffes, durch Aufstreuen des festen Wirkstoffes oder durch Durchziehen der Folie durch die Wirkstofflösung auf die Papierfolie gebracht. Das diskontinuierliche Verfahren der gesonderten Herstellung der Folie und Aufbringung des Wirkstoffes hat den Nachteil, daß die Dosierungsgenauigkeit nicht sehr gut ist, was bei den heute niedrig dosierten Wirkstoffen jedoch von großer Wichtigkeit ist. Ungenauigkeiten entstehen nicht nur bei dem Aufbringen des Wirkstoffes, sondern auch bei der Herstellung und Vorbehandlung des Trägers und durch Veränderungen bei der Lagerung des Trägermaterials. So hat es sich zum Beispiel gezeigt, daß

nach der Rezeptur der belgischen Patentschrift bei Verwendung von Folienziehmaschinen keine gleichmäßige Folienschicht entsteht und daß die Folie bei der Trocknung

schrumpft. Es ist jedoch leicht einzusehen, daß bei nicht einheitlichem Material auch die Wirkstoffaufnahme nicht gleichmäßig sein wird. Ein nur oberflächlich gebundener Wirkstoff kann außerdem bei der Handhabung der Folien, wie zum Beispiel bei der Verpackung, teilweise wieder abgelöst werden. Die als Bindemittel verwendete Natrium-Carboxymethylcellulose wird im Magen angelöst und setzt dabei die Carboxymethylcellulose frei, die den Wirkstoff teilweise einschließt und nur verzögert oder überhaupt nicht freigibt.

Es wurde nun gefunden, daß man Folien mit gleichbleibender Dicke und gleichmäßiger Wirkstoffverteilung erhält, wenn man Folien mit inkorporiertem Wirkstoff herstellt und Folienbildner verwendet, die in Wasser oder in organischen Lösungsmitteln löslich sind. Bevorzugt geeignet sind Folienbildner, die sich sowohl in Wasser als auch in organischen Lösungsmitteln lösen.

Als Folienbildner kommen zum Beispiel Poly-N-Vinylpyrrolidon, Vinylpyrrolidon-Vinylacetat, Methyl- und Äthylcellulose, vorzugsweise jedoch nichtionogene, wasserlösliche Hydroxyalkyläther der Cellulose, wie Hydroxypropylcellulose, Hydroxyäthylcellulose und Methylhydroxypropylcellulose, in Betracht.

Dem Folienbildner können Füllstoffe und Wirkstoffe und zweckmäßigerweise eine geringe Menge eines Trennmittels zugesetzt werden.

Geeignete Trennmittel sind u.a. Polyoxyäthylenpolyoxypropylenpolymeres (PLURONIC F 68 (R)), Polyoxylstearate, Alkyl- bzw. Acylsubstiutierte Polyadditionsprodukte des Äthylenoxids zum Beispiel CREMOPHOR EL (R), Silikone und Silkontrennemulsionen, Glycerin, Propylenglykol und Metallseifen.

Als Füllstoffe sind zum Beispiel Cellulose, Zucker, wie zum Beispiel Lactose, Dextrose, Rohrzucker usw., Stärken, mehrwertige Alkohole, wie zum Beispiel Mannit, Calciumcarbonat, Calciumphosphat, Talkum und Farbstoffe in löslicher Form oder als Pigmente geeignet. Die Füllstoffe können teilweise oder vollständig durch Wirkstoffe ersetzt werden. Werden lösliche Füll- bzw. Wirkstoffe verwendet, entsteht eine transparente, glatte Folie, werden unlösliche Füll- bzw. Wirkstoffe verwendet, entsteht eine weiße oder farbige, papierartige Folie.

Erfindungsgemäß können alle in der Human- und Veterinärmedizin verwendeten Wirkstoffe eingesetzt werden. Für die innere Anwendung kommt insbesondere die orale Verabreichung infrage. Unter der äußeren Anwendung sollen insbesondere die topikale Verabreichung auf der Haut und in Körperhöhlungen wie Nase, Ohr, Vagina usw. verstanden werden. Als Wirkstoffe seien

beispielsweise genannt: Gestagene, Östrogene, Gemische aus Gestagenen und Östrogenen, Tranquilizer, Antidiabetika, Sulfonamide, Antibiotika, Trichomonadenmittel, Entzündungshemmer, wie zum Beispiel Corticoide, usw.
Der Azneimittelwirkstoff kann im Trägermaterial gelöst oder gleichmäßig suspendiert vorliegen. Der Wirkstoffanteil in der Folie kann etwa 0-60 % betragen. Als Einzeldosis (Einheit) werden Flächen geschnitten bwz. perforiert, die Wirkstoffmengen enthalten wie sie üblicherweise auch in Tabletten, Dragees, Salben, Zäpfchen usw. enthalten sind. So kann die Wirkstoffmenge pro Einzeldosis je nach Anwendungsart beliebig hoch sein und zwischen etwa 1µg und 0,5 g betragen, wobei die untere und obere Dosis leicht unter- oder überschritten werden können. Selbstverständlich können auch wirkstofffreie Träger (Placebos) hergestellt werden.

Zur Herstellung des erfindungsgemäßen Arzneimittels in Folienform werden der Wirkstoff und/oder das Trennmittel gelöst bzw. suspendiert, der Folienbildner und gegebenenfalls der Füllstoff eingetragen, gegebenenfalls homogenisiert und die Lösung bzw. Suspension auf einer Folienziehmaschine zu einem Ausstrich ausgezogen. Die durch Trocknung des Ausstrichs erhaltene Folie wird in beliebige Abschnitte (Einheiten) aufgeteilt.

In der Lösung bzw. Suspension wird der Folienbildner in Gewichtsmengen von etwa 6-20 %, der Füllstoff in Gewichtsmengen von etwa

0-30 % und das Trennmittel vorzugsweise in Gewichtsmengen von 0,01-2 % eingesetzt.

Das Lösungs- bzw. Suspensionsmittel ist zu etwa 48-84 % (W/W) enthalten und besteht aus Wasser und/oder einem oder mehreren organischen Lösungsmitteln. Als organische Lösungsmittel kommen physiologisch verträgliche Lösungsmittel oder solche Lösungsmittel in Betracht, die bei der Trocknung bis auf einen physiologisch unbedenklichen Rest entfernt werden können. Solche Lösungmittel sind zum Beispiel Äthylalkohol, Isopropanol, Methylenchlorid usw. und ihre Mischungen. Wasser und Äthylalkohol bzw. Gemische aus Wasser und Äthylalkohol werden bevorzugt angewandt.

Die Schichtdicke des nassen Ausstrichs beträgt etwa 0,1 bis 2 mm und die der trockenen Folie etwa 0,05 bis 1 mm, vorzugsweise 0,07 bis 0,3 mm.

Das Verfahren zur Herstellung des Arzneimittels in Folienform in einem Arbeitsgang (kontinuierliches Verfahren) bietet den Vorteil, daß der Wirkstoff homogen und gleichmäßig verteilt in dem Wirkstoffträger vorliegt. Durch die Konzentration des Wirkstoffs im Träger, die Dicke der Folie und die Fläche der Folie kann man die Einzeldosis sehr einfach variieren.

Die Erfindung betrifft auch die Verwendung von in Wasser und/oder organischen Lösungsmitteln löslichen Filmbildern für die Herstellung von Arzneimittelwirkstoffträgern, insbesondere die Verwendung von nichtionogenen, wasserlöslichen Hydroxyalkyläthern der Cellulose, wie Hydroxypropylcellulose, Hydroxyäthylcellulose und/oder Methylhydroxypropylcellulose.

2432925

B e i s p i e l 1

Herstellung für 1000 Einheiten

0,25	g	D-Norgestrel
0,05	g	Äthinylöstradiol
		und
0,84	g	Polyoxyäthylenpolyoxypropylenpolymeres
		werden in
95,00	g	Äthylalkohol unter Rühren gelöst, in diese
		Lösung wird eine Pulvermischung aus
16,93	g	Hydroxypropylcellulose und
16,93	g	Cellulose eingetragen.

Die erhaltene Suspension wird auf einem geeigneten Folienziehgerät zu einem Ausstrichmit einer Schichtdicke von 500 µm ausgezogen und anschließend getrocknet.

Zusammensetzung für eine Einheit:

0,25 mg	D-Norgestrel
0,05 mg	Äthinylöstradiol
0,84 mg	Polyoxyäthylenpolyoxypropylenpolymeres
16,93 mg	Hydroxypropylcellulose
16,93 mg	Cellulose
35,00 mg	

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Eine Einheit entspricht einer Fläche von ca. 3 cm^2.

Aussehen der Folie: weiß, papierartig.

Die trockene Folie hat eine Dicke von ca. 170 µm.

Beispiel 2

Herstellung für 1000 Einheiten

1,10	g	Cremophor EL (R) werden in
152,00	g	Wasser gelöst. In dieser Lösung werden
0,25	g	mikronisiertes D-Norgestrel und
0,05	g	mikronisiertes Äthinylöstradiol suspendiert und evtl homogenisiert. In die Suspension werden
22,10	g	Hydroxypropylcellulose und
16,50	g	Cellulose eingetragen.

Die erhaltene Suspension wird auf einem geeigneten Folienziehgerät zu einem Ausstrich mit einer Schichtdicke von 500 µm ausgezogen und anschließend getrocknet.

Zusammensetzung für eine Einheit:

0,25	mg	D-Norgestrel
0,05	mg	Äthinylöstradiol
1,10	mg	Cremophor EL (R)
22,10	mg	Hydroxypropylcellulose
16,50	mg	Cellulose
40,00	mg	

Eine Einheit entspricht einer Fläche von ca. 3 cm^2.

Aussehen der Folie: weiß, papierartig.

Die trockene Folie hat eine Dicke von ca. 170 µm.

B e i s p i e l 3

Herstellung für 1000 Einheiten

0,03	g	D-Norgestrel und
0,84	g	Polyoxyl-40-stearat werden in
95,00	g	Äthylalkohol unter Rühren gelöst.
		In diese Lösung wird eine Pulvermischung aus
16,93	g	Hydroxypropylcellulose und
17,20	g	Cellulose eingetragen.

Die erhaltene Suspension wird auf einem geeigneten Folienziehgerät zu einem Ausstrich mit einer Schichtdicke von 500 µm ausgezogen und anschließend getrocknet.

Zusammensetzung für eine Einheit:

0,03	mg	D-Norgestrel
0,84	mg	Polyoxyl-40-stearat
16,93	mg	Hydroxypropylcellulose
17,20	mg	Cellulose
35,00	mg	

Eine Einheit entspricht einer Fläche von ca. 3 cm^2.

Aussehen der Folie: weiß, papierartig.

Die trockene Folie hat eine Dicke von ca. 170 µm.

B e i s p i e l 4

Herstellung für 1000 Einheiten

1,10	g	Polyoxyäthylenpolyoxypropylenpolymeres werden in
152,00	g	demineralisiertem Wasser gelöst.
		In dieser Lösung werden
0,03	g	mikronisiertes D-Norgestrel suspendiert und evtl. homogenisiert.
		In die Suspension werden
22,10	g	Hydroxypropylcellulose und
16,77	g	Cellulose eingetragen.

Die erhaltene Suspension wird auf einem geeigneten Folienziehgerät zu einem Ausstrich mit einer Schichtdicke von 500 µm ausgezogen und anschließend getrocknet.

Zusammensetzung für eine Einheit:

0,03	mg	D-Norgestrel
1,10	mg	Polyoxyäthylenpolyoxypropylenpolymeres
22,10	mg	Hydroxypropylcellulose
16,77	mg	Cellulose
40,00	mg	

Eine Einheit entspricht einer Fläche von ca. 3 cm^2.

Aussehen der Folie: weiß, papierartig.

Die trockene Folie hat eine Dicke von ca. 170 µm.

Beispiel 5

Herstellung für 1000 Einheiten

0,025	g	Fluocortolontrimethylacetat und
0,183	g	Glycerin werden in
30,000	g	Äthylalkohol gelöst.
		In diese Lösung werden
7,292	g	Hydroxypropylcellulose eingetragen.

Die erhaltene Lösung wird auf einem geeigneten Folienziehgerät zu einem Ausstrich miteiner Schichtdicke von 500 µm ausgezogen und anschließend getrocknet.

Zusammensetzung für eine Einheit:

0,025	mg	Fluocortolontrimethylacetat
0,183	mg	Glycerin
7,292	mg	Hydroxypropylcellulose
7,500	mg	

Eine Einheit entspricht einer Fläche von ca. 1 cm^2.

Aussehen der Folie: transparent.

Die trockene Folie hat eine Dicke von ca. 70 µm.

Beispiel 6

Herstellung für 1000 Einheiten

10,00	g	7-Chlor-2-methylamino-5-phenyl-3H-1,4-benzodiazepin-4-oxid und
0,84	g	Polyoxyäthylenpolyoxypropylenpolymeres werden in
95,00	g	Äthylalkohol gelöst.
		In diese Lösung wird ein Pulvergemisch aus
16,93	g	Hydroxypropylcellulose und
7,23	g	Cellulose eingetragen.

Die erhaltene Suspension wird auf einem geeigneten Folienziehgerät zu einem Ausstrich mit einer Schichtdicke von 500 µm ausgezogen und anschließend getrocknet.

Zusammensetzung für eine Einheit:

10,00	mg	7-Chlor-2-methylamino-5-phenyl-3H-1,4-benzodiazepin-4-oxid
0,84	mg	Polyoxyäthylenpolyoxypropylenpolymeres
16,93	mg	Hydroxypropylcellulose
7,23	mg	Cellulose
35,00	mg	

Eine Einheit entspricht einer Fläche von ca. 3 cm^2.

Aussehen der Folie: gelb, papierartig.

Die trockene Folie hat eine Dicke von ca. 170 µm.

Beispiel 7

Herstellung für 1000 Einheiten

1,00	g	Norethisteronacetat
0,03	g	Äthinylöstradiol und
0,84	g	Polyoxyäthylenpolyoxypropylenpolymeres werden in
95,00	g	Äthylalkohol gelöst.
		In diese Lösung wird ein Pulvergemisch aus
16,93	g	Hydroxypropylcellulose und
16,20	g	Cellulose eingetragen.

Die erhaltene Suspension wird auf einem geeigneten Folienziehgerät zu einem Ausstrichmit einer Schichtdicke von 500 µm ausgezogen und anschließend getrocknet.

Zusammensetzung für eine Einheit:

1,00	mg	Norethisteronacetat
0,03	mg	Äthinylöstradiol
0,84	mg	Polyoxyäthylenpolyoxypropylenpolymeres
16,93	mg	Hydroxypropylcellulose
16,20	mg	Cellulose
35,00	mg	

Eine Einheit entspricht einer Fläche von ca. 3 cm^2.

Aussehen der Folie: weiß, papierartig.

Die trockene Folie hat eine Dicke von ca. 170 µm.

Beispiel 8

Herstellung für 1000 Tabletten:

1,00	g	Norethisteronacetat
0,03	g	Äthinylöstradiol und
0,84	g	Propylenglykol werden in einem Gemisch aus
101,60	g	Methylenchlorid und
26,40	g	Äthylalkohol gelöst.
		In diese Lösung wird ein Pulvergemisch aus
8,47	g	Hydroxypropylcellulose
8,47	g	Hydroxyäthylcellulose und
16,19	g	Cellulose eingetragen.

Die erhaltene Suspension wird auf einem geeigneten Folienziehgerät zu einem Ausstrich miteiner Schichtdicke von 500 µm ausgezogen und anschließend getrocknet.

Zusammensetzung für eine Einheit:

1,00	mg	Norethisteronacetat
0,03	mg	Äthinylöstradiol
0,84	mg	Propylenglykol
8,47	mg	Hydroxypropylcellulose
8,47	mg	Hydroxyäthylcellulose
16,19	mg	Cellulose
35,00	mg	

Eine Einheit entspricht einer Fläche von ca. 3 cm^2.

Aussehen der Folie: weiß, papierartig.

Die trockene Folie hat eine Dicke von ca. 170 µm.

Beispiel 9

Herstellung für 1000 Einheiten:

1,00	g	Norethisteronacetat
0,03	g	Äthinylöstradiol und
0,84	g	Polyoxyäthylpolyoxypropylenpolymeres werden in einem Gemisch aus
101,60	g	Methylenchlorid und
25,40	g	Äthylalkohol gelöst.
		In diese Lösung wird ein Pulvergemisch aus .
16,93	g	Hydroxyäthylcellulose und
16,20	g	Stärke eingetragen.

Die erhaltene Suspension wird auf einem geeigneten Folienziehgerät zu einem Ausstrich miteiner Schichtdicke von 500 µm ausgezogen und anschließend getrocknet.

Zusammensetzung für eine Einheit:

1,00	mg	Norethisteronacetat
0,03	mg	Äthinylöstradiol
0,84	mg	Polyoxyäthylenpolyoxypropylenpolymeres
16,93	mg	Hydroxyäthylcellulose und
16,20	mg	Stärke
35,00	mg	

Eine Einheit entspricht einer Fläche von ca. 3 cm^2.

Aussehen der Folie: weiß, papierartig.

Die trockene Folie hat eine Dicke von ca. 170 µm.

Beispiel 10

Herstellung für 1000 Einheiten:

1,00	g	Norethisteronacetat
0,03	g	Äthinylöstradiol und
0,84	g	Polyoxyl-40-stearat werden in
95,00	g	Äthylalkohol gelöst.
		In diese Lösung wird ein Pulvergemisch aus
16,93	g	Hydroxypropylcellulose
8,10	g	Lactose und
8,10	g	Maisstärke eingetragen.

Die erhaltene Suspension wird auf einem geeigneten Folienziehgerät zu einem Ausstrich mit einer Schichtdicke von 500 µm ausgezogen und anschließend getrocknet.

Zusammensetzung für eine Einheit:

1,00	mg	Norethisteronacetat
0,03	mg	Äthinylöstradiol
0,84	mg	Polyoxyl-40-stearat
16,93	mg	Hydroxypropylcellulose
8,10	mg	Lactose
8,10	mg	Maisstärke
35,00	mg	

Eine Einheit entspricht einer Fläche von ca. 3 cm^2.

Aussehen der Folie: weiß, papierartig.

Die trockene Folie hat eine Dicke von ca. 170 µm.

Beispiel 11

Herstellung für 1000 Einheiten:

25,0	g	5-Morpholinomethyl-3-(5-nitro-1-methyl-2-imidazolyl)-methylamino-2-oxazolidinon · HCl werden in
2,1	g	Cremophor EL (R) gelöst in
152,0	g	Alkohol und Wasser 1 x 1 suspendiert. In diese Suspension werden
42,3	g	Methylhydroxypropylcellulose und
18,1	g	Cellulose eingetragen.

Die erhaltene Suspension wird auf einem geeigneten Folienziehgerät zu einem Ausstrich mit einer Schichtdicke von 500 µm ausgezogen und getrocknet.

Zusammensetzung für eine Einheit:

25,0	mg	5-Morpholinomethyl-3-(5-nitro-1-methyl-2-imidazolyl) methylamino-2-oxazolidinon · HCl
2,1	mg	Cremophor EL (R)
42,3	mg	Methylhydroxypropylcellulose
18,1	mg	Cellulose
87,5	mg	

Eine Einheit entspricht einer Fläche von ca. 8 cm^2.

Aussehen der Folie: hellgelb, papierartig.

Die trockene Folie hat eine Dicke von ca. 170 µm.

Beispiel 12

Herstellung für 1000 Einheiten:

4,0	g	Glisoxepid in mikronisierter Form werden in
0,9	g	Polyoxyl-40-stearat gelöst in
152,0	g	Wasser suspendiert und eventuell homogenisiert.
		In die Suspension werden
15,0	g	Hydroxyäthylcellulose und
15,1	g	Calciumcarbonat eingetragen.

Die erhaltene Suspension wird auf einem geeigneten Folienziehgerät zu einem Ausstrich mit einer Schichtdicke von 500 µm ausgezogen und getrocknet.

Zusammensetzung für eine Einheit:

4,00 mg	Glisoxepid
0,90 mg	Polyoxyl-40-stearat
15,00 mg	Hydroxyäthylcellulose
15,10 mg	Calciumcarbonat
35,00 mg	

Eine Einheit entspricht einer Fläche von ca. 3 cm^2.

Aussehen der Folie: weiß, papierartig.

Die trockene Folie hat eine Dicke von ca. 170 µm.

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Beispiel 13

Herstellung für 1000 Einheiten:

0,030	g	D-Norgestrel werden in
40,000	g	Methylenchlorid und
55,000	g	Äthanol gelöst.
		In diese Lösung werden
0,840	g	Silikonöl
6,930	g	Methylcellulose und
10,000	g	Poly-N-vinylpyrrolidon und
17,200	g	Stärke eingetragen, eventuell homogenisiert.

Die erhaltene Suspension wird auf einem geeigneten Folienziehgerät zu einem Ausstrich mit einer Schichtdicke von 500 µm ausgezogen und getrocknet.

Zusammensetzung für eine Einheit:

0,030	mg	D-Norgestrel
0,840	mg	Silikonöl
6,930	mg	Methylcellulose
10,000	mg	Poly-N-vinylprrolidon
17,200	mg	Stärke
35,000	mg	

Eine Einheit entspricht einer Fläche von ca. 3 cm^2.

Aussehen der Folie: weiß, papierartig.

Die trockene Folie hat eine Dicke von ca. 170 µm.

Beispiel 14

Herstellung für 1000 Einheiten

0,84 g Polyoxyäthylenpolyoxypropylenpolymeres
werden in
95,00 g Äthylalkohol unter Rühren gelöst, in diese
Lösung wird eine Pulvermischung aus
17,08 g Hydroxypropylcellulose und
17,08 g Cellulose eingetragen.

Die erhaltene Suspension wird auf einem geeigneten Folienziehgerät zu einem Ausstrich mit einer Schichtdicke von 500 µm ausgezogen und anschließend getrocknet.

Zusammensetzung für eine Einheit:

0,84 mg Polyoxyäthylenpolyoxypropylenpolymeres
17,08 mg Hydroxypropylcellulose
17,08 mg Cellulose
35,00 mg

Patentansprüche

1.) Arzneimittelstoffträger in Folienform mit inkorporiertem Wirkstoff, dadurch gekennzeichnet, daß er in Wasser oder organischen Lösungsmitteln lösliche Folienbildner enthält.

2.) Arzneimittel nach Anspruch 1, dadurch gekennzeichnet, daß die Folienbildner in Wasser und in organischen Lösungsmitteln löslich sind.

3.) Arzneimittel nach Anspruch 1 und 2, dadurch gekennzeichnet, daß nichtionogene, wasserlösliche Hydroxyalkyläther der Cellulose als Folienbildner verwendet werden.

4.) Arzneimittel nach Anspruch 1 bis 3, dadurch gekennzeichnet, daß Hydroxypropylcellulose, Hydroxyäthylcellulose und/oder Methylhydroxypropylcellulose als Folienbildner verwendet werden.

5.) Arzneimittel nach Anspruch 1, dadurch gekennzeichnet, daß der Wirkstoffanteil in der Folie etwa 0-60 % beträgt.

6.) Arzneimittel nach Anspruch 1 und 5, dadurch gekennzeichnet, daß der Arzneimittelwirkstoff im Trägermaterial gelöst oder gleichmäßig suspendiert ist.

7.) Verfahren zur Herstellung eines Arzneimittels in Folienform, dadurch gekennzeichnet, daß man den Wirkstoff und/oder das Trennmittel löst bzw. suspendiert, einen Folienbildner und gegebenenfalls einen Füllstoff einträgt, gegebenenfalls homogenisiert, die Lösung bzw. Suspension auf einer Folienziehmaschine zu einem Ausstrich auszieht und die durch Trocknung des Ausstrichs erhaltene Folie in beliebige Abschnitte (Einheit) aufteilt.

8.) Verfahren nach Anspruch 7, dadurch gekennzeichnet, daß man den Folienbildner in Mengen von etwa 6-20 %, den Füllstoff in Mengen von etwa 0-30 % und das Trennmittel vorzugsweise in Mengen von 0,01-2 % einsetzt.

9.) Verfahren nach Anspruch 7, dadurch gekennzeichnet, daß man als Lösungs- bzw. Suspensionsmittel Wasser und/oder ein organisches Lösungsmittel verwendet.

10.) Verfahren nach Anspruch 7 und 9, dadurch gekennzeichnet, daß das Lösungs- bzw. Suspensionsmittel zu etwa 48-84 % enthalten ist.

11.) Verfahren nach Anspruch 7, dadurch gekennzeichnet, daß die Schichtdicke des Ausstrichs etwa 0,1-2 mm beträgt und die der trockenen Folie etwa 0,05-1 mm beträgt.

12.) Verwendung von in Wasser und/oder organischen Lösungsmitteln löslichen Filmbildnern für die Herstellung von Arzneimittelwirkstoffträgern.

13.) Verwendung nach Anspruch 12 von nichtionogenen, wasserlöslichen Hydroxyalkyläthern der Cellulose.

14.) Verwendung nach Anspruch 12 von Hydroxypropylcellulose, Hydroxyäthylcellulose und/oder Methylhydroxypropylcellulose.

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Arzneimittel in Folienform mit inkorporiertem Wirkstoff

Das Hauptpatent ..... (Patentanmeldung P 24 32 925.7) betrifft Arzneimittelwirkstoffträger in Folienform mit inkorporiertem Wirkstoff zu inneren und äußeren Anwendung.

Es wurde gefunden, daß man Folien mit inkorporiertem Wirkstoff bei gleichbleibender Dicke und gleichmäßiger Wirkstoffverteilung erhält, wenn man Folienbildner verwendet, die in Wasser und/oder organischen Lösungsmitteln löslich sind.

Zur Herstellung des erfindungsgemäßen Arzneimittels in Folienform werden der Wirkstoff und/oder das Trennmittel gelöst bzw. suspendiert, der Folienbildner und gegebenenfalls der Füllstoff eingetragen, gegebenenfalls homogenisiert und die Lösung bzw. Suspension auf einer Folienziehmaschine zu einem Ausstrich ausgezogen. Die durch Trocknung des Ausstrichs erhaltene Folie wird in beliebige Abschnitte (Dosierungseinheiten) aufgeteilt.

In Weiterentwicklung der Erfindung des Hauptpatents wurde nun gefunden, daß man mit einem Ausstrich Folien herstellen kann, in denen nebeneinander unterschiedliche Wirkstoffe und/oder

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verschiedene Wirkstoffkonzentrationen inkorporiert sind. Mit Hilfe eines Spezialrakels, das aus zwei oder mehreren Kammern besteht, können unterschiedliche Lösungen bzw. Suspensionen ohne Vermischen zu einem zusammenhängenden Ausstrich ausgezogen werden. Die Breite und die Dicke des Ausstrichs ist für jede Kammer separat einstellbar. Gewünschtenfalls können Zonen (Streifen) mit unterschiedlichen Wirkstoffen bzw. verschiedenen Konzentrationen durch unterschiedliche Farbstoffe sichtbar gemacht werden. Durch Trocknung des nassen Ausstrichs wird eine Folie erhalten, die bei entsprechender Teilung, zum Beispiel durch Perforation, Einheiten mit verschiedenen Wirkstoffen und/oder Wirkstoffkonzentrationen bzw. Einheiten ohne Wirkstoff liefert. Folien mit unterschiedlichen Wirkstoffen und/oder verschiedenen Wirkstoffkonzentrationen werden zur Herstellung von Mehrphasenpräparaten benötigt, beispielsweise zur Herstellung von Präparaten zur Konzeptionsverhütung.

Durch die Möglichkeit der räumlichen Trennung von miteinander inkompatibler Wirkstoffe in einer Folieneinheit wird die Stabilität der einzelnen Wirkstoffe verbessert.

Die Erfindung betrifft demnach Arzneimittelwirkstoffträger in Folienform mit inkorporiertem Wirkstoff gemäß Hauptpatent ..... (Patentanmeldung P 24 32 925.7), dadurch

gekennzeichnet, daß in einer Folie für mehrere Dosierungseinheiten nebeneinander unterschiedliche Wirkstoffe und/oder verschiedene Wirkstoffkonzentrationen inkorporiert sind.

Erfindungsgemäß werden Folienbildner verwendet, die in Wasser oder in organischen Lösungsmitteln löslich sind. Bevorzugt geeignet sind Folienbildner, die sich sowohl in Wasser als auch in organischen Lösungsmitteln lösen.

Als Folienbildner kommen zum Beispiel in Betracht: Poly-N-Vinylpyrrolidon, Vinylpyrrolidon-Vinylacetat, Methyl- und Äthylcellulose, vorzugsweise jedoch nichtionogene, wasserlösliche Hydroxyalkyläther der Cellulose, wie Hydroxypropylcellulose, Hydroxyäthylcellulose und Methylhydroxypropylcellulose.

Dem Folienbildner können Füllstoffe und Wirkstoffe und zweckmäßigerweise eine geringe Menge eines Trennmittels zugesetzt werden.

Geeignete Trennmittel sind u.a. Polyoxyäthylenpolyoxypropylenpolymeres (PLURONIC F 68 (R)), Polyoxylstearate, Alkyl- bzw. Acylsubstituierte Polyadditionsprodukte des Äthylenoxids, zum Beispiel CREMOPHOR EL (R), Silikone und Silkontrennemulsionen, Glycerin, Propylenglykol und Metallseifen.

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Als Füllstoffe sind zum Beispiel Cellulose, Zucker, wie zum Beispiel Lactose, Dextrose, Rohrzucker usw., Stärken, mehrwertige Alkohole, wie zum Beispiel Mannit, Calciumcarbonat, Calciumphosphat, Talkum, Geschmacks- und Farbstoffe geeignet. Farbstoffe werden in löslicher Form oder als Pigmente eingesetzt. Die Füllstoffe können teilweise oder vollständig durch Wirkstoffe ersetzt werden. Werden lösliche Füll- bzw. Wirkstoffe verwendet, entsteht eine transparente, glatte Folie, werden unlösliche Füll- bzw. Wirkstoffe verwendet, entsteht eine weiße oder farbige, papierartige Folie.

Erfindungsgemäß können alle in der Human- und Veterinärmedizin verwendeten Wirkstoffe eingesetzt werden. Für die innere Anwendung kommt insbesondere die orale Verabreichung infrage. Unter der äußeren Anwendung sollen insbesondere die topikale Verabreichung auf der Haut und in Körperhöhlungen wie Nase, Ohr, Vagina usw. verstanden werden. Als Wirkstoffe seien beispielsweise genannt: Gestagene, Östrogene, Gemische aus Gestagenen und Östrogenen, Tranquilizer, Antidiabetika, Sulfonamide, Antibiotika, Trichomonadenmittel, Entzündungshemmer, wie zum Beispiel Corticoide, usw.

Der Arzneimittelwirkstoff kann im Trägermaterial gelöst oder gleichmäßig suspendiert vorliegen. Der Wirkstoffanteil in der

Folie kann etwa 0-60 % betragen. Als Einzeldosis (Einheit) werden Flächen geschnitten bzw. perforiert, die Wirkstoffmengen enthalten wie sie üblicherweise auch in Tabletten, Dragees, Salben, Zäpfchen usw. enthalten sind. So kann die Wirkstoffmenge pro Einzeldosis je nach Anwendungsart beliebig hoch sein und zwischen etwa 1 µg und 0,5 g betragen, wobei die untere und obere Dosis leicht unter- oder überschritten werden können. Selbstverständlich können auch wirkstofffreie Träger (Placebos) hergestellt werden.

Zur Herstellung der Folien mit unterschiedlichen Wirkstoffen und/oder verschiedenen Wirkstoffkonzentrationen werden zwei oder mehrere unterschiedliche Lösungen bzw. Suspensionen aus Wirkstoff und/oder Trennmittel, Folienbildner und gegebenenfalls Füllstoff hergestellt, die unterschiedlichen Lösungen bzw. Suspensionen mit Hilfe eines Spezialrakels, das aus zwei oder mehreren Kammern besteht, auf einer Folienziehmaschine zu einem Ausstrich ausgezogen und die durch Trocknung des Ausstrichs erhaltene Folie in Einheiten mit unterschiedlichen Wirkstoffen und/oder verschiedenen Wirkstoffkonzentration bzw. Einheiten ohne Wirkstoff geteilt.

Pro Lösung bzw. Suspension wird der Folienbildner in Gewichtsmengen von etwa 6-20 %, der Füllstoff in Gewichtsmengen von etwa 0-30 % und das Trennmittel vorzugsweise in Gewichtsmengen von 0,01-2 % eingesetzt.

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Das Lösungs- bzw. Suspensionsmittel ist zu etwa 48-84 % (W/W) enthalten und besteht aus Wasser und/oder einem oder mehreren organischen Lösungsmitteln. Als organische Lösungsmittel kommen physiologisch verträgliche Lösungsmittel oder solche Lösungsmittel in Betracht, die bei der Trocknung bis auf einen physiologisch unbedenklichen Rest entfernt werden können. Solche Lösungsmittel sind zum Beispiel Äthylalkohol, Isopropanol, Methylenchlorid usw. und ihre Mischungen. Wasser und Äthylalkohol bzw. Gemische aus Wasser und Äthylalkohol werden bevorzugt angewandt.

Die Schichtdicke des nassen Ausstrichs beträgt etwa 0,1 bis 2 mm und die der trockenen Folie etwa 0,05 bis 1 mm, vorzugsweise 0,07 bis 0,3 mm.

Die Erfindung betrifft auch die Verwendung von in Wasser und/oder organischen Lösungsmitteln löslichen Folienbildnern für die Herstellung von Arzneimittelwirkstoffträgern in Folienform mit inkorporiertem Wirkstoff, wobei in einer Folie für mehrere Dosierungseinheiten unterschiedliche Wirkstoffe und/oder ver-

schiedene Wirkstoffkonzentrationen inkorporiert sind, insbesondere die Verwendung von nichtionogenen, wasserlöslichen Hydroxyäthern der Cellulose, wie Hydroxypropylcellulose, Hydroxyäthylcellulose und/oder Methylhydroxypropylcellulose.

Das Verfahren zur Herstellung des Arzneimittels in Folienform in einem Arbeitsgang (kontinuierliches Verfahren) bietet den Vorteil, daß der Wirkstoff homogen verteilt in dem Wirkstoffträger vorliegt. Durch die Konzentration des Wirkstoffs im Träger, die Dicke der Folie und die Fläche der Folie kann man die Einzeldosis sehr einfach variieren.

Aus der belgischen Patentschrift Nr. 637 363 ist ein diskontinuierliches Verfahren der gesonderten Herstellung einer Folie und der nachträglichen Aufbringung des Wirkstoffes bekannt: Das bekannte Verfahren hat den Nachteil, daß die Dosierungsgenauigkeit nicht sehr gut ist und daß der nur oberflächlich gebundene Wirkstoff leicht abgelöst wird. Außerdem enthält die dort beschriebene Folie Carboxymethylcellulose, die den Wirkstoff teilweise einschließt und nur verzögert oder überhaupt nicht freigibt.

Die beispielsmäßig beschriebenen Folien sind vorwiegend für die orale Applikation geeignet.

B e i s p i e l 1

Zweiphasenpräparat

Teil 1 : 21 Einheiten mit Wirkstoff

Teil 2 : 7 Einheiten ohne Wirkstoff

Herstellung für 3000 Einheiten Teil 1

0,75 g D-Norgestrel,
0,15 g Äthinylöstradiol und
0,54 g Polyoxyäthylenpolyoxypropylenpolymeres werden in einer Mischung aus
237,00 g Äthylalkohol und
12,00 g Wasser gelöst. In diese Lösung werden
44,28 g Hydroxypropylcellulose und
44,28 g Cellulose eingetragen und gegebenenfalls homogenisiert.

Herstellung für 1000 Einheiten Teil 2

0,18 g Polyoxyäthylenpolyoxypropylenpolymeres werden in einer Mischung aus
79,00 g Äthylalkohol und
4,00 g Wasser gelöst. In diese Lösung werden
14,91 g Hydroxypropylcellulose und
14,91 g Cellulose eingetragen und gegebenenfalls homogenisie

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Die so erhaltenen Suspensionen werden auf einem geeigneten Folienziehgerät mit einem Zweikammer-Spezialrakel (Breite der Kammern: 1 = 54 mm; 2 = 18 mm) zu einem Ausstrich von 0,5 mm ausgezogen und anschließend getrocknet. Bei entsprechender Teilung in Einheiten zu 18 x 18 mm, zum Beispiel durch Perforation, können über die Breite der Folie drei Einheiten mit Wirkstoff und eine wirkstofffreie Einheit abgeteilt werden. Aus dem Folienband lassen sich nun beliebig viele Abschnitte im Verhältnis von drei Einheiten mit Wirkstoff und einer Einheit ohne Wirkstoff herstellen.

Zusammensetzung für je eine Einheit:

Teil 1 (wirkstoffhaltig)		Teil 2 (wirkstofffrei)
0,25 mg	D-Norgestrel	-
0,05 mg	Äthinylöstradiol	-
14,76 mg	Hydroxypropylcellulose	14,91 mg
14,76 mg	Cellulose	14,91 mg
0,18 mg	Polyoxyäthylenpolyoxypropylenpolymeres	0,18 mg
30,00 mg	Gewicht pro Einheit	30,00 mg

Fläche pro Einheit: ca. 3 cm^2.

Aussehen: weiß.

Beispiel 2

Dreiphasenpräparat (Zweiwirkstoffstufenpräparat)

Teil 1 : 11 Einheiten mit 0,05 mg D-Norgestrel
0,05 mg Äthinylöstradiol

Teil 2 : 10 Einheiten mit 0,125 mg D-Norgestrel
0,050 mg Äthinylöstradiol

Teil 3 : 7 Einheiten ohne Wirkstoff

Herstellung für 1100 Einheiten Teil 1:

0,055 g D-Norgestrel,
0,055 g Äthinylöstradiol und
0,198 g Polyoxyäthylenpolyoxypropylenpolymeres werden in einer Mischung aus
86,900 g Äthylalkohol und
4,400 g Wasser gelöst. In diese Lösung werden
16,346 g Hydroxypropylcellulose und
16,346 g Cellulose eingetragen und gegebenenfalls homogenisiert.

Herstellung für 1000 Einheiten Teil 2:

0,125 g D-Norgestrel,
0,050 g Äthinylöstradiol und
0,180 g Polyoxyäthylenpolyoxypropylenpolymeres werden in einer Mischung aus

79,000 g Äthylalkohol und
4,000 g Wasser gelöst. In diese Lösung werden
14,823 g Hydroxypropylcellulose und
14,822 g Cellulose eingetragen und gegebenenfalls homogenisiert.

Herstellung für 700 Einheiten Teil 3:

0,189 g Polyoxyäthylenpolyoxypropylenpolymeres werden in einer Mischung aus
82,950 g Äthylalkohol und
4,200 g Wasser gelöst. In diese Lösung werden
15,656 g Hydroxypropylcellulose und
15,655 g Cellulose eingetragen und gegebenenfalls homogenisiert.

Die so erhaltenen Suspensionen werden auf einem geeigneten Folienziehgerät mit einem Dreikammer-Spezialrakel (Breite pro Kammer 18 mm) zu einem Ausstrich ausgezogen und getrocknet. Bei entsprechender Teilung, zum Beispiel durch Perforation, zu Einheiten von 18 x 18 mm für Teil 1, 18 x 19,8 mm für Teil 2 und 18 x 28 mm für Teil 3 können über die Breite der Folie drei Einheiten mit unterschiedlichem Wirkstoffgehalt abgeteilt werden. Aus dem Folienband lassen sich Präparate mit 11 Einheiten Teil 1, 10 Einheiten Teil 2 und 7 Einheiten Teil 3 abtrennen.

Zusammensetzung pro Einheit:

Teil 1	Teil 2	Teil 3	Inhaltsstoffe
0,050 mg	0,125 mg	-	D-Norgestrel
0,050 mg	0,050 mg	-	Äthinylöstradiol
0,180 mg	0,180 mg	0,270 mg	Polyoxyäthylenpolyoxypropylenpolymeres
14,860 mg	14,823 mg	22,366 mg	Hydroxypropylcellulose
14,860 mg	14,822 mg	22,364 mg	Cellulose
30,000 mg	30,000 mg	45,000 mg	Gewicht pro Einheit
ca. 3 cm^2	ca. 3,5 cm^2	ca. 5 cm^2	Fläche pro Einheit
weiß	weiß	weiß	Aussehen

B e i s p i e l 3

Dreiphasenpräparat

Teil 1 : 11 Einheiten mit 0,05 mg D-Norgestrel
0,05 mg Äthinylöstradiol

Teil 2 : 10 Einheiten mit 0,125 mg D-Norgestrel
0,050 mg Äthinylöstradiol

Teil 3 : 7 Einheiten mit 50,00 mg Eisen(II)fumarat

Herstellung für 1100 Einheiten Teil 1:

0,066 g Lebensmittelgelb Nr. 2 (Tartrazin; E 102) werden in
4,400 g Wasser gelöst und anschließend in
86,900 g Äthylalkohol eingetragen. In dieser Lösung werden
0,055 g D-Norgestrel,
0,055 g Äthinylöstradiol und
0,198 g Polyoxyäthylenpolyoxypropylenpolymeres gelöst.
In diese Lösung werden
16,313 g Hydroxypropylcellulose und
16,313 g Cellulose eingetragen und gegebenenfalls homogenisiert.

Herstellung für 1000 Einheiten Teil 2:

0,065 g Lebensmittelorange Nr. 2 (Sunset Yellow; E 110) werden in
4,000 g Wasser gelöst und anschließend in
79,000 g Äthylalkohol eingetragen. In dieser Lösung werden
0,125 g D-Norgestrel,
0,050 g Äthinylöstradiol und
0,180 g Polyoxyäthylenpolyoxypropylenpolymeres gelöst.
In diese Lösung werden
14,790 g Hydroxypropylcellulose und
14,790 g Cellulose eingetragen und gegebenenfalls homogenisiert.

Herstellung für 700 Einheiten Teil 3:

0,042 g Saccharin,

0,042 g Sahne-Essenz und

0,406 g Polyoxyäthylenpolyoxypropylenpolymeres werden in einer Mischung aus

55,300 g Äthylalkohol und

2,800 g Wasser gelöst. In diese Lösung werden

35,000 g Eisen(II)fumarat,

17,500 g Hydroxypropylcellulose,

5,950 g Kakao und

4,060 g Cellulose eingetragen und gegebenenfalls homogenisiert.

Die so erhaltenen Suspensionen werden auf einem geeigneten Folienziehgerät mit einem Dreikammer-Spezialrakel (Breite pro Kammer 18 mm) zu einem Ausstrich ausgezogen und anschließend getrocknet. Bei entsprechender Teilung, zum Beispiel durch Perforation, zu Einheiten von 18 x 18 mm für Teil 1, 18 x 19,8 mm für Teil 2 und 18 x 28 mm für Teil 3 können über die Breite der Folie drei Einheiten mit unterschiedlichem Wirkstoffgehalt abgeteilt werden. Aus dem Folienband lassen sich Präparate mit 11 Einheiten Teil 1, 10 Einheiten Teil 2 und 7 Einheiten Teil 3 abtrennen.

Zusammensetzung pro Einheit:

Teil 1	Teil 2	Teil 3	Inhaltsstoffe
0,050 mg	0,125 mg	-	D-Norgestrel
0,050 mg	0,050 mg	-	Äthinylöstradiol
-	-	50,000 mg	Eisen(II)fumarat
0,180 mg	0,180 mg	0,580 mg	Polyoxyäthylenpolyoxypropylen-polymeres
0,060 mg	-	-	Lebensmittelgelb Nr. 2
-	0,065 mg	-	Lebensmittelorange Nr. 2
14,830 mg	14,790 mg	25,000 mg	Hydroxypropylcellulose
14,830 mg	14,790 mg	5,800 mg	Cellulose
-	-	8,500 mg	Kakao
-	-	0,060 mg	Saccharin
-	-	0,060 mg	Sahne-Essenz
30,000 mg	30,000 mg	90,000 mg	Gewicht pro Einheit
ca.3 cm^2	ca.3,5 cm^2	ca.5 cm^2	Fläche pro Einheit
gelb	orange	braun	Aussehen

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Patentansprüche

1.) Arzneimittelwirkstoffträger in Folienform mit inkorporiertem Wirkstoff gemäß Hauptpatent.....(Patentanmeldung P 24 32 925.7), dadurch gekennzeichnet, daß in einer Folie für mehrere Dosierungseinheiten nebeneinander unterschiedliche Wirkstoffe und/oder verschiedene Wirkstoffkonzentrationen inkorporiert sind.

2.) Arzneimittel nach Anspruch 1, dadurch gekennzeichnet, daß sie in Wasser oder organischen Lösungsmitteln lösliche Folienbildner enthalten.

3.) Arzneimittel nach Anspruch 1, dadurch gekennzeichnet, daß die Folienbildner in Wasser und in organischen Lösungsmitteln löslich sind.

4.) Arzneimittel nach Anspruch 1 bis 3, dadurch gekennzeichnet, daß nichtionogene, wasserlösliche Hydroxyalkyläther der Cellulose als Folienbildner verwendet werden.

5.) Arzneimittel nach Anspruch 1 bis 4, dadurch gekennzeichnet, daß Hydroxypropylcellulose, Hydroxyäthylcellulose und/oder Methylhydroxypropylcellulose als Folienbildner verwendet werden.

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6.) Arzneimitel nach Anspruch 1, dadurch gekennzeichnet, daß der Wirkstoffanteil in der Folie etwa 0-60 % beträgt.

7.) Arzneimittel nach Anspruch 1 und 6, dadurch gekennzeichnet, daß der Arzneimittelwirkstoff im Trägermaterial gelöst oder gleichmäßig suspendiert ist.

8.) Verfahren zur Herstellung von Folien mit unterschiedlichen Wirkstoffen und/oder verschiedenen Wirkstoffkonzentrationen, dadurch gekennzeichnet, daß man zwei oder mehrere unterschiedliche Lösungen bzw. Suspensionen aus Wirkstoff und/oder Trennmittel, Folienbildner und gegebenenfalls Füllstoff gemäß Hauptpatent.....(Patentanmeldung P 24 32 925.7) herstellt, die unterschiedlichen Lösungen bzw. Suspensionen mit Hilfe eines Spezialrakels, das aus zwei oder mehreren Kammern besteht, auf einer Folienziehmaschine zu einem Ausstrich auszieht und die durch Trocknung des Ausstrichs erhaltene Folie in Einheiten mit unterschiedlichen Wirkstoffen und/oder verschiedenen Wirkstoffkonzentrationen bzw. Einheiten ohne Wirkstoff teilt.

9.) Verfahren nach Anspruch 8, dadurch gekennzeichnet, daß man den Folienbildner in Mengen von etwa 6-20 %, den Füllstoff in Mengen von etwa 0-30 % und das Trennmittel vorzugsweise in Mengen von 0,01-2 % einsetzt.

10.) Verfahren nach Anspruch 8, dadurch gekennzeichnet, daß man als Lösungs- bzw. Suspensionsmittel Wasser und/oder ein organisches Lösungsmittel verwendet.

11.) Verfahren nach Anspruch 8 und 10, dadurch gekennzeichnet, daß das Lösungs- bzw. Suspensionsmittel zu etwa 48-84 % enthalten ist.

12.) Verfahren nach Anspruch 8, dadurch gekennzeichnet, daß die Schichtdicke des Ausstrichs etwa 0,1-2 mm beträgt und die der trockenen Folie etwa 0,05-1 mm beträgt.

13.) Verwendung von in Wasser und/oder organischen Lösungsmitteln löslichen Folienbildnern für die Herstellung von Arzneimittelwirkstoffträgern nach Anspruch 1.

14.) Verwendung nach Anspruch 13 von nichtionogenen, wasserlöslichen Hydroxyalkyläthern der Cellulose.

15.) Verwendung nach Anspruch 13 von Hydroxypropylcellulose, Hydroxyäthylcellulose und/oder Methylhydroxypropylcellulose.

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Prüfungsantrag gem. § 44 PatG ist gestellt

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

Eine neue Darreichungs- und Dosierungsform für Arzneimittelwirkstoffe, Reagentien oder andere Wirkstoffe besteht aus einem Trägermaterial in Form eines Releasepapiers, eines Releasefilms oder einer Releasefolie, die einseitig mit einer wirkstoffhaltigen Beschichtung versehen ist, welche nach Vorzerteilung in Dosiseinheiten von dem Trägermaterial dosisweise abziehbar ist. Die abgezogenen wirkstoffhaltigen Abschnitte eignen sich insbesondere als orale Arzneimittel.

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Patentansprüche

1. Darreichungs- und Dosierungsform für Arzneimittelwirkstoffe, Reagentien 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 Zusammensetzug mit Hilfe von Walzen auf die nichthaftend ausgerüstete Seite eines Releasepapiers, eines Releasefilms oder einer Releasefolie aufbringt.

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 bekanntgeworden, welche aus wirkstoffhaltigen Folien bestehen. Gemäß der BE-PS 6 37 363 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. 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 entsprechen

de 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 verschiedenen 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 darüber hinaus 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 Beschichtungsmasse 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, Hytostatika 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 Beschichtungsmasse wird dabei au einem geschlossenen Auftragssystem 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 beschichtete 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/m²) wurde eine Beschichtungsmasse gemäß folgender Rezeptur hergestellt:

Gelatine	10,0 Gew.-Teile =	22,22%
Kartoffelstärke	3,0 Gew.-Teile =	6,67%
Glycerin	1,5 Gew.-Teile =	3,33%
Titandioxid	0,3 Gew.-Teile =	0,67%
α-Actyldigoxin	0,2 Gew.-Teile =	4,44%
Wasser	30,0 Gew.-Teile =	66,67%

Diese Beschichtungsmasse wurde in einer Schichtdikke von 90 g/m² mittels Walzen auf das Releasepapier aufgebracht. Nach dem Trocknen wies die Beschichtung einen Restwassergehalt von 11,76% auf. Das Beschichtungsgewicht lag bei 34 g/m², was einem Arzneimittelanteil von 0,4 g/m² entspricht. Ein Abschnitt von 2 × 2,5 cm = 5 cm² (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/m²) wurde eine Beschichtungsmasse von schleimartiger Konsistenz nach folgender Rezeptur hergestellt:

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

Die Beschichtungsmasse wurde mittels eines Walzenübertragungsverfahrens mit einem Beschichtungsgewicht von 45 g/m² auf das Releasepapier aufgebracht. Nach dem Trocknen wies die Beschichtung einen Restwassergehalt von 11,76% auf. Bei einem Beschichtungsgewicht von 17 g/m² betrug der Arzneimittelanteil 0,03 g/m².

Ein Abschnitt von 2,5 × 4 cm bzw. zwei Abschnitte von 2,5 × 2 cm = 10 cm² enthalten somit 0,03 mg Levonorgestrel, was dem Gehalt der handelsüblichen Dragees entspricht.

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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: Material	Adhesive Film: Drug and Its Content (wt%)	Adhesive Film: Thickness (μm)	Support: Material	Support: Drug and Its Content (wt%)	Support: 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 Material	Drug and Its Content (wt%)	Thickness (μm)	Support 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

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

$\lfloor\overline{456}$ 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 $\lfloor\overline{345}$ of a patient (45-year-old, male) with adult periodentitis having deep pockets once a day for 4 weeks. As a control, $\lfloor\underline{345}$ 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 $\lfloor\underline{4}$. 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 $\lfloor\overline{2}$. 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.

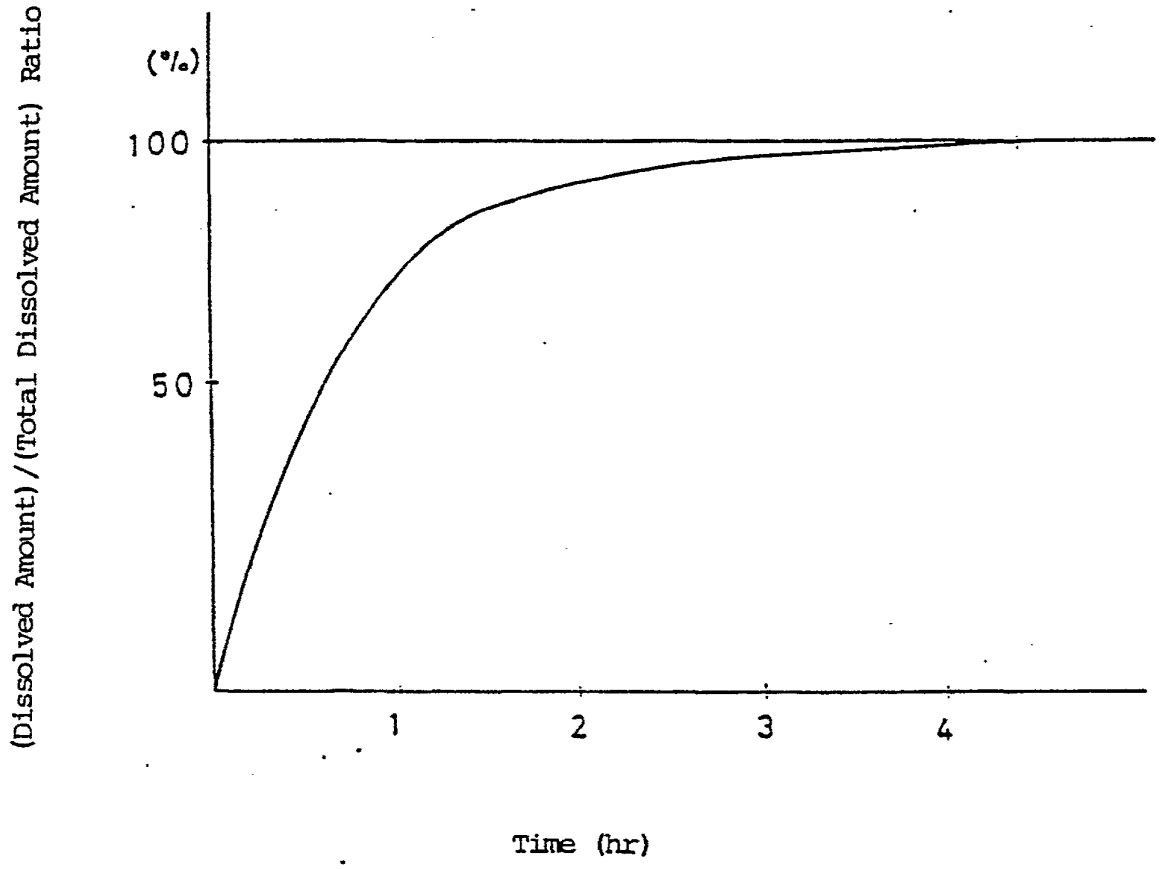
8. Oraler Verband gemäss Anspruch 6, worin die genannte Mischung eines niederen Alkohols und Wasser oder eines niederen Alkohols, eines organischen Lösungsmittels und Wasser nicht mehr als 30 Gew.-% Wasser enthält.

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.


(Dissolved Amount)/(Total Dissolved Amount) Ratio
(%)
100
50
1
2
3
4
Time (hr)

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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 wasserlösliche 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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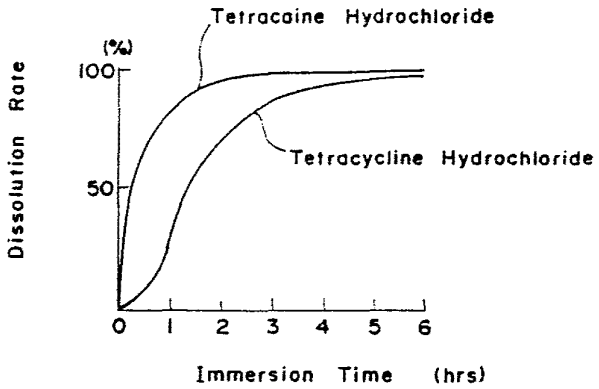
(54) Pharmaceutical composition for treating periodontal diseases.

(57) A pharmaceutical composition for treating periodontal diseases which comprises one or more of therapeutically active ingredients dispersed in a carrier, characterized in that said carrier consists of

(A) water soluble polymer, and

(B) polymeric particles having a limited solubility in water, said particles being dispersed in said water soluble polymer.

Fig. 1



EP 0 241 178 A1

PHARMACEUTICAL COMPOSITION FOR TREATING PERIODONTAL DISEASES

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 "juvenilie 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 periodontal pockets, bleeding and pus discharge from said periodontal pockets, and it brings about resorption of alveolar bone, loose tooth, and shedding of tooth.

The consensus of most investigators is that the periodontal diseases is 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 a certain nigral pigment-producing bacteria, such as genus Bacteroides. However, other genus 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 has previously been treated by several ways, such as exhaustive scaling of plaques in periodontal pockets, root planning, 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 a drug selected from germicides, anti-inflammatory agents, plaque solubilizing agents, hemostyptics, and the like. These drugs are used in the form of the formulation suited for internal use or massotherapy (e.g., dentifrices, ointments, and the like). 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 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 gingival resion (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 each other in terms of pharmacological activity and therapeutically effective dose, it has been impossible to prepare the 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 therapeutical 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 of 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.

Thus, the present invention provides a pharmaceutical composition for treating periodontal diseases, which comprises one or more of therapeutically active ingredients dispersed in a carrier, characterized in that said carrier consists of

(A) water soluble polymer, and

(B) polymeric particles having a limited solubility, said particles being dispersed in said water soluble polymer.

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.

The term "a polymer having a limited solubility in water" herein used includes an insoluble polymer, a sparingly soluble polymer, and a polymer which dissolves in an aqueous medium within a limited pH range.

For the purpose of the present invention, the term "insoluble polymer" means a polymer which dissolves in an aqueous medium, particularly in water, in a concentration of less than 0.1% by weight, irrespective of pH.

"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. "Sparlingly soluble polymer" means a polymer which has a solubility between the soluble polymer and the insoluble polymer or decomposes to dissolve in vivo slowly. The term "polymer which dissolves in an aqueous medium within a limited pH range" means a polymer which dissolves in an aqueous medium, particularly in water, having a pH higher than 4 or lower than 6, in a concentration of more than 1% by weight.

For the purpose of simplicity, the insoluble polymer, sparlingly soluble polymer and the polymer which dissolves in an aqueous medium within a limited pH range 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.

Specific examples of the insoluble polymer are ethyl cellulose, cellulose acetate, ethyl methacrylate / trimethylammonioethyl methacrylate chloride copolymer, and the like. The sparlingly soluble polymer includes, for instance, biodegradable polymer such as polyglycolic aicd, polylactic acid, polytetramethylglycolide, polydiethylglycolide, poly--caprolactone, poly(DL-decalactone), poly-(alkyleneadipate), copolymers thereof, and ion exchange resins.

The polymer which dissolves in an aqueous medium having a pH above 4 includes copolymers consisting of acrylic acid, methacrylic acid and/or esters thereof, such as methyl acrylate / methacrylic acid copolymer, methyl acrylate / methacrylic acid / octyl acrylate copolymer, ethyl acrylate / methacrylic acid copolymer, methyl acrylate / methacrylic acid / methyl methacrylate copolymer, and methyl methacrylate / methacrylic acid copolymer, hemiesters of organic bivalent acid with polysaccharide acetates such as cellulose acetate phthalate, cellulose acetate succinate, cellulose acetate maleate, starch acetate phthalate, and amylose acetate phthalate, hemiesters of organic bivalent acid with alkylated polysaccharides such as methyl cellulose phthalate, hemiesters of organic bivalent acid with hydroxypropylmethyl cellulose phthalate, and hydroxyethyl ethyl cellulose phthalate, hydroxypropylmethyl cellulose acetate succinate, alkyl ethers of carboxyalkylated polysaccharide such as carboxymethylethyl cellulose, hemiesters of organic bivalent acid with polyvinyl alcohol and its derivatives such as polyvinyl alcohol phthalate, polyvinyl acetate phthalate, polyvinyl acetal phthalate, and polyvinyl butylate phthalate.

The polymer which dissolves in an aqueous medium having a pH below 6 includes dimethylaminoethyl methacrylate / methyl methacrylate copolymer, polyvinylacetal / dimethylamino acetate, cellulose acetate dibutylhydroxypropyl ether, and the like.

Specific examples of the soluble polymer are, for instance, methyl cellulose, hydroxypropyl cellulose, sodium carboxymethylcellulose, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, sodium alginate, propylene glycol alginate, pulluran, tragacanth, xanthan gum, chitosan, polyethylene oxide, polyvinyl pyrrolidone, polyvinyl alcohol, polyacrylic acid, polymethacrylic acid, and a salt thereof.

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 of 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 of 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 1μ to 500μ depending on the contemplated release pattern of the active ingredient. However, the size between 1μ and 300μ is generally preferred.

On the other hand, one or more of water soluble polymers are dissolved in a suitable solvent. The solvent may contain, if desired, one or more of 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 may range 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, cetylpyridinium chloride, and the like; antimicrobial agents, such as ampicillin, tetracycline, benzylpenicillin, clindamycin, cefalexin, erythromycin, chloramphenicol, fragiomycin sulfate, and the like; anti-inflammatory agents, such as ibuprofen, indomethacin, ketoprofen, mefenamic acid, antipyrine, pranoprofen, ibufenac, tiaramide hydrochloride, prednisolon, dexamethasone, triamcinolone acetonide, prostaglandine, and the like; plaque solubilizing agents, such as dextranase, protease, amylase and the like; collagenase inhibitors obtained from the extraction of crude drugs, such as gambir-catechu known in the name of "asenyaku"; local anesthetics, such as tetracaine hydrochloride, ethyl aminobenzoate, and the like; antihistaminic agents, such as chlorphenilamine maleate, diphenhydramine, and the like; hemostatic agents such as tranexamic acid, and the like.

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, is 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 50μ.

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 casted into a sheet, which is then pulverized into particles having an average size of 80μ.

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) are 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 500μ thickness.

Experiment 1

The controlled release of an active ingredient was evaluated on the 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 casted on a Teflon tray and dried at 40°C. The resultant sheet was pulverized into particles of 105μ to 177μ 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, casted on a Teflon tray with care to ensure the constant thickness, and air-dried to yield a film having 300μ 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, casted on a Teflon tray, air-dried to obtain a film having 300 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 the same and identical active ingredient rather than the two active ingredients is employed in this experiment.

Claims

1. A pharmaceutical composition for treating periodontal diseases which comprises one or more of therapeutically active ingredients dispersed in a carrier, characterized in that said carrier consists of

(A) water soluble polymer, and

(B) polymeric particles having a limited solubility in water,

said particles being dispersed in said water soluble polymer.

2. A pharmaceutical composition according to Claim 1 in the form of gel, sheet, film or bar.

3. A pharmaceutical composition according to Claim 1 or 2 wherein said particles are composed of one or more of compounds selected from ethyl cellulose, cellulose acetate, ethyl methacrylate / trimethylammonioethyl methacrylate chloride copolymer, ion-exchange resins, poly(glycolic acid), poly(lactic acid), polytetramethylglycolide, polydiethylglycolide, poly-ε-caprolactone, poly(DL-decalactone), poly(alkyleneadipate), methyl acrylate / methacrylic acid copolymer, methyl acrylate / methacrylic acid / octylacrylate copolymer, ethyl acrylate / methacrylic acid copolymer, methyl acrylate / methacrylic acid / methylmethacrylate copolymer, methyl methacrylate / 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 ethyl cellulose phthalate, hydroxypropylmethyl cellulose acetate succinate, carboxymethylethyl cellulose, polyvinylalcohl phthalate, polyvinyl acetate phthalate, polyvinylacetal phthalate, polyvinylbutylate phthalate, methyl methacrylate / dimethylaminoethyl methacrylate copolymer, polyvinylacetal / dimethylamino acetate, and cellulose acetate dibutylhydroxypropyl ether.

4. A pharmaceutical composition according to Claim 1, 2, or 3 wherein said water soluble polymer is selected from methyl cellulose, hydroxypropyl cellulose, sodium carboxymethylcellulose, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, sodium alginate, propylene glycol alginate, pullulan, tragacanth, xanthan gum, chitosan, polyethylene oxide, polyvinyl pyrrolidone, polyvinyl alcohol, polyacrylic acid, polymethacrylic acid, and a salt thereof.

5. A pharmaceutical composition according to any preceding claim wherein said particles have an average size ranging from 1μm to 500 μm.

Fig. 1

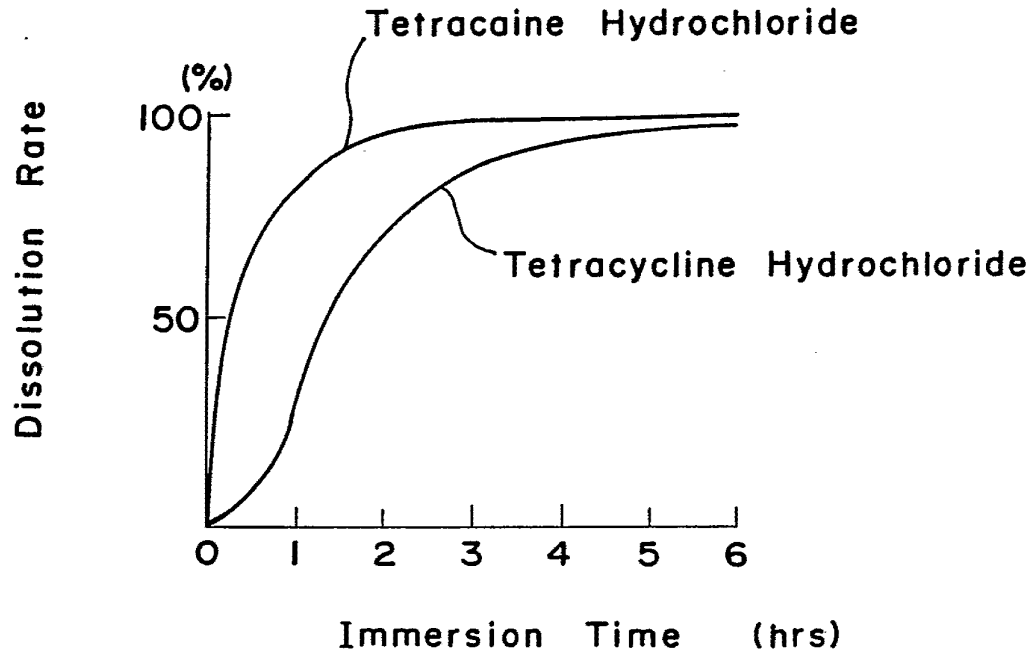
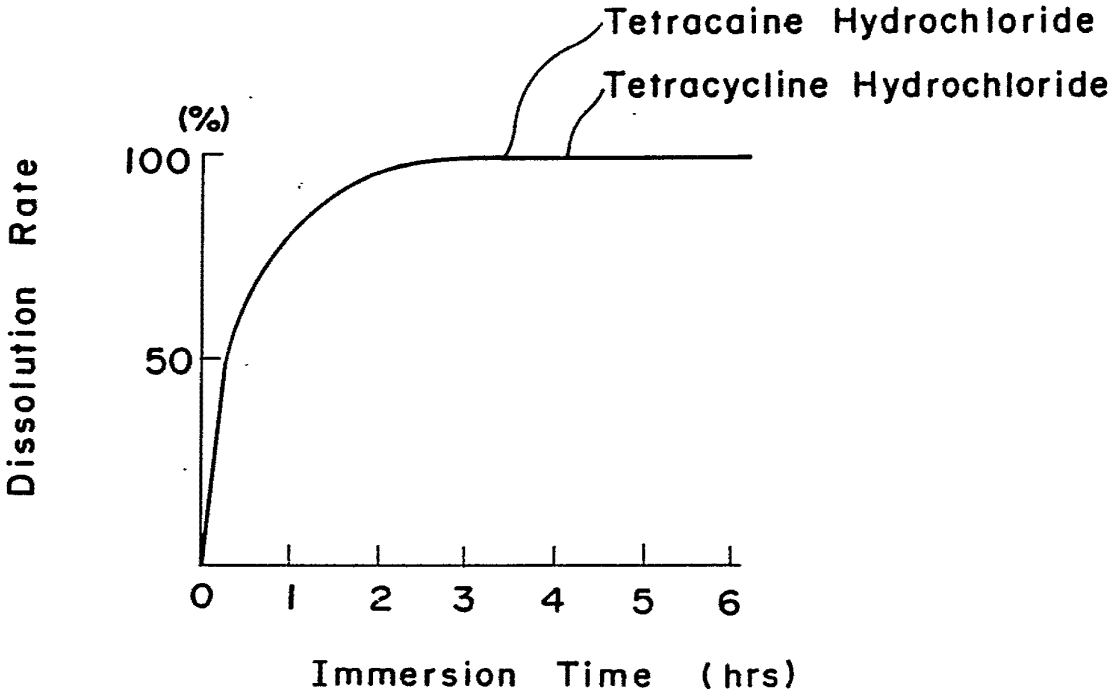


Fig. 2



European Patent Office

EUROPEAN SEARCH REPORT

Application number

EP 87 30 2514

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.4)
P,X	EP-A-0 184 389 (SUNSTAR K.K. & LEDERLE (JAPAN) LTD.) * Page 4, lines 5-25; page 10, line 10 - page 11, line 8; page 12, lines 9-26 *	1-3	A 61 K 9/70 A 61 K 47/00
Y	DE-A-3 432 573 (THE KENDALL CO.) * Page 1, claim 1; page 9, line 1 - page 10, line 1; page 11, line 25 - page 13, line 32; page 14, line 28 - page 15, line 4; page 17, lines 4-21 *	1-4	
Y	US-A-4 568 535 (W.J. LOESCHE) * Column 1, lines 11-19; column 4, lines 57-69; column 7, lines 27-55 *	1-3	
Y	EP-A-0 135 022 (BEECHAM GROUP PLC) * Page 2, lines 5-28; page 3, lines 6-23; page 4, lines 1-21 *	4	TECHNICAL FIELDS SEARCHED (Int. Cl.4) A 61 K A 61 L C 08 L
A	FR-A-2 148 045 (THE NATIONAL CASH REGISTER CO.) * Page 1, lines 1-7,22-27,35-39; page 2, line 9 - page 3, line 18; page 5, line 37 - page 6, line 10 *	1-3	

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	11-08-1987	MUELLNERS W.

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

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

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EP-A- 0 063 604
EP-A- 0 155 229
FR-A- 2 450 610

PATENT ABSTRACTS OF JAPAN, vol. 7, no. 185 (C-181)[1330], 13th August 1983; & JP-A-58 90 507 (NIPPON SODA K.K.) 30-05-1983

CHEMICAL ABSTRACTS, vol. 102, no.24, June 1985, page 366, abstract no. 209484e, Columbus, Ohio, US; & JP-A-60 05 159 (LION CORP.) 11-01-1985

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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 × 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 × 4 cm bzw. zwei Abschnitte von 2,5 × 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

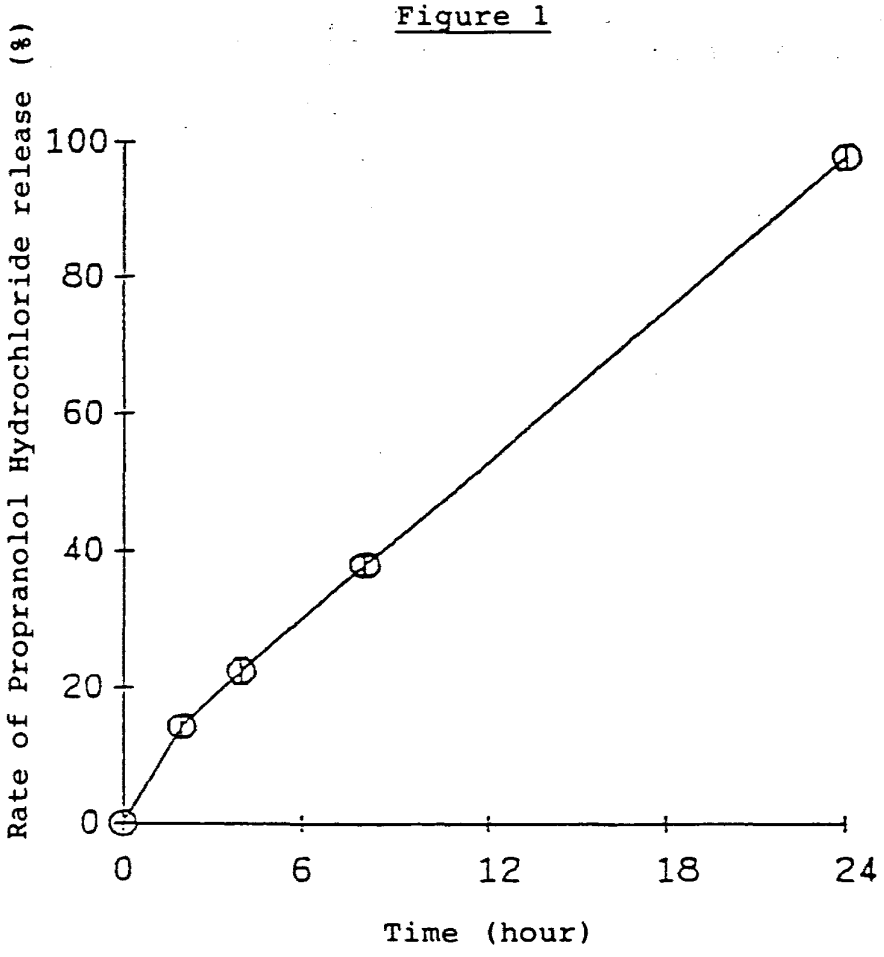
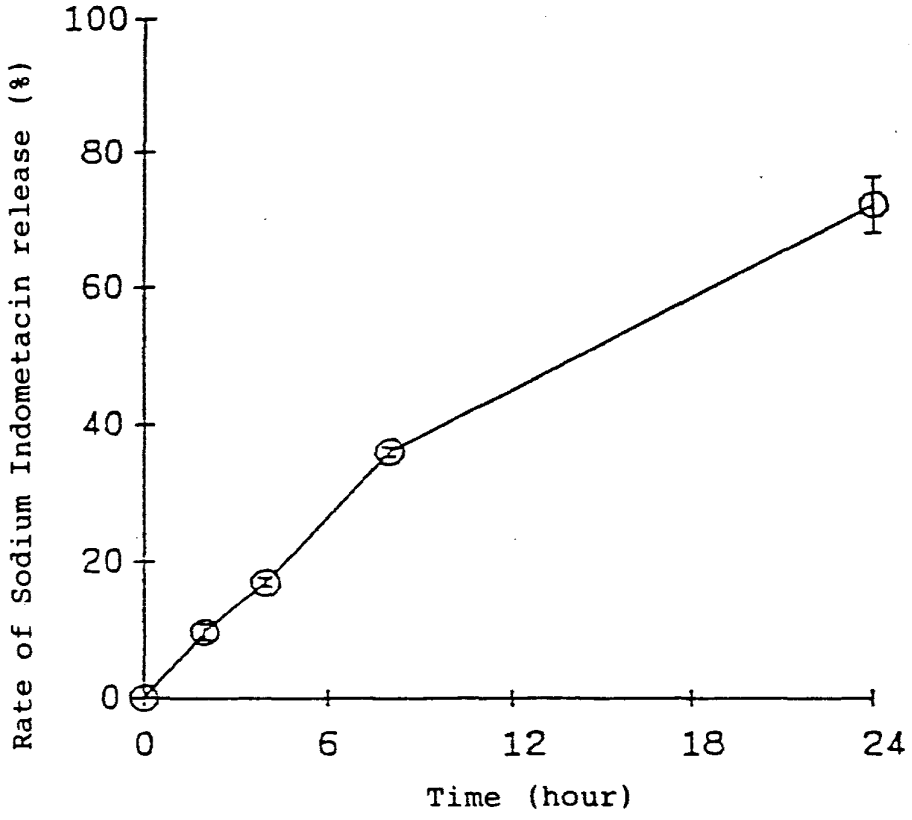


Figure 2



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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.

(57) Type I collagen gel with an H_2O content not exceeding 20% by weight, in the form of a sheet of thickness between 0.02 and 2 mm, of compact transparent structure, with a capacity for absorbing aqueous biological liquids limited to a maximum of 15 times its weight, being free from native collagen degradation products, and suitable for the therapeutic treatment of wounds and burns.

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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 "Il 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.

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, 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 30 mmHg 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 20-60 mmHg, preferably about 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 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 30 mmHg), 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

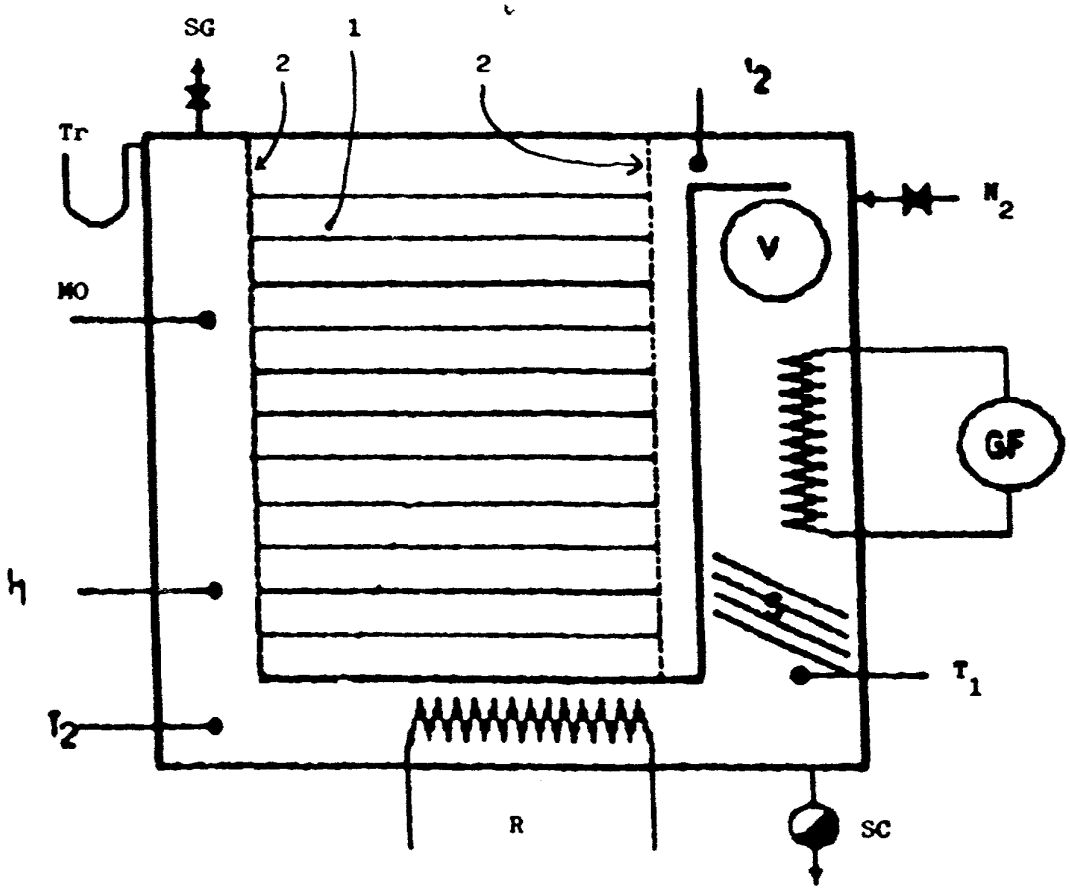
1. Type I collagen gel with an H_2O content not exceeding 20% by weight, in the form of a sheet of thickness between 0.02 and 2 mm, of compact transparent structure, with a capacity for absorbing aqueous biological liquids limited to a maximum of 15 times its weight, being free from native collagen degradation products, and suitable for the therapeutic treatment of wounds and burns.

2. A method for preparing collagen gel sheets 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 filter being under a vacuum of 20-60 mmHg and provided with a device for preventing the incorporation of gas bubbles into the filtrate, then drying the liquid gel contained in trays with a nitrogen stream under controlled temperature and relative humidity conditions.

3. A device suitable for filtering the collagen gel in accordance with claim 2, consisting of a metal mesh with a mesh size of less than 0.1 mm and provided with a pack of parallel plates in the region below the filter mesh, for the purpose of conveying the filtrate as a continuous liquid film.

4. A device suitable for drying the collagen gel in accordance with claim 2, comprising a drying region for the liquid contained in trays, means for circulating a nitrogen stream in closed circuit through the drying region and through the cooling and heating regions, and means for controlling the cooling and heating temperature to obtain a gas stream of controlled relative humidity entering the drying region.

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	-

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

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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

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
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22-02-2001

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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
Internationales Büro
INTERNATIONALE ANMELDUNG VERÖFFENTLICHT NACH DEM VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT)

(51) Internationale Patentklassifikation 5 :		(11) Internationale Veröffentlichungsnummer: WO 91/05540
A61K 7/16	A1	(43) Internationales Veröffentlichungsdatum: 2. Mai 1991 (02.05.91)

(21) Internationales Aktenzeichen: PCT/EP90/01936

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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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BB	Barbados	FR	Frankreich	MR	Mauritanien
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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

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 * [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
A	EP, A, 0219762 (DESITIN ARZNEIMITTEL GmbH) 29 April 1987 see the whole document (cited in the application)	1,2,5,6
A	GB, A, 2186190 (COLGATE-PALMOLIVE COMPANY) 12 August 1987 see claims 1,2,4,8	1,2,5,6
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A	GB, A, 1476057 (UNICLIFFE LTD) 10 June 1977 see pages 1-3	1,3

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* 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
15 March 1991 (15.03.91)	11 April 1991 (11.04.91)

International Searching Authority	Signature of Authorized Officer
EUROPEAN PATENT OFFICE	

Form PCT/ISA/210 (second sheet) (January 1985)

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. EP 9001936 SA 41110

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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. EP 9001936 SA 41110

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INTERNATIONALER RECHERCHENBERICHT

Internationales Aktenzeichen PCT/EP 90/01936

I. KLASSIFIKATION DES ANMELDUNGSGEGENSTANDS (bei mehreren Klassifikationssymbolen sind alle anzugeben)[6]

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II. RECHERCHIERTE SACHGEBIETE

Recherchierter Mindestprüfstoff[7]

Klassifikationssystem	Klassifikationssymbole
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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
A	EP, A, 0259749 (DESITIN ARZNEIMITTEL GmbH) 16. März 1988 siehe das ganze Dokument in der Anmeldung erwähnt ---	1,2,5,6
A	GB, A, 2163348 (DENTAB UK LTD) 26. Februar 1986 siehe Patentansprüche 1,4,9,14 --- ./.	1

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IV. BESCHEINIGUNG

Datum des Abschlusses der internationalen Recherche	Absendedatum des internationalen Recherchenberichts
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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.
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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 17β-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

17β-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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"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)

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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	Signature of Authorized Officer
EUROPEAN PATENT OFFICE	Mme Dagmar FRANK

Form PCT/ISA/210 (second sheet) (January 1985)

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