sweeteners, plasticizers and drugs. These allegedly flexible films are disclosed as being useful for oral, topical or enteral use. Examples of specific uses disclosed by Fuchs include application of the films to mucosal membrane areas of the body, including the mouth, rectal, vaginal, nasal and ear areas.

Examination of films made in accordance with the process disclosed in Fuchs, however, reveals that such films suffer from the aggregation or conglomeration of particles, i.e., self-aggregation, making them inherently non-uniform. This result can be attributed to Fuchs' process parameters, which although not disclosed likely include the use of relatively long drying times, thereby facilitating intermolecular attractive forces, convection forces, air flow and the like to form such agglomeration.

The formation of agglomerates randomly distributes the film components and any active present as well. When large dosages are involved, a small change in the dimensions of the film would lead to a large difference in the amount of active per film. If such films were to include low dosages of active, it is possible that portions of the film may be substantially devoid of any active. Since sheets of film are usually cut into unit doses, certain doses may therefore be devoid of or contain an insufficient amount of active for the recommended treatment. Failure to achieve a high degree of accuracy with respect to the amount of active ingredient in the cut film can be harmful to the patient. For this reason, dosage forms formed by processes such as Fuchs, would not likely meet the stringent standards of governmental or regulatory agencies, such as the U.S. Federal Drug Administration ("FDA"), relating to the variation of active in dosage forms. Currently, as required by various world regulatory authorities, dosage forms may not vary more than 10% in the amount of active present. When applied to dosage units based on films, this virtually mandates that uniformity in the film be present.

The problems of self-aggregation leading to non-uniformity of a film were addressed in U.S. Patent No. 4,849,246 to Schmidt ("Schmidt"). Schmidt specifically pointed out that the methods disclosed by Fuchs did not provide a uniform film and recognized that that the creation of a non-uniform film necessarily prevents accurate dosing, which as discussed above is especially important in the pharmaceutical area. Schmidt abandoned the idea that a mono-layer film, such as described by Fuchs, may provide an accurate dosage form and instead attempted to solve this problem by forming a multi-layered film. Moreover, his

process is a multi-step process that adds expense and complexity and is not practical for commercial use.

Other U.S. Patents directly addressed the problems of particle self-aggregation and non-uniformity inherent in conventional film forming techniques. In one attempt to overcome non-uniformity, U.S. Patent 5,629,003 to Horstmann et al. and U.S. Patent 5,948,430 to Zerbe et al. incorporated additional ingredients, i.e. gel formers and polyhydric alcohols respectively, to increase the viscosity of the film prior to drying in an effort to reduce aggregation of the components in the film. These methods have the disadvantage of requiring additional components, which translates to additional cost and manufacturing steps. Furthermore, both methods employ the use the conventional time-consuming drying methods such as a high-temperature air-bath using a drying oven, drying tunnel, vacuum drier, or other such drying equipment. The long length of drying time aids in promoting the aggregation of the active and other adjuvant, notwithstanding the use of viscosity modifiers. Such processes also run the risk of exposing the active, i.e., a drug, or vitamin C, or other components to prolonged exposure to moisture and elevated temperatures, which may render it ineffective or even harmful.

In addition to the concerns associated with degradation of an active during extended exposure to moisture, the conventional drying methods themselves are unable to provide uniform films. The length of heat exposure during conventional processing, often referred to as the "heat history", and the manner in which such heat is applied, have a direct effect on the formation and morphology of the resultant film product. Uniformity is particularly difficult to achieve via conventional drying methods where a relatively thicker film, which is well-suited for the incorporation of a drug active, is desired. Thicker uniform films are more difficult to achieve because the surfaces of the film and the inner portions of the film do not experience the same external conditions simultaneously during drying. Thus, observation of relatively thick films made from such conventional processing shows a non-uniform structure caused by convection and intermolecular forces and requires greater than 10% moisture to remain flexible. The amount of free moisture can often interfere over time with the drug leading to potency issues and therefore inconsistency in the final product.

Conventional drying methods generally include the use of forced hot air using a drying oven, drying tunnel, and the like. The difficulty in achieving a uniform film is directly

related to the rheological properties and the process of water evaporation in the film-forming composition. When the surface of an aqueous polymer solution is contacted with a high temperature air current, such as a film-forming composition passing through a hot air oven, the surface water is immediately evaporated forming a polymer film or skin on the surface. This seals the remainder of the aqueous film-forming composition beneath the surface, forming a barrier through which the remaining water must force itself as it is evaporated in order to achieve a dried film. As the temperature outside the film continues to increase, water vapor pressure builds up under the surface of the film, stretching the surface of the film, and ultimately ripping the film surface open allowing the water vapor to escape. As soon as the water vapor has escaped, the polymer film surface reforms, and this process is repeated, until the film is completely dried. The result of the repeated destruction and reformation of the film surface is observed as a "ripple effect" which produces an uneven, and therefore non-uniform film. Frequently, depending on the polymer, a surface will seal so tightly that the remaining water is difficult to remove, leading to very long drying times, higher temperatures, and higher energy costs.

Other factors, such as mixing techniques, also play a role in the manufacture of a pharmaceutical film suitable for commercialization and regulatory approval. Air can be trapped in the composition during the mixing process or later during the film making process, which can leave voids in the film product as the moisture evaporates during the drying stage. The film frequently collapse around the voids resulting in an uneven film surface and therefore, non-uniformity of the final film product. Uniformity is still affected even if the voids in the film caused by air bubbles do not collapse. This situation also provides a non-uniform film in that the spaces, which are not uniformly distributed, are occupying area that would otherwise be occupied by the film composition. None of the above-mentioned patents either addresses or proposes a solution to the problems caused by air that has been introduced to the film.

Therefore, there is a need for methods and compositions for film products, which use a minimal number of materials or components, and which provide a substantially non-self-aggregating uniform heterogeneity throughout the area of the films. Desirably, such films are produced through a selection of a polymer or combination of polymers that will provide a desired viscosity, a film-forming process such as reverse roll coating, and a controlled, and desirably rapid, drying process which serves to maintain the uniform distribution of non-self-

aggregated components without the necessary addition of gel formers or polyhydric alcohols and the like which appear to be required in the products and for the processes of prior patents, such as the aforementioned Horstmann and Zerbe patents. Desirably, the films will also incorporate compositions and methods of manufacture that substantially reduce or eliminate air in the film, thereby promoting uniformity in the final film product.

SUMMARY OF THE INVENTION

In one aspect of the present invention, there is provided a film and a method of forming same which can be divided into equally sized dosage units having substantially equal amounts of each compositional component present. This advantage is particularly useful because it permits large area films to be initially formed, and subsequently cut into individual dosage units without concern for whether each unit is compositionally equal. For example, the films of the present invention have particular applicability as pharmaceutical dosage delivery systems because each dosage unit, e.g., each individual dosage film unit, will contain the proper amount of drug. Pharmaceutical film dosage forms to date have not been marketed largely due to the inability to achieve this result.

In a further aspect of the present invention, there is provided a film product that is formed by combining a polymer and a polar solvent, forming the combination into a film, and drying the film in a controlled manner, desirably by initially only applying heat to the bottom side of the film, in order to maintain a non-self-aggregating uniform heterogeneity. Desirably, during the initial bottom drying stage, substantially no convection currents, i.e. hot air currents, are permitted to travel across the tops of the films. Once the visco-elastic properties of the film are such that the film components are "locked" in place and cannot move to cause non-uniformity, other methods of heating may then be employed. The polar solvent may be water, a polar organic solvent, or a combination thereof. An active ingredient may be added to the polymer and water combination prior to the drying step. Alternatively, or in addition to controlling the drying the film, the polymer may be selected in order to provide a viscosity that maintains the non-self-aggregating uniform heterogeneity. Moreover, the composition desirably is mixed in a manner to minimize the incorporation of air into the mixture and is desirably deaerated, such as by conditioning at room temperature, vacuum treatment or the like, to allow trapped air to escape prior to the drying process. This serves to eliminate bubble and void formation in the final film product, thereby further improving

uniformity. Reverse roll is one particularly useful coating technique may also be used to form the film.

In another aspect of the invention, there is a process for preparing a film with a substantially uniform distribution of components. The process includes the steps of combining a polymer component and water to form a uniformly distributed matrix. This matrix is then formed into a film and fed onto the top side of a substrate surface having top and bottom sides. Heat is applied to the bottom side of the substrate surface in order to dry the film. The matrix from which the film is formed may also include an active ingredient. Also, either alternatively, or in addition to the particular method used to dry the film, the polymer may be selected in order to provide a viscosity that maintains the non-self-aggregating uniform heterogeneity. Reverse roll coating technique may also be used to form the film.

A further aspect of the present invention is a method of orally administering an active including 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 the material into a film; and
  (iii) drying the film in a controlled manner to maintain the non-self-aggregating uniform heterogeneity; and
(b) introducing the film to the oral cavity of a mammal.

An even further aspect of the present invention is method of introducing an active component to liquid including 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 the material into a film; and
  (iii) drying the film in a controlled manner to maintain the non-self-aggregating uniform heterogeneity; and
(b) placing the film into a liquid; and
(c) allowing the film to dissolve.

A still further aspect of the present invention provides a dosage form for the administration of an active including:

(a) a first layer including a film formed 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) a substantially non-water soluble second layer.

Another aspect of the present invention provides a method of preparing a dosage form for the administration of an active including the steps of:

(a) combining a polymer, an active component, and water to form a material with a non-self-aggregating uniform heterogeneity;
(b) forming the material into a film;
(c) applying the film to a substantially non-water soluble support; and
(d) drying the film in a controlled manner to maintain the non-self-aggregating uniform heterogeneity.

In still another aspect of the present invention there is provided another method of administering an active including the steps of:

(a) preparing dosage form 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 the material into a film;
    (iii) applying the film to a substantially non-water soluble support; and
    (iv) drying the film in a controlled manner to maintain the non-self-aggregating uniform heterogeneity;
(b) removing the film from said support; and
(c) applying the film to the oral cavity of a mammal.

Another aspect of the invention provides a film product formed by the steps of:

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

(b) forming said material into a film; and

(c) removing said liquid carrier, for example, by evaporative methods or by permitting volatilization to occur at selected temperatures, from said film in a manner to maintain said non-self-aggregating uniform heterogeneity.

Also provided is a process for making a film having a substantially uniform distribution of components including:

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

(b) forming a film from said matrix; and

(c) removing said liquid carrier, for example, by evaporative methods or by permitting volatilization to occur at selected temperatures, from said film in a manner to maintain said uniform distribution.

A still further aspect of the present invention provides process for making a film having a substantially uniform distribution of components including:

(a) combining a polymer component and a 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; and

(b) forming a film from said matrix.

The invention also includes films and a process for preparing films having a substantially uniform distribution of components. The process includes the steps of combining a polymer component and water to form a uniformly distributed matrix. This matrix is then formed into a film and fed onto a substrate surface having top and bottom sides where the bottom side is in substantially uniform contact with a bottom drying medium, such as a water bath or heated air space controlled at a temperature sufficient to dry the film. Desirably, no external air currents or heat is applied directly to the exposed top surface of the film during the drying process until the film structure has solidified sufficiently to prevent flow, migration and intermolecular attractive forces from creating aggregates or conglomerates. Desirably the heat is controllably conducted by the substrate surface to the

film to effectuate drying. The matrix from which the film is formed may also include an active ingredient. Also, either alternatively, or in addition to rapidly drying the film, the polymer may be selected in order to provide a viscosity that maintains the non-self-aggregating uniform heterogeneity.

A pharmaceutical and/or cosmetic dosage form is also provided that includes a film having a uniformly dispersed composition including 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.

A still further aspect of the present invention includes a pharmaceutical and/or cosmetic dosage form including a polymeric film having no more than a 10% variance of a pharmaceutical and/or cosmetic active per unit area.

The present invention also 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 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.

A pharmaceutical dispenser is also provided that includes individual unit dosage forms of the pharmaceutical compositions and films of the present invention. The dosage forms may be optionally stacked in a dispenser or in a roll.

Yet another aspect of the present invention provides an ingestible water-soluble delivery system in the form of a film composition that includes a water-soluble polymer and an anti-foaming or defoaming agent, such as simethicone, which includes a combination of a polymethylsiloxane and silicon dioxide. Simethicone can act as either an anti-foaming or defoaming agent, or both, 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 composition may also include a pharmaceutical and/or cosmetic active ingredient, flavors, sweeteners, plasticizers, surfactants, or other ingredients to alter the film properties to produce the desired product.

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

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.

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.

While the proper viscosity uniformity in mixture and stable suspension of particles, and casting method are important in the initial steps of forming the composition and film to promote uniformity, the method of drying the wet film is also important. Although these parameters and properties assist uniformity initially, a controlled rapid drying process ensures that the uniformity will be maintained until the film is dry.

The wet film is then dried using controlled bottom drying or controlled microwave drying, desirably in the absence of external air currents or heat on the top (exposed) surface of the film 48 as described herein. Controlled bottom drying or controlled microwave drying advantageously allows for vapor release from the film without the disadvantages of the prior art. Conventional convection air drying from the top is not employed because it initiates drying at the top uppermost portion of the film, thereby forming a barrier against fluid flow, such as the evaporative vapors, and thermal flow, such as the thermal energy for drying. Such dried upper portions serve as a barrier to further vapor release as the portions beneath are dried, which results in non-uniform films. As previously mentioned some top air flow can be used to aid the drying of the films of the present invention, but it must not create a condition that would cause particle movement or a rippling effect in the film, both of which would result in non-uniformity. If top air is employed, it is balanced with the bottom air drying to avoid non-uniformity and prevent film lift-up on the carrier belt. A balance top and bottom air flow may be suitable where the bottom air flow functions as the major source of drying and the top air flow is the minor source of drying. The advantage of some top air flow is to move the exiting vapors away from the film thereby aiding in the overall drying process. The use of any top air flow or top drying, however, must be balanced by a number of factors including, but not limited, to rheological properties of the composition and mechanical

aspects of the processing. Any top fluid flow, such as air, also must not overcome the inherent viscosity of the film-forming composition. In other words, the top air flow cannot break, distort or otherwise physically disturb the surface of the composition. Moreover, air velocities are desirably below the yield values of the film, i.e., below any force level that can move the liquids in the film-forming compositions. For thin or low viscosity compositions, low air velocity must be used. For thick or high viscosity compositions, higher air velocities may be used. Furthermore, air velocities are desirable low so as to avoid any lifting or other movement of the film formed from the compositions.

Moreover, the films of the present invention may contain particles that are sensitive to temperature, such as flavors, which may be volatile, or drugs, 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.

Consideration of the above discussed parameters, such as but not limited to rheology properties, viscosity, mixing method, casting method and drying method, also impact material selection for the different components of the present invention. Furthermore, such consideration with proper material selection provides the compositions of the present invention, including a pharmaceutical and/or cosmetic dosage form or film product having no more than a 10% variance of a pharmaceutical and/or cosmetic active per unit area. In other words, the uniformity of the present invention is determined by the presence of no more than a 10% by weight of pharmaceutical and/or cosmetic variance throughout the matrix. Desirably, the variance is less than 5% by weight, less than 2% by weight, less than 1% by weight, or less than 0.5% by weight.

Film-Forming Polymers

The polymer may be water soluble, water swellable, water insoluble, or a combination of one or more either water soluble, water swellable or water insoluble polymers. The polymer may include cellulose or a cellulose derivative. Specific examples of useful water soluble polymers include, but are not limited to, pullulan, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, polyvinyl pyrrolidone, carboxymethyl cellulose, polyvinyl alcohol, sodium aginate, polyethylene glycol, xanthan gum, tragancanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof. Specific examples of useful water insoluble polymers include, but are not limited to, ethyl cellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate and combinations thereof.

As used herein the phrase "water soluble polymer" and variants thereof refer to a polymer that is at least partially soluble in water, and desirably fully or predominantly soluble in water, or absorbs water. Polymers that absorb water are often referred to as being water swellable polymers. The materials useful with the present invention may be water soluble or water swellable at room temperature and other temperatures, such as temperatures exceeding room temperature. Moreover, the materials may be water soluble or water swellable at pressures less than atmospheric pressure. Desirably, the water soluble polymers are water soluble or water swellable having at least 20 percent by weight water uptake. Water swellable polymers having a 25 or greater percent by weight water uptake are also useful. Films or dosage forms of the present invention formed from such water soluble polymers are desirably sufficiently water soluble to be dissolvable upon contact with bodily fluids.

Other polymers useful for incorporation into the films of the present invention include biodegradable polymers, copolymers, block polymers and combinations thereof. Among the known useful polymers or polymer classes which meet the above criteria are: poly(glycolic acid) (PGA), poly(lactic acid) (PLA), polydioxanoes, polyoxalates, poly(α-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof. Additional useful polymers include, stereopolymers of L- and D-lactic acid, copolymers of bis(p-carboxyphenoxy) propane acid and sebacic acid, sebacic acid copolymers, copolymers of caprolactone, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, copolymers of polyurethane and (poly(lactic acid), copolymers of polyurethane and poly(lactic acid), copolymers of α-amino acids, copolymers of α-amino acids and caproic acid, copolymers of α-benzyl glutamate and polyethylene glycol, copolymers of succinate and poly(glycols), polyphosphazene, polyhydroxy-alkanoates and mixtures thereof. Binary and ternary systems are contemplated.

Other specific polymers useful include those marketed under the Medisorb and Biodel trademarks. The Medisorb materials are marketed by the Dupont Company of Wilmington, Delaware and are generically identified as a "lactide/glycolide co-polymer" containing "propanoic acid, 2-hydroxy-polymer with hydroxy-polymer with hydroxyacetic acid." Four such polymers include lactide/glycolide 100L, believed to be 100% lactide having a melting point within the range of 338°-347°F (170°-175°C); lactide/glycolide 100L, believed to be 100% glycolide having a melting point within the range of 437°-455°F (225°-235°C);

lactide/glycolide 85/15, believed to be 85% lactide and 15% glycolide with a melting point within the range of 338°-347°F (170°-175° C); and lactide/glycolide 50/50, believed to be a copolymer of 50% lactide and 50% glycolide with a melting point within the range of 338°-347°F (170°-175°C).

The Biodel materials represent a family of various polyanhydrides which differ chemically.

Although a variety of different polymers may be used, it is desired to select polymers to provide a desired viscosity of the mixture prior to drying. For example, if the active or other components are not soluble in the selected solvent, a polymer that will provide a greater viscosity is desired to assist in maintaining uniformity. On the other hand, if the components are soluble in the solvent, a polymer that provides a lower viscosity may be preferred.

The polymer plays an important role in affecting the viscosity of the film. Viscosity is one property of a liquid that controls the stability of the active in an emulsion, a colloid or a suspension. Generally the viscosity of the matrix will vary from about 400 cps to about 100,000 cps, preferably from about 800 cps to about 60,000 cps, and most preferably from about 1,000 cps to about 40,000 cps. Desirably, the viscosity of the film-forming matrix will rapidly increase upon initiation of the drying process.

The viscosity may be adjusted based on the selected active depending on the other components within the matrix. For example, if the component is not soluble within the selected solvent, a proper viscosity may be selected to prevent the component from settling which would adversely affect the uniformity of the resulting film. The viscosity may be adjusted in different ways. To increase viscosity of the film matrix, the polymer may be chosen of a higher molecular weight or crosslinkers may be added, such as salts of calcium, sodium and potassium. The viscosity may also be adjusted by adjusting the temperature or by adding a viscosity increasing component. Components that will increase the viscosity or stabilize the emulsion/suspension include higher molecular weight polymers and polysaccharides and gums, which include without limitation, alginate, carrageenan, hydroxypropyl methyl cellulose, locust bean gum, guar gum, xanthan gum, dextran, gum arabic, gellan gum and combinations thereof.

It has also been observed that certain polymers which when used alone would ordinarily require a plasticizer to achieve a flexible film, can be combined without a plasticizer and yet achieve flexible films. For example, HPMC and HPC when used in combination provide a flexible, strong film with the appropriate plasticity and elasticity for manufacturing and storage. No additional plasticizer or polyalcohol is needed for flexibility.

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.

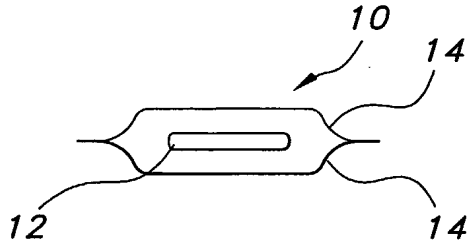

FIG. 1

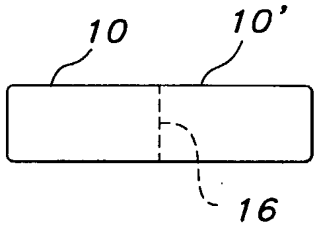

FIG. 2

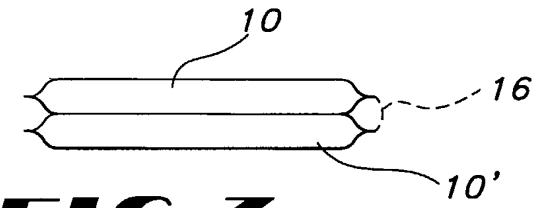

FIG. 3

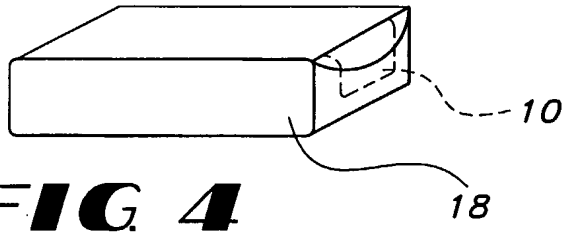

FIG. 4

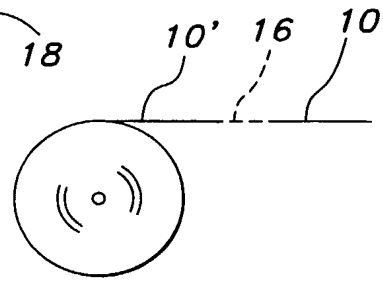

FIG. 5

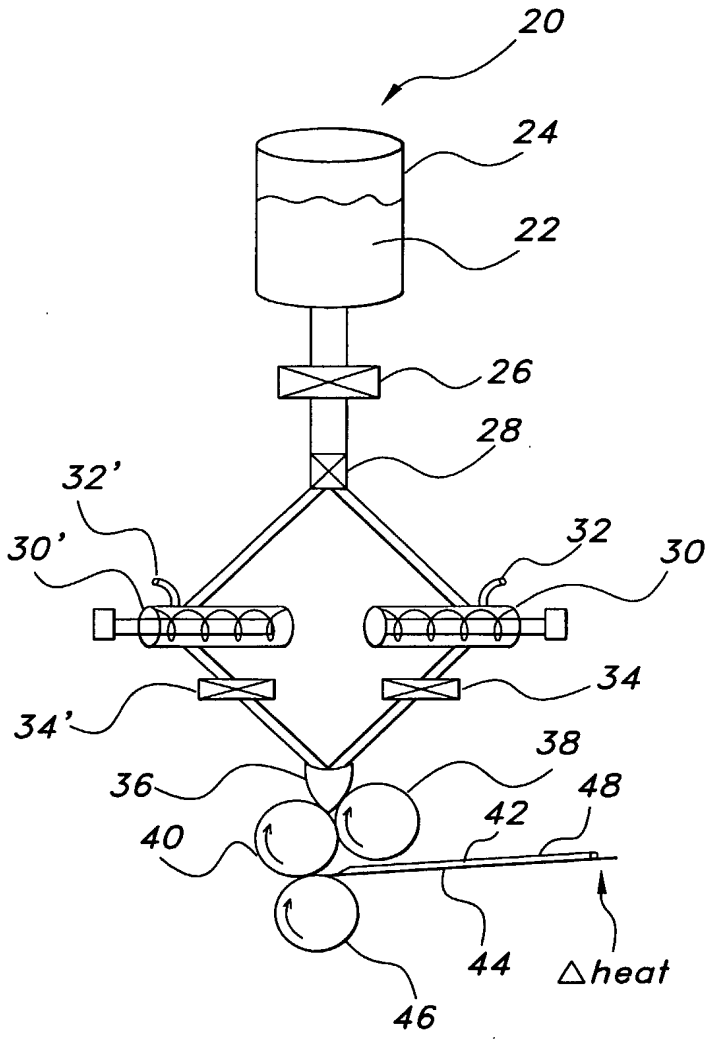

FIG. 6

3/3

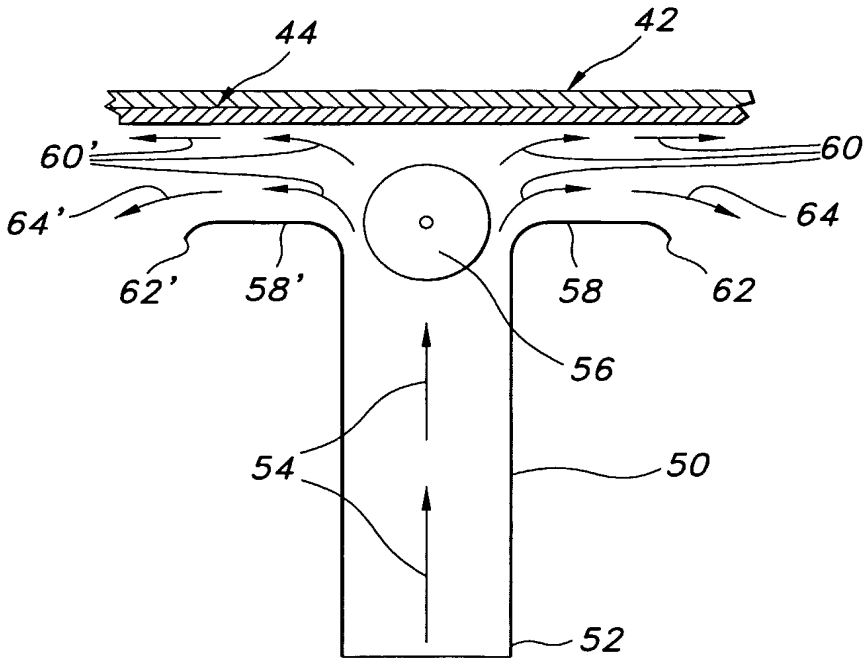

FIG. 7

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)

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
X	EP 0 514 691 A (EURORESEARCH SRL) 25 November 1992 (1992-11-25) page 4, column 2	1-76
X	US 4 925 670 A (SCHMIDT WOLFGANG) 15 May 1990 (1990-05-15) page 4, line 65 -page 5, line 2	1-79
A	US 5 629 003 A (HORSTMANN MICHAEL ET AL) 13 May 1997 (1997-05-13) cited in the application the whole document	1-76
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

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Declaration under Rule 4.17:
— *of inventorship (Rule 4.17(iv)) for US only*

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/030883 A1

(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-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.

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.

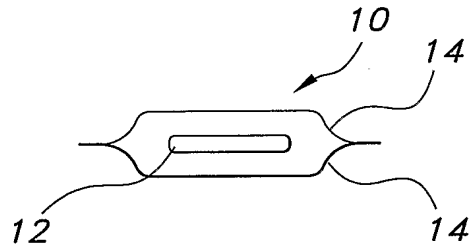

FIG. 1

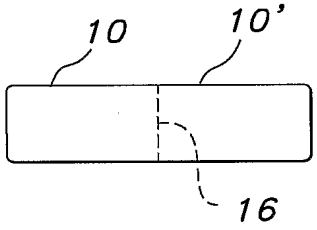

FIG. 2

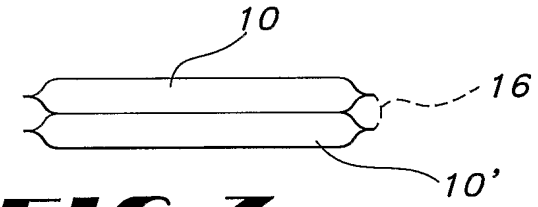

FIG. 3

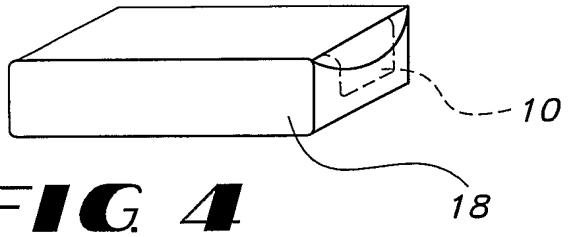

FIG. 4

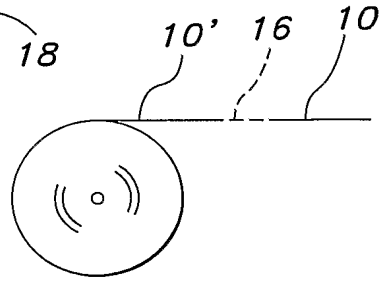

FIG. 5

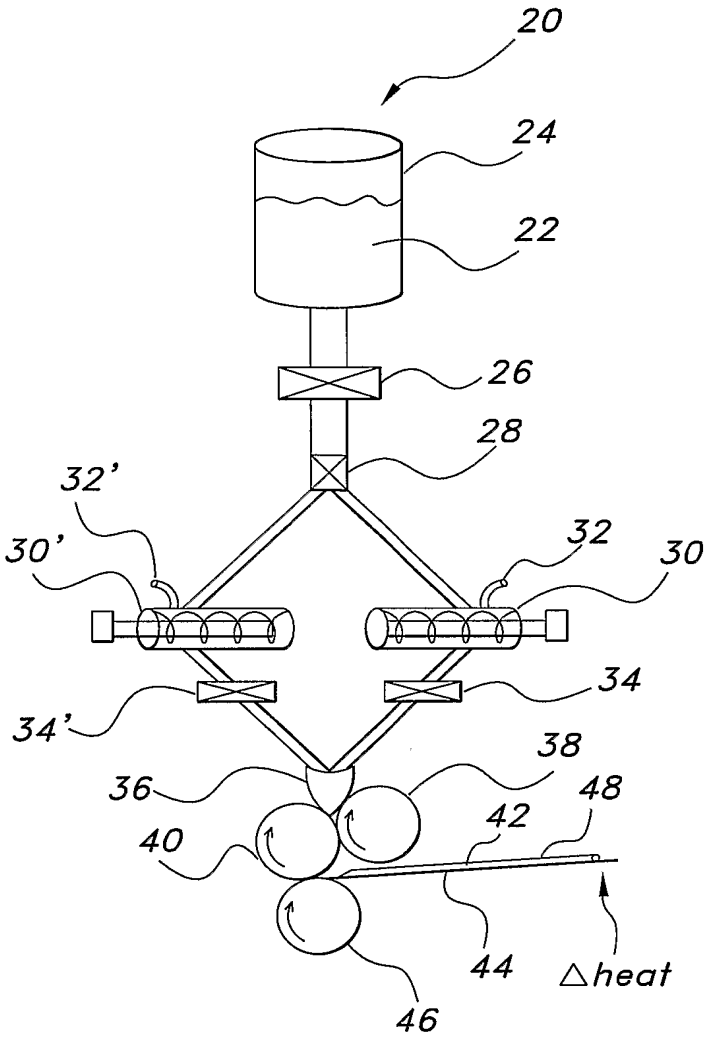

FIG. 6

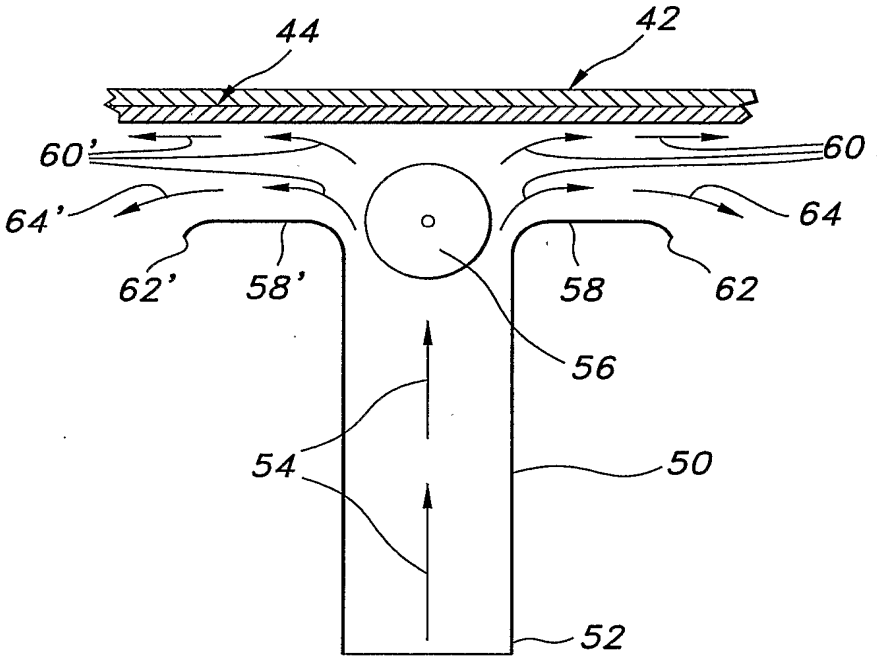

FIG. 7

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
	-/--	

[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

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"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

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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 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)

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
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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

ıational 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.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte al Application No
PCT/US 02/32594

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In ıl Application No
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(19) World Intellectual Property Organization
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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

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Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) **Title:** Pharmaceutical compositions for acute glucocorticoid therapy

(57) **Abstract:** The present invention relates to glucocorticoid-containing pharmaceutical compositions or kits for use in acute emergency situations where acute glucocorticoid therapy is required. Notably, the invention relates to pharmaceutical compositions and kits that are designed to be administered by non-medically trained persons outside a hospital or another medical or clinical setting. The invention also relates to a method for treating a disorder requiring acute glucocorticoid therapy by providing a fast onset of action of a glucocorticoid

WO 2005/102287 A2

Pharmaceutical compositions for acute glucocorticoid therapy

Field of the invention

The present invention relates to glucocorticoid-containing pharmaceutical compositions or kits for use in acute emergency situations where acute glucocorticoid therapy is required. Notably, the invention relates to pharmaceutical compositions and kits that are designed to be administered by non-medically trained persons outside a hospital or another medical or clinical setting. The invention also relates to a method for treating a disorder requiring acute glucocorticoid therapy by providing a fast onset of action of a glucocorticoid.

Background of the invention

Glucocorticoids are important steroids for intermediary metabolism, immune function, musculoskeletal and connective tissue as well as the brain. The importance of the glucocorticoids is best understood in patients with glucocorticoid deficiency. In such patients, the one-year survival rate was only 20% in the 1950s before the availability of glucocorticoid replacement therapy. The major use of glucocorticoids in clinical practice began, however, with their use in the treatment of rheumatoid arthritis in the 1940s. Both natural and synthetic glucocorticoids have been employed in the management of a wide variety of conditions and they play a crucial part of many emergency treatments involving allergic and inflammatory disorders.

The endogenous glucocorticoids are steroids predominantly produced in the adrenal cortex. The main glucocorticoid in the body is cortisol. The production and secretion of cortisol is governed by a complex and highly efficient system that includes the hypothalamus, pituitary and the adrenal glands i.e. hypothalamic-pituitary-adrenal axis (HPA). Cortisol secretion has a circadian release rhythm with peak values in early morning and trough values at midnight. The HPA axis is also activated by several physical and psychological stressors. Thus, under stress conditions, such as physical activity, fever, surgery or mental stress, the serum cortisol concentration is increased.

Adrenocortical deficiency results in a number of complex symptoms that results from deficiency of adrenocortical hormone activity. It may be of a primary type as a result of a disease in the adrenal cortex, a secondary (central) type due to the specific pathology in the hypothalamus and/or the pituitary gland, or a tertiary type due to a suppressed HPA axis after long-term high dose glucocorticoid treatment.

The onset of adrenocortical insufficiency may vary from insidious to an acute life-threatening situation with severe salt and water deficit, which leads to shock and death if not treated fast and adequately.

Therapy of e.g. acute adrenal crisis requires that the one or more glucocorticoids quickly enter (are absorbed) into the systemic circulation at a therapeutically effective concentration interval (therapeutic window). Although a number of various glucocorticoid-containing pharmaceutical compositions already are on the market, most of these are not suitable for the treatment of a disorder requiring acute glucocorticoid therapy as they either result in a too slow appearance in the systemic circulation (e.g. conventional tablets) or in a too low, if any, glucocorticoid serum level (many glucocorticoid-containing pharmaceutical compositions are intended for local treatment e.g. in the nose or on the skin).

There are today two ways of administering glucocorticoids in medical emergencies. One is the parenteral route where an intravenous (IV) infusion has to be set up or a deep intramuscular (IM) injection has to be given. However, one disadvantage of this administration is that an IV route can be challenging to establish particularly in patients with compromised peripheral circulation. Furthermore, parenteral administration requires qualified personnel and is therefore limited to well-crewed ambulances and in-hospital settings.

The other administration route is traditionally by oral administration using a dissolvable betamethasone tablet in water. This route is mainly used in outpatient clinics and for patient self-medication. However, the disadvantages are the considerable lag-time when preparing the solution and the time from intake until a significant serum level of the drug is obtained. The maximum plasma concentration (C_{max}) is usually reached within 1 to 3 hours after administration (T_{max}) It is also well known that the onset of intestinal absorption cannot be earlier than 0.5 hour for these oral immediate release products of a rapidly dissolved and rapidly absorbed drug (a class I drug according to the FDA's Biopharmaceutics Classification System), the gastric emptying being very variable both in the fasted and fed state. Furthermore, it is mandatory that the patient is conscious and has unaffected ability to swallow the solution since a weak gastrointestinal motility results in a further delay in gastric emptying and reduced intestinal absorption (both rate and extent).

Examples of such cumbersome oral administrations are obtained in patients with acute laryngitis, patients with severe distress due to breathlessness, children with croup or severe angiooedema, and in patients with gastroenteritis where gastrointestinal absorption is uncertain.

Accordingly, it would be of great therapeutic advantage to develop pharmaceutical compositions that enable self-administration by patients and administration to patients by non-medically trained persons outside of a hospital, clinic, ambulance, paramedical or similar medical settings and at the same time result in a sufficient treatment of a disorder requiring acute glucocorticoid therapy (e.g. acute adrenal crises) by providing a fast onset of action after administration. Moreover, there is also a need for pharmaceutical compositions that can be administered to a patient who e.g. is unconscious or otherwise unable to swallow a composition (e.g. a tablet or solution) and that does not require medically trained personnel or need be done in a medical setting.

Detailed disclosure of the invention

The present invention meets the above-described needs by providing a pharmaceutical composition comprising one or more glucocorticoids for substantially immediate release, wherein at least about 60% of the one or more glucocorticoids are released from the composition within the first 30 min after start of an in vitro dissolution test according to USP employing USP Dissolution Apparatus No. 2 (paddle), 50 rpm and a suitable dissolution medium such as, e.g., water, simulated saliva or simulated intestinal fluid without enzymes, and wherein a glucocorticoid serum level of a subject of at least 20% of C_{max} is reached within 20 min after administration of the composition via a mucosa of the subject.

The dissolution medium can be chosen depending on the type of composition in question. Accordingly, water or simulated saliva can be used for compositions intended for administration to the oral cavity. A person skilled in the art will know how to chose the right dissolution medium depending on the formulation in question. Normally a dissolution medium based on water and adjusted to a pH in the range of from pH 4.5 to about 8 is suitable irrespective of whether the compositions are intended for administration via nasal, rectal, vaginal mucosa.

In the present context the term "substantially immediate release" is intended to include all types of release which differ from the release obtained from plain tables and provide a release, which is faster than that obtained from plain tablets. In particular, the term is related to a rapid release of the one or more glucocorticoids in an *in vitro* dissolution test according to USP employing USP Dissolution Apparatus No. 2 (paddle), 50 rpm and simulated intestinal fluid without enzymes as dissolution medium.

The term "C_{max}" denotes the average maximum serum//plasma/blood concentration or serum//plasma/blood level obtained after administration of the composition to at least six normal healthy human subjects.

The term "via a mucosa" indicates that the one or more glucocorticoids must enter into the systemic circulation in order to obtain the desired effect and that the administration route is different from that of topical, intravenous and intramuscular administration.

In another aspect, the invention relates to a kit for treating a subject suffering from a disorder requiring acute glucocorticoid therapy comprising one or more containers for housing a pharmaceutical composition according to the invention and instructions for use thereof. In a specific embodiment, the one or more containers are in the form of blisters or blister packs.

In a further aspect, the invention relates to a method for treating a subject suffering from a disorder requiring acute glucocorticoid therapy, the method comprises administering via a mucosa of the subject an effective amount of one or more glucocorticoids to obtain a fast rise in the glucocorticoid serum level to at least 20% of C_{max} within 20 min after administration.

In a still further aspect, the invention relates to the use of an amount of one or more glucocorticoids for the preparation of a pharmaceutical composition or kit as defined herein for the treatment of a disorder requiring acute glucocorticoid therapy by providing a fast rise in the glucocorticoid serum level to at least 20% of C_{max} within 20 min after administration via a mucosa.

As mentioned above, in order to obtain a fast onset of action it is required that a fast rise of glucocorticoid serum level is obtained after administration of a composition of the invention. Accordingly, in specific embodiments least 40% of C_{max} is reached within

30 min and/or at least 75% of C_{max} is reached within 45 min after administration of the composition via a mucosa of the subject.

Normally, T_{max} (i.e. the time it takes to obtain the maximum serum/plasma/blood concentration in the serum/plasma/blood concentration time profile) is reached within 60 min after administration of the composition via a mucosa of the subject. T_{max} is typically within a range of from about 30 to about 75 min such as in a range of from about 45 to about 60 min.

As mentioned above, the pharmaceutical compositions and kits of the present invention are suitable for use in the treatment of a disorder requiring acute glucocorticoid therapy. Examples of such disorders are acute adrenal crises relating to a primary, secondary or tertiary adrenal insufficiency, an anaphylactic reaction, an Addison crisis, a status asthmaticus, a blood transfusion reaction, a brain edema, acute kidney transplant rejection, systemic lupus erythematosus or a severe allergic reaction. Other examples include inflammatory disorders, autoimmune disorders, or medical disorders in which a glucocorticoid forms a part of the first line emergency medical treatment or intense short-time medical treatment. Specific examples of disorders that can be treated according to the present invention are given in the following.

Active substance, dosage and administration routes

In the present context, the term "glucocorticoid" or "glucocorticosteroid" is intended to denote a therapeutically, prophylactically and/or diagnostically active glucocorticoid or a glucocorticoid that has physiologic effect. The term is intended to include the glucocorticoid in any suitable form such as e.g. a pharmaceutically acceptable salt, complex, solvate, ester, active metabolites or prodrug thereof of in any physical form such as, e.g., in the form of crystals, amorphous or a polymorphous form or, if relevant, in any stereoisomer form including any enantiomeric or racemic form, or a combination of any of the above. The glucocorticoid may be a synthetic glucocorticoid.

The one or more glucocorticoids used according to the invention are selected from the group consisting of hydrocortisone, cortisone, prednisolone, prednisone, methylprednisone, triamcinolone, paramethasone, betamethasone, dexamethasone and fludrocortisone including pharmaceutically acceptable esters, salts, complexes and mixtures thereof. In a preferred embodiment of the invention, the glucocorticoid is betamethasone.

Specific examples of pharmaceutically acceptable salt suitable for use according to the invention are phosphates, succinates, lysinates, acetates, cypionates, valerates, hemisuccinates, butyrates and trometamole salts.

As the glucocorticoid is intended for immediate release, the release and/or absorption into the systemic circulation takes place already in the oral cavity in the case the composition is administered orally. In such cases, the glucocorticoid of choice for the first part may be any other than hydrocortisone (as such) or cortisone as these two active substances have a bitter taste. However, these substances may be employed provided that a sufficient taste masking is obtained. In the paragraph relating to "Pharmaceutically acceptable excipients" taste-masking is discussed in more detail. Accordingly, the one or more glucocorticoids of the first part may have an acceptable taste, may be tasteless or it may be effectively taste-masked.

Furthermore, in specific embodiments of the invention, the glucocorticoid used may be a readily water-soluble glucocorticoid (e.g. a water-soluble salt of the glucocorticoid) in order to ensure a fast dissolution of the glucocorticoid from the composition.

In a preferred embodiment of the invention the glucocorticoid is hydrocortisone trometamole (or succinate) due to its high solubility in water, which in turn leads to a rapid absorption into the systemic circulation.

Dosage

In general, the dosage of the glucocorticoids present in a composition according to the invention depends *inter alia* on the specific drug substance, the age and condition of the patient and of the disease to be treated.

The term "hydrocortisone equivalents" is used herein to define the amount in mg of a specific glucocorticoid that corresponds to 1 mg of hydrocortisone for the purpose of glucocorticoid therapy as generally understood by medical practitioners. The term is based on the fact that the individual glucocorticoids have different potency and in order to achieve a desired therapeutic effect different doses of the individual glucocorticoids are required. Equivalent doses of the glucocorticoids can be calculated based on the following table.

Glucocorticoid	Equivalent amount (mg)	Hydrocortisone equivalent (1 mg of the glucocorticoid corresponds to the listed amount in mg of hydrocortisone)
Cortisone acetate	25	0.8
Hydrocortisone	20	1
Prednisolone	5	4
Prednisone	5	4
Methylprednisolone	4	5
Triamcinolone	4	5
Paramethasone	2	10
Betamethasone	0.75	26.66
Dexamethasone	0.75	26.66
Fludrocortisone	0.05	400

In general, a pharmaceutical composition according to the invention contains a total amount of the one or more glucocorticoids expressed as hydrocortisone of from about 1 to about 200 mg. In specific embodiments, the total amount of the one or more glucocorticoids expressed as hydrocortisone is from about 1 to about 175 mg such as, e.g., from about 1 to about 150 mg, from about 1 to about 100, from about 1 to about 75 mg, from about 1 to about 70 mg, from about 1 to about 60 mg, from about 5 to about 50 mg, from about 5 to about 40 mg or from about 10 to about 30 mg.

More specifically, normal dose ranges are given below for acute glucocorticoid therapy

Hydrocortisone	1-200 mg; in acute adrenal crises about 100 mg
Cortisone	1-200 mg such as about 100 mg
Betamethasone	1-20 mg; in increased intracranial pressure e.g. brain oedema about 4 mg daily In chemotherapy or radiation induced nausea 4-8 mg
Prednisolon	1-100 mg; such as from 1 to 30 mg daily; in severe cases 50-60 mg/day

Dexamethasone	0.1-6 mg such as 0.5-2 mg or 1.5-3 mg; in severe cases up to 6 mg/day
Fludrocortisone	0.05-5 mg; in Addison disease to correct inadequate electrolyte balance 0-05-0.2 mg daily; Cortical adrenal hyperplasia ("salt losing adrenogental syndrome") 0.1-0.2 mg
Prednisone	10-100 mg such as 50 mg
Methylprednisolone	2-40 mg such as 2-20 mg

In the following are given suitable doses of the individual glucocorticoids in various treatment regimens.

Acute asthma – adults

betamethasone	4-8 mg
prednisolone	30-60mg
methylprednisolone	40 mg

Acute anaphylaxia - adults

betamethasone	5 mg up to 20 mg
hydrocortisone	200 mg
dexamethasone	4-20mg –80mg

Acute anaphylaxia - children

hydrocortisone	100-200 mg

Septic shock - adults

hydrocortisone	200-300 mg/day
methylprednisone	30 mg/kg

Acute bacterial meningitis

dexamethasone	0.3 mg/kg/dose (max 10 mg) x 4 times daily for 2-4 days
betamethasone	8 mg x 4 times daily

Acute RSV (respiratory syncytial virus) infection with bronchiolitis in children

betamethasone 4-6 mg

Acute croup-children
betamethasone 4-6 mg

Mononucleosis with complications (airway obstruction, thrombocytopenia or haemolytical anaemia)
betamethasone 5-6 mg

Tonsillitis/peritonsillitis – children with airway obstruction
betamethasone 4-6 mg

A composition according to the invention is designed to provide a fast onset of action and upon administration a fast rise in glucocorticoid serum/plasma/blood level is obtained. In the case hydrocortisone is used as the glucocorticoid a serum level of at least about 200 nmol/l is obtained within 20 min after administration. In the case that another glucocorticoid than hydrocortisone is used, a person skilled in the art will know how to determine suitable equivalent serum/plasma/blood concentrations.

For example, hydrocortisone can be rapidly released from a composition during a time period of from about 0 to abut 30 minutes after administration and 5-10 mg of hydrocortisone can be rapidly administered as an extra dose in conjunction with fever etc in patients with adrenal insufficiency. Likewise, 5-20 mg of betamethasone can be rapidly released for most indications in which a rapid glucocorticoid effect is of value.

Administration routes

As mentioned above, the one or more glucocorticoids used according to the invention are administered to the subject (preferably a human) via a mucosa into the systemic circulation. In particular, in specific embodiments of the invention, the mucosa is the mucosa in the oral cavity, the nose, the rectum or in the vagina or via pulmonary, bronchial or respiratory mucosa and ephithelia. Preferably, the mucosa is the oral mucosa.

Figures 11 and 12 show sites of oral mucosal administration suitable for use. Four well-defined sites may be used, namely

"buccal" administration that includes the term "labial" administration and is used for administration of a pharmaceutical composition to a mucosa between the gums (gingiva) and the inside of the cheeks;
"sublingual" administration that refers to administration of a pharmaceutical composition under the tongue;
"palatal" administration that refers to administration of a pharmaceutical composition to the hard and/or soft palate; and
"gingival" administration that refers to administration of a pharmaceutical composition to the upper and/or lower gingiva.

All the above-mentioned sites are suitable for use to obtain a very fast onset of action due to a rapid absorption (transport of active drug) into the systemic circulation. In specific embodiments of the invention the buccal administration route is preferred, i.e. administration of a composition to the oral mucosa between the gums and the inside of the cheeks and thus enabling the absorption to take place from two sites, namely the gingival mucosa and the buccal mucosa.

Pharmaceutical compositions

In the following is given a description of pharmaceutical compositions according to the invention.

Release of the one or more glucocorticoids

A rapid release of the one or more glucocorticoids is necessary in order to obtain a fast onset of action after administration via a mucosa where the glucocorticoid is rapidly absorbed (transported) into the systemic circulation. Accordingly a general requirement is that at least 60% of the one or more glucocorticoids contained in the composition must be released within 30 min when tested in an *in vitro* dissolution test as defined herein. Specific embodiments of the composition fulfil one or more of the requirements given in the following table. In general, it is preferred that the requirement stated within 30 min after start of the dissolution test is fulfilled. In preferred embodiments, at least 70% or at least 80% of the one or more glucocorticoids contained in the composition are released within the first 20 min of the dissolution test.

time after start of the dissolution test	% hydrocortisone equivalents released (based on the content in the

	composition)
within 30 min	at least about 60% such as, e.g., at least about 70%, preferably at least about 80% or more preferably at least about 90%
within 20 min	at least about 60%, preferably at least about 70%, at least about 80% or even more preferred at least about 90%
within 15 min	at least about 60% such as, e.g., at least about 70%, preferably at least about 80%or at least about 90%
within 10 min	at least about 60% such as, e.g., at least about 70%, preferably at least about 80% or at least about 90%
within 5 min	at least about 60%

In specific embodiments (cf. the examples herein) more than 50 % of the one or more glucocorticoids can be released within 2 min, between 50 and 90 % can be released within 5-8 min, and more than 90 % of the dose can be released within 15 min.

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A pharmaceutical composition according to the invention is designed for systemic administration via a mucosa. In a preferred embodiment the mucosa is the mucosa in the oral cavity.

The pharmaceutical composition may be in any suitable form including liquid, semi-solid or solid form.

In a preferred aspect of the invention the pharmaceutical composition is in the form of a dosage form such as a unit dosage form.

Examples of compositions according to the invention suitable for administration via the oral mucosa into the systemic circulation are typically solid or semi-solid dosage forms. The solid dosage form is typically selected from the group consisting of granules, beads, pellets and powders and - when presented in unit dosage form - it may be in the form of a tablet including a chewable tablet, a suckable tablet, an effervescent tablet, a sublingual tablet, a rapid-burst tablet, an immediate release tablet, a rapidly dissolvable tablet, melt tablets, lozenges, pastilles or it may be presented in a more candy-like form, or the like.

A pharmaceutical composition for administration via the oral mucosa into the systemic circulation may also be in the form of a spray, a wafer, a film, a gel, a hydrogel, a patch, a gingival patch, a bioadhesive patch, a sachet, a solution, an inhaler or the like.

Examples of compositions according to the invention suitable for administration via the mucosa in the nose into the systemic circulation are typically in the form of nasal sprays, nasal aerosols, nasal solutions including nasal drops and the like.

Examples of compositions according to the invention suitable for administration via the pulmonary, bronchial and respiratory mucosa and epithelia into the systemic circulation are inhalers including powder inhalers.

Examples of compositions according to the invention suitable for administration via the mucosa in the rectum or the vagina into the systemic circulation include suppositories, vagitories, clysmas etc.

A pharmaceutical composition according to the invention may also have bio/mucoadhesive properties. The absorption of drugs into the systemic circulation from a mucosal drug delivery system is significantly improved if a mucosal bioadhesive component is added in the formulation. It will prevent both swallowing and create a high local concentration of the glucocorticoid adjacent to the absorption site. The mucoadhesive component will be mixed in an appropriate way together with the glucocorticoid and other ingredients in the dosage form. The term "bio/mucoadhesive is used to denote that the composition is able to reversible adhere to a biological mucosa. In some cases a bio/mucoadhesion promoting agent is included in the composition to promote adherence to the mucosa.

In the term bio/mucoadhesion promoting agent mucoadhesion and bioadhesion are used interchangeable even if bioadhesion may have a wider definition meaning that an adhesion to any biological feature available at the mucosa takes place. If present, the bio/mucoadhesion promoting agent may be a polymeric substance, preferable a substance having an average molecular weight above 5 kD. The hydration property is crucial for the bio/mucoadhesion forces and therefore a rapid swelling of the polymer will initiate the bio/mucoadhesion process. A swelling factor by volume when brought into contact with the saliva fluid should be between 10 and 20.

A pharmaceutical composition according to the invention typically contains one or more pharmaceutically acceptable excipients. A general description of pharmaceutically acceptable excipients suitable for use in a composition according to the present invention is given in the paragraph under the heading "Pharmaceutically acceptable excipients". Depending on the specific kind of dosage form a person skilled in the art will know which kinds of excipients to choose, if necessary guided by the teaching in handbooks like Remington's Pharmaceutical Science and Handbook of Pharmaceutical Excipients. In the following is given a description of specific kinds of excipients suitable for use in the formulation of compositions in the form of film or patches especially for administration to the oral cavity.

When the pharmaceutical composition is in the form of a film, patch, wafer, gel, sachet, gingival patch or the like it may contain a pharmaceutically acceptable excipient selected from the group consisting of an acrylic polymer including a derivative thereof, a cellulose derivative, modified starch, polyethylene oxide, chitosan, gelatin, sodium alginate, pectin, scleroglucan, xanthan gum, guar gum, or poly-co-(methyl vinyl ether-maleic anhydride), alone or in combinations thereof. The cellulose derivative may be selected from the group consisting of hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, sodium carboxymethyl cellulose, methyl cellulose, ethyl hydroxyethyl cellulose, carboxymethyl cellulose, microcrystalline cellulose, modified cellulose gum, or crosscaramellose.

A pharmaceutical composition according to the invention may also contain the one or more bio/mucoadhesion promoting agents. Normally such bio/mucoadhesion promoting agents are present in concentration of from about 0.1 to about 25% w/w. Examples of bio/mucoadhesion promoting agents include polymers including synthetic polymers, natural polymers and derivatives thereof, and mixtures thereof. The polymer

may be selected from a carbomer, a polyethylene oxide, a poly co-(methylvinyl ether/maleic anhydride, and mixtures thereof; or it may be a polysaccharide. The polysaccharide may be selected from the group consisting of gelatin, sodium alginate, pectin, scleroglucan, xanthan gum; guar gum, microcrystalline cellulose, crosscaramellose, hydroxypropyl cellulose, methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, ethyl hydroxyethyl cellulose, carboxymethyl cellulose, sodium carboxymethyl cellulose, moderately cross-linked starch, and chitosan.

A pharmaceutical composition according to the invention may also containg a dissolution promoting agent. If present, a dissolution promoting agent is present in a concentration of from about 0.05 to about 5% w/w of the total weight of the composition. The dissolution promoting agent may be selected from the group consisting of sodium lauryl sulphate, a polysorbate, a bile acid, a bile salt, a salt of cholic acid or cholanic acid, isopropyl myristate, methyl laurate, oleic acid, oleyl alcohol, glycerol monoleate, glycerol dioleate, glycerol trioleate, glycerol monostearate, glycerol monolaurate, propylene glycol monolaurate, sodium dodecyl sulfate, and a sorbitan ester.

In specific embodiment the one or more glucocorticoids in a composition of the invention are present as microparticles or nanoparticles. In general, he mean particle size of such particles is 10 μm or less. Furthermore, the micro- or nanoparticles may be encapsulated such as coated with a coating comprising a lechitin or a lechitin based compound.

When the glucocorticoid is present in the form of micro- or nanoparticles, a pharmaceutical composition according to the invention may also comprise a disintegrating agent. Such agents promote the dispersion of microparticles of the glucucorticoid over the administration site in for example the labial and gingival mucosa. Examples of pharmaceutically acceptable disintegrating agents are cross-linked polyvinylpyrrolidone, carboxymethyl starch, natural starch, microcrystalline cellulose, and cellulose gum. If present, it is normally used in a concentration of from 0.5 to 10 w/w based on the total weigh of the composition Different pharmaceutical excipients, such as mannitol and lactose, have been found to be particularly suitable as excipients.

As mentioned above, the pharmaceutical composition according to the invention may further comprise a taste-masking agent. Examples of a taste-masking agent are e.g. menthol, peppermint, vanillin, a terpene based compound, or an artificial sweetener. In a specific embodiment, the one or more glucocorticoids are taste masked by incorporation into an inclusion complex by means of alpha-, beta-, or gamma-cyclodextrins, preferably by beta-cyclodextrins.

In general, the composition of the invention contains from 0.05 up to 50 weight percent such as, e.g., from 0.05 up to 40 weight percent, 0.05 up to 30 weight percent or from about 0.05 up to 20 weight percent of glucocorticoid. More preferably, the compositions contains from 0.05 to 10 weight per cent of glucocorticoid, and especially from 0.1 to 5 weight per cent. The contents can also be expressed as the amount of glucocorticoid in a dose unit of the composition, such as a tablet. In this connection a dose refers to the therapeutically amount of the at least one glucocorticoid, or its derivative, which is to be administered at one time. When the glucocorticoid is used in the form of a pharmaceutically acceptable salt, these percentages and amounts should be recalculated accordingly.

Pharmaceutically acceptable excipients

In the present context the terms "pharmaceutically acceptable excipients" are intended to denote any material, which is inert in the sense that it substantially does not have any therapeutic and/or prophylactic effect *per se*. Such an excipient may be added with the purpose of making it possible to obtain a pharmaceutical, which have acceptable technical properties.

Examples of suitable excipients for use in a solid dosage form according to the invention include fillers, diluents, disintegrants, binders, lubricants etc. or mixture thereof. As the individual parts of a composition or kit according to the invention are used for different purposes (e.g. immediate and extended release), the choice of excipients is normally made taken such different uses into considerations. A person skilled in the art will know which kinds of pharmaceutically acceptable excipients that are suitable choices depending on the specific dosage form in question. Other pharmaceutically acceptable excipients for suitable use are e.g. acidifying agents, alkalising agents, preservatives, antioxidants, buffering agents, chelating agents, colouring agents, complexing agents, emulsifying and/or solubilizing agents, flavours and perfumes, humectants, sweetening agents, wetting agents etc.

Examples of suitable fillers, diluents and/or binders include lactose (e.g. spray-dried lactose, α-lactose, β-lactose, Tabletose®, various grades of Pharmatose®, Microtose® or Fast-Floc®), microcrystalline cellulose (various grades of Avicel®, Elcema®, Vivacel®, Ming Tai® or Solka-Floc®), hydroxypropylcellulose, L-hydroxypropylcellulose (low substituted), hydroxypropyl methylcellulose (HPMC) (e.g. Methocel E, F and K, Metolose SH of Shin-Etsu, Ltd, such as, e.g. the 4,000 cps grades of Methocel E and Metolose 60 SH, the 4,000 cps grades of Methocel F and Metolose 65 SH, the 4,000, 15,000 and 100,000 cps grades of Methocel K; and the 4,000, 15,000, 39,000 and 100,000 grades of Metolose 90 SH), methylcellulose polymers (such as, e.g., Methocel A, Methocel A4C, Methocel A15C, Methocel A4M), hydroxyethylcellulose, sodium carboxymethylcellulose, carboxymethylene, carboxymethylhydroxyethylcellulose and other cellulose derivatives, sucrose, agarose, sorbitol, mannitol, dextrins, maltodextrins, starches or modified starches (including potato starch, maize starch and rice starch), calcium phosphate (e.g. basic calcium phosphate, calcium hydrogen phosphate, dicalcium phosphate hydrate), calcium sulfate, calcium carbonate, sodium alginate, collagen etc.

Specific examples of diluents are e.g. calcium carbonate, dibasic calcium phosphate, tribasic calcium phosphate, calcium sulfate, microcrystalline cellulose, powdered cellulose, dextrans, dextrin, dextrose, fructose, kaolin, lactose, mannitol, sorbitol, starch, pregelatinized starch, sucrose, sugar etc.

Specific examples of disintegrants are e.g. alginic acid or alginates, microcrystalline cellulose, hydroxypropyl cellulose and other cellulose derivatives, croscarmellose sodium, crospovidone, polacrillin potassium, sodium starch glycolate, starch, pregelatinized starch, carboxymethyl starch (e.g. Primogel® and Explotab®) etc.

Specific examples of binders are e.g. acacia, alginic acid, agar, calcium carrageenan, sodium carboxymethylcellulose, microcrystalline cellulose, dextrin, ethylcellulose, gelatin, liquid glucose, guar gum, hydroxypropyl methylcellulose, methylcellulose, pectin, PEG, povidone, pregelatinized starch etc.

Glidants and lubricants may also be included in the composition. Examples include stearic acid, magnesium stearate, calcium stearate or other metallic stearate, talc, waxes and glycerides, light mineral oil, PEG, glyceryl behenate, colloidal silica,

hydrogenated vegetable oils, corn starch, sodium stearyl fumarate, polyethylene glycols, alkyl sulfates, sodium benzoate, sodium acetate etc.

Other excipients which may be included in a composition of the invention are e.g. flavoring agents, coloring agents, taste-masking agents, pH-adjusting agents, buffering agents, preservatives, stabilizing agents, anti-oxidants, wetting agents, humidity-adjusting agents, surface-active agents, suspending agents, absorption enhancing agents, agents for modified release etc.

The composition or kit components according to the invention may also be coated with a film coating, a protective coating, an anti-adhesive coating etc.

A composition according to the invention may also be coated in order to obtain suitable properties e.g. with respect to taste-masking of the one or more glucocorticoids. The coating may also be applied as a readily soluble film. The coating may be applied on single unit dosage forms (e.g. tablets) or it may be applied on a multiple-unit dosage form or on its individual units.

Suitable coating materials are e.g. methylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, acrylic polymers, ethylcellulose, cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl methylcellulose phthalate, polyvinylalcohol, sodium carboxymethylcellulose, cellulose acetate, cellulose acetate phthalate, gelatin, methacrylic acid copolymer, polyethylene glycol, shellac, sucrose, titanium dioxide, carnauba wax, microcrystalline wax, glyceryl monostearate, zein.

Plasticizers and other ingredients may be added in the coating material. The same or different active substance may also be added in the coating material.

Taste masking

In general, it is difficult in most cases to prepare a formulation for oral mucosa or nasal administration with satisfactory safety and stability from a drug having irritating properties or capable of forming molecular aggregates, although it depends on the kind of the drug used. In the case of hydrocortisone, the base has a distinctively bitter taste and a formulation has to be taste masked in order to be applicable for repeated use.

The taste masking agent can be a menthol, a peppermint, a vanillin, or a terpene based compound. In addition, the taste masking agent can be an artificial sweetener, e.g. sorbitol, xylitol or aspartame. Taste masking can also be achieved by microencapsulation of the glucocorticoid as particles. This is for example accomplished with lecithin based compounds. The taste masking agent is carefully mixed with the active drug in order to be present both at the surface and within the administration formulation. Taste masking can also be achieved by formation of inclusion complexes with cyclodextrins.

Typical examples of the cyclodextrin compound are alpha.-cyclodextrin, .beta.-cyclodextrin, .gamma.-cyclodextrin, hydroxypropyl .beta.-cyclodextrin, dimethyl .beta.-cyclodextrin, maltosyl .beta.-cyclodextrin and .beta.-cyclodextrin sulfate. Particularly preferred are .alpha.-cyclodextrin, .beta.-cyclodextrin and .gamma.-cyclodextrin. These cyclodextrin compounds may be used alone or in combination.

The amount of cyclodextrin compound to be used may vary with its solubility and the concentration of hydrocortisone. It is, however, desirable that the amount of cyclodextrin compound is 0.5 to 4.0 moles, preferably 2.0 to 4.0 moles, as much as the mole of hydrocortisone.

Method aspect

A pharmaceutical composition or a kit according to the invention is suitable for use in the treatment of a subject such as a mammal including a human suffering from a disorder requiring acute glucocorticoid therapy.

Accordingly, in a separate aspect the invention relates to a method for treating a subject suffering from a disorder requiring acute glucocorticoid therapy, the method comprises administering via a mucosa of the subject an effective amount of one or more glucocorticoids to obtain a fast rise in the glucocorticoid serum level to at least 20% of C_{max} within 20 min after administration.

Normally, it is preferred that at least 40% of C_{max} is reached within 30 min after administration in order to obtain a fast onset of action. In specific preferred embodimentd, at least 75% of C_{max} is reached within 45 min after administration and/or T_{max} is reached within 60 min after administration of the composition via a mucosa of the subject.

Details concerning other aspects of the invention are described hereinbefore and apply also to the method aspect of the invention.

The method according to the invention can be carried out by the patient itself or by non-medically trained persons due to the fact that the one or more glucocorticoids are not presented in the form of a composition for injection or infusion. Normally, medically trained personnel can only administer such compositions. Accordingly, the present invention provides a method that compared to the known treatment methods requiring acute glucocorticoids is much more simple to handle without the necessity of specialized equipment. It is therefore contemplated that the present invention provides a method that enables a treatment when the condition of the patient requires it, i.e. there is no need for bringing the patient to a hospital or a medical clinic in order to be able to give the necessary treatment.

Moreover, due to the development of compositions that enable a fast onset of action after administration and that can be administered without the need of the patient to swallow the composition (e.g. compositions of the invention in the form of films, bio/mucoadhesive compositions, patches, gingival patches, sprays etc.), the patient may be unconscious or otherwise unable to swallow normal tablets and still be correctly treated with glucocorticoids in acute situations.

Use of a composition or a kit according to the invention

In another separate aspect, the invention relates to the use one or more glucocorticoids for the preparation of a pharmaceutical composition or kit as defined hereinbefore for the treatment of a disorder requiring acute glucocorticoid therapy and to provide a serum level as defined herein.

In the above is given a detailed description of the invention relating one or more aspects of the invention, in particular relating to pharmaceutical compositions. However, all details and particulars disclosed under this aspect of the invention apply *mutatis mutandis* to the other aspects of the invention.

Legends to figures

Figure 1 shows results from Example 11. The plasma concentration-time profile of cortisol following a single dose administration of composition A to a human subject.

Figure 2 shows results from Example 11. The plasma concentration-time profile of cortisol following a single dose administration of composition B to a human subject.

Figure 3 shows results from Example 11. The plasma concentration-time profile of cortisol following a single dose administration of composition C to a human subject.

Figure 4 shows results from Example 12. The plasma concentration-time profile of cortisol following a single dose administration of film A to a human subject. Non-mucoadhesive thin-layer film, 6 cm^2, 10 mg hydrocortisone, buccal administration. Subject has the endogenous glucocorticoid secretion suppressed by synthetic glucocorticoids.

Figure 5 shows results from Example 12. The plasma concentration-time profile of cortisol following a single dose administration of film B to a human subject. Non-mucoadhesive thin-layer film, 6 cm^2, 11.2 mg hydrocortisone acetate, buccal administration. Subject has the endogenous glucocorticoid secretion suppressed by synthetic glucocorticoids.

Figure 6 shows results from Example 13. The plasma concentration-time profile of cortisol following a single dose administration of composition A to a human subject. In vivo plasma profile. Muocadhesive thin-layer film, 10 mg hydrocortisone, buccal administration. Subject has the endogenous glucocorticoid secretion suppressed by synthetic glucocorticoids

Figure 7 shows results from Example 13. The plasma concentration-time profile of cortisol following a single dose administration of composition A to a human subject. Mucoadhesive thin-layer film, 10 mg hydrocortisone, buccal administration. Subject has the endogenous glucocorticoid secretion suppressed by synthetic glucocorticoids

Figure 8 shows results from Example 14. The plasma concentration-time profile of cortisol following a single dose administration of composition C. In vivo plasma profile. Mucoadhesive rapid-release tablet, 10 mg hydrocortisone, buccal administration.

Subject has the endogenous glucocorticoid secretion suppressed by synthetic glucocorticoids

Figure 9 shows results from Example 15 (Composition C from Example 14).

Figure 10 shows results from Example 15 (Composition A from Example 13).

Figures 11 and 12 illustrates different administration sites within the oral cavity

The invention is further illustrated in the following non-limiting examples.

Materials

The materials used in the following examples were

Trade name	*Chemical substance*	*Manufacturer*
Betamethasone	USP/NF	
Carboxymetylcellulose	USP/NF	
Chitosan glutamate	USP/NF	
Crospovidone	USP/NF	
Hydrocortisone	Ph. Eur., Qual. D	Aventis, Switzerland (by Apoteksbolaget)
Hydrocortisone acetate	USP/NF	
Hydrocortisone 21-hemisuccinate sodium	Ph. Eur	Aventis, Switzerland (by Apoteksbolaget)
2-OH-propyl-β-cyclodextrin		
Hydroxypropylmethylcellulose	USP/NF	
Levomenthol	USP/NF	
Menthol	USP/NF	
Methocel E5	Hydroxypropyl-methyl cellulose	Dow Chemicals, USA (by Colorcon)
Methocel® KV 100 LV	USP/NF	Dow Chemicals, USA (by Colorcon)
Metolose®		
Microcrystalline cellulose, Avicel® PH-102	USP/NF	FMC Corporation

Paraffin powder	USP/NF	
PEG 300	USP/NF	
PEG 6000	Polyethylene glycol	Svenska Hoechst AB
PEG 400	Polyethylene glycol	Fluka, Switzerland
Prednisolone	USP/NF	
Polyox WSR 301	Polyethylene oxide	Dow Chemicals, USA
Na-alginate PH157		
Sodium dihydrogen phosphate	$NaH_2PO_4 \cdot 2\ H_2O$	
Sodium stearyl fumarate	USP/NF	
Sorbitol	USP/NF	
Sugar	USP/NF	
Sugar/starch seeds	USP/NF	
Talc	USP/NF	
Triethyl citrate	USP/NF	
Xylitab 300 Xylisorb 300		Xyrofin Kotka, Finland (Danisco Sweeteners Ltd, UK
Xylitol	USP/NF	Roquette, France

Methods

The in vivo experiments reported herein were carried out on healthy volunteers. At 6 pm and 11 pm the day before administration of the test composition, the endogenous cortisol secretion was suppressed by oral administration of 2 mg of betamethasone. The test composition was administered to healthy volunteers. The volunteers were in fasted state and were not allowed to take any food until noon. In the case a tablet is administered, it is ingested together with 200 ml of water. The test composition is administered between 8 am and 10 am on the day following the suppression of endogenous glucocorticoid secretion.

Examples

Example 1

Capsules containing an immediate release pellets (IR pellets)

IR pellets

Sugar/starch seeds, diameter 0.25-0.35 mm	1 kg

are coated in a fluidised bed equipped with a Wurster column with a water suspension containing

Hydrocortisone 21-hemisuccinate sodium	10 %
Hydroxypropyl methylcellulose, 6 cps	3 %
Talc	10 %

to a weight gain of approximately 75 %.

An amount of IR pellets containing 13.4 mg of hydrocortisone 21-hemisuccinate sodium (approximately 70 mg) are filled into hard gelatine capsules size No 3 in a capsule-filling machine.

70 mg pellets will easily fit into a capsule size No. 3 (or even size No. 4) and can be filled in a normal capsule filling machine.

Example 2

Immediate release (IR) tablet

IR tablets for oral or sublingual use:

	Mg per tablet
Betamethasone	0.4
Xylitab®300[a]	40
Lactose anhydrous USP/NF	5
Microcrystalline cellulose USP/NF	10
Crospovidone USP/NF	4
Sodium stearyl fumarate	1
Water	qs

[a] Direct compression xylitol from Danisco Sweeteners Ltd UK

Dry mix lactose and microcrystalline cellulose. Dissolve betamethasone in a small amount of water and disperse the solution over the powder blend. Mix and dry. Add Xylitab and crospovidone and dry mix until the blend is homogeneous.

Add sodium stearyl fumarate and continue blending for another 2 minutes.
Compress the blend to tablets in a tablet press using 6 mm round concave punches.

Example 3

Immediate release (IR) film

Thin films for administration to the oral cavity:

	% by weight
Prednisolone	0.75
PEG 400 USP/NF	2
Methocel E5, Dow Chemical	4
Xylitol, Roquette France	1
Water	up to 100

Methocel was added to approximately 90% of the total amount of distilled water and stirred with a magnetic stirrer until Methocel was completely dissolved. PEG 400 was added under continued stirring, followed by xylitol and prednisolone. Water was added to final weight and stirring was continued during four hours.

330 µl of the solution was pipetted into 16 mm diameter flat-bottomed PVC blisters. The solutions were allowed to dry at room temperature over night and the blister packs were sealed with heat-seal lacquered aluminium foil.

Example 4

Immediate release (IR) oral solution

Oral solution:

Prednisolone acetate	0.9 mg
Sorbitol	60 mg
Menthol	1.2 mg
Sterile water	5 ml

Make a solution and fill into a moisture tight aluminium foliated sachet.

Example 5

Immediate release (IR) sublingual spray

Sublingual spray of hydrocortisone:

	mg/ml
Hydrocortisone acetate	10
Carboxymetylcellulose	0.8 (0.08%)
2-OH-propyl-β-cyclodextrin	40
PEG 300	5
Menthol	0.3
Sorbitol	12
Levomenthol	2.0
$NaH_2PO_4 \cdot 2\ H_2O$	2
Water	qs

Dissolve hydrocortisone acetate in a small amount of water. Mix with 2-OH-propyl-β-cyclodextrin, let stand for 1 hour. Add carboxymetylcellulose and mix. Add PEG 300, menthol, sorbitol, levomenthol and $NaH_2PO_4 \cdot 2\ H_2O$. Add water up to final volume. Dispense into a spray package that delivers 0.58 ml per dose (5 mg of hydrocortisone).

Example 6

Betamethasone IR tablet for peroral or buccal administration

	Mg per tablet
Betamethasone	0.4
Xylitab®300[a)]	45
Microcrystalline cellulose NF	10
Crospovidone NF	4
Water	qs
Sodium stearyl fumarate NF	1

[a)] Direct compression xylitol from Danisco Sweeteners Ltd, UK

Dissolve betamethasone in a small amount of water.
Disperse the solution over the microcrystalline cellulose. Mix and dry.

Add Xylitab and crospovidone and dry mix in a suitable mixer until a homogeneous blend is achieved.
Then add sodium stearyl fumarate and continue mixing another two minutes.
Compress the powder blend in a suitable tablet press using 6 mm round concave punches.

Example 7
Sublingual spray of betamethasone

	mg/ml
Betamethasone	0.4
Carboxymetylcellulose	0.8 (0.08%)
PEG 300	5
Menthol	0.3
Sorbitol	12
Levomenthol	2.0
NaH_2PO_4*2 H_2O	2
Water	qs

Dissolve betamethasone in a small amount of water. Add carboxymetylcellulose and mix. Add PEG 300, menthol, sorbitol, levomenthol and NaH_2PO_4*2 H_2O. Add water up to final volume.

Example 8
Sublingual spray of betamethasone

	mg/ml
Betamethasone	0.4
Chitosan glutamate	10
Menthol	0.1
Levomenthol	1.5
NaH_2PO_4*2 H_2O	2
Water	qs

Dissolve betamethasone in a small amount of water. Add chitosan glutamate and mix. Filter through 0.2µm membrane filter. Add menthol, levomenthol and NaH_2PO_4*2 H_2O. Add water up to final volume.

Example 9

Sublingual spray of hydrocortisone

	mg/ml
Hydrocortisone acetate	10
Carboxymetylcellulose	0.8 (0,08%)
2-OH-propyl-β- cyclodextrin	40
PEG 300	5
Menthol	0.3
Sorbitol	12
Levomenthol	2.0
NaH_2PO_4*2 H_2O	2
Water	qs

Dissolve hydrocortisone in a small amount of water. Mix with 2-OH-propyl-β-cyclodextrin, let stand for 1 hour. Add carboxymetylcellulose and mix. Add PEG 300, menthol, sorbitol, levomenthol and NaH_2PO_4*2 H_2O. Add water up to final volume.

Example 10

Sublingual spray of hydrocortisone

	mg/ml
Hydrocortisone acetate	10
Chitosan glutamate	10
2-OH-propyl-β- cyclodextrin	40
Menthol	0.1
Levomenthol	1.5
NaH_2PO_4*2 H_2O	2
Water	qs

Dissolve hydrocortisone in a small amount of water. Mix with 2-OH-propyl-β-cyclodextrin, let stand for 1 hour. Add chitosan glutamate and mix. Filter through 0.2

µm membrane filter. Add menthol, levomenthol and NaH_2PO_4*2 H_2O. Add water up to final volume.

Example 11

Thin-layer film of hydrocortisone

Composition A:

	% w/w
Hydrocortisone	3%
Na-alginate PH157	2%
Water	95%

Composition B:

Hydrocortisone acetate	3.4%
Na-alginate PH157	2%
Water	94.6%

Composition C:

Hydrocortisone	3%
Metolose 60SH-50	2%
Water	95%

The films were made as described in the following:

1. Amount polymer, glucocorticoid and H_2O were weighed.
2. The glucocorticoid was added to the water during stirring.
3. The formulation was kept on stirring until a suspension was obtained.
4. The polymer was added to the suspension.
5. The formulation was kept on stirring until a uniform gel was obtained (minimum 2h).
6. 0.5g gel was weighed in empty blisters and placed in a heating cupboard (Drying: 25°C for 22h).

Table. In vitro dissolution (rotating basket 100 rpm, phosphate buffer pH=7.0, one unit per 500 ml medium) after 1, 3 ,5, 10 and 15 min as a percentage of 10 mg

hydrocortisone. Units with 10 mg hydrocortisone in polymers of sodium alginate (Na-alg), hypromellose (HPMC) and approx. 7 mg/unit. Two units were tested with Na-alg and HPMC. The mean value is tabulated. The results in the following table reflect the rank order regarding viscosity, i.e. HPMC has the lowest viscosity and Na-alg the highest.

Composition	Polymer	1 min,%	3 min,%	5 min,%	10 min,%	15 min,%
A	Na-alg	15	25	38	65	84
B	Na-alg	15	25	38	65	84
C	HPMC	18	48	67	88	92

In vivo plasma profiles in humans, N=1 per composition
Dexamethasone suppression test, fasting state, otherwise as described in the paragraph denoted "Method".

The results show that the use of hydrocortisone acetate does not seem to be suitable for an immediate release composition. This was further investigated in the following example.

Example 12
Non-mucoadhesive immediate release films

Two films were prepared essentially similar to Example 13 – composition A. Film A contains 10 mg of hydrocortisone and film B contains 11.2 mg of hydrocortisone acetate. The results from in vivo testing after buccal administration are shown in Figures 4 and 5. The results show that even if the films are not bioadhesive, a fast onset of the absorption into the systemic circulation after single dose administration of Film A is obtained. In contrast, the results obtained with the film containing hydrocortisone acetate indicate that this compound does not seem to be suitable when a fast onset of the absorption into the systemic circulation of the glucocorticoid is required.

Example 13
Thin-layer films for immediate release

Batches of glucocorticoid films were prepared from the following compositions A and B:

Rapid-release composition A:

Component	*% w/w*
PEG 400	2.0
Hydrocortisone	3.0
Methocel E5	4.0
Xylitol	1.0
Water	90

Slower release composition B:

Component	*w/w %*
PEG 400	1.3
Hydrocortisone	3.0
Methocel E5	5.7
Water	90

To distilled water (18 ml) in 50 ml round-bottomed glass flask provided with a magnetic stirred was added Methocel E5. After the Methocel had dissolved completely PEG 400 was added under continued stirring, followed by xylitol (Composition A only) and hydrocortisone. Stirring was continued for 4 h.

Into flat-bottomed PVC-blisters (Inpack AB, Lund, Sweden) 16 mm in diameter was pipetted (Finnpipette; automatic) 330 µl of solution A or B into each blister trough. The solutions were allowed to dry at room temperature over night. The next day 10 films were removed for dose analysis. Each film was dissolved in 100 ml of water/ethanol (95%) 9:1 (w/w). The solutions were analysed by UV spectroscopy at 242 nm. Mean contents of 10.19 mg and 9.83 mg hydrocortisone per blister (SD 0.29 and 0.14, respectively) were found for Compositions A and B, respectively.

The hydrocortisone compositions were tested in two human subjects after labial administration. The subjects had their endogenous glucocorticoid secretion suppressed by synthetic glucocorticoids. The plasma concentration of cortisol was monitored during 360 min after the labial administration, and the serum concentration time profiles from these two subjects are shown in Figures 6 and 7.

It is clearly seen that the rate and extent of mucosal uptake of hydrocortisone is high and the appearance of cortisol in serum is rapid, as the first measured plasma concentration was attained already at 10-15 min.

These serum pharmacokinetic data illustrate that a formulation of the invention for oral mucosa administration results in a high rate and extent of mucosal absorption of the active drug, even though a small volume of fluid is available for dissolution at the site of administration and absorption in this route drug delivery.

Example 14

Glucocorticoid tablets for immediate release

Glucocorticoid tablets were manufactured by direct compression of the dry-mixed powderous components to the following composition C:

Rapid-release composition C:	*Component*	*Per Batch*
	PEG 6000	8.7 g
	Hydrocortisone	2.5 g
	Xylitab 300	8.7 g
	Mg stearate	0.16 g

Batch size 100 tablets

The powderous components were sieved (mesh size 0.7 mm) and dry-mixed by shaking by hand in a small tin can for five min. The homogeneity of the mixture was analyzed by the same method as used for analysis of the tablets. Tabletting was carried out with a DIAF tabletting machine using a flat circular punch 7 mm in diameter (with a dividing score). The hydrocortisone dose in 10 tablets was assessed by the same method as used for the films. Mean contents of 9.53 mg hydrocortisone per tablet (SD 0.15) were found for composition C.

Tablet thickness (10 tablets): 1.72-1.76 mm (C);
Friability (20 tablets): 0.6% (C);
Tablet hardness (10 tablets): 23.7 N (C).

The compositions were tested after oral administration to two human subjects (see Figure 8).

The rate of absorption of the glucocorticoid into the systemic circulation from the solid dosage forms of Example 14 was somewhat slower than that of compositions from Example 13, which means that it is possible to adjust the absorption rate of hydrocortisone into the systemic circulation by introducing changes in the composition and function of the labial pharmaceutical formulation.

Example 15

In vitro dissolution profile

The *in vitro* dissolution profiles of hydrocortisone from drug formulations according to Example 20 and 21 were followed over time in a standardized controlled *in vitro* environment. A United States Pharmacopoeia dissolution apparatus II (paddle) coupled to automatic sampling devices and software was used for acquiring release profiles of the drug formulations in a neutral pH environment. The dissolution profile was acquired at 37 °C, 50 rpm of the paddles, in a total of 300 ml of water. Sampling was performed at 0, 1, 3, 5, 7, 10 and 15 minutes following the insertion of the pharmaceutical composition in the example in the dissolution medium.

The dissolution profile from each formulation was monitored in two experiments up to 360 min after administration, and the corresponding dissolution time profiles are shown in Figs. 9 and 10, respectively. The release rate is given as the per cent of dose over time.

The release rate from the solid dosage forms of Example 21 was somewhat slower (Fig. 10). This means that it is possible to adjust the release rate of hydrocortisone by introducing changes in the composition and function of the oronasopharyngeal pharmaceutical preparation.

Claims

1. A pharmaceutical composition comprising one or more glucocorticoids for substantially immediate release, wherein at least about 60% of the one or more glucocorticoids are released from the composition within the first 30 min after start of an in vitro dissolution test according to USP employing USP Dissolution Apparatus No. 2 (paddle), 50 rpm and a suitable dissolution medium, and wherein a glucocorticoid serum level of a subject of at least 20% of C_{max} is reached within 20 min after administration of the composition via a mucosa of the subject.

2. A pharmaceutical composition according to claim 1, wherein at least 40% of C_{max} is reached within 30 min after administration of the composition via a mucosa of the subject.

3. A pharmaceutical composition according to claim 1 or 2, wherein at least 75% of C_{max} is reached within 45 min after administration of the composition via a mucosa of the subject.

4. A pharmaceutical composition according to any of the preceding claims, wherein T_{max} is reached within 60 min after administration of the composition via a mucosa of the subject.

5. A pharmaceutical composition according to any of the preceding claims, wherein at least about 60% of the one or more glucocorticoids are released from the composition within the first 20 min or 15 min of the dissolution test defined in claim 1.

6. A pharmaceutical composition according to any of the preceding claims, wherein at least about 60% of the one or more glucocorticoids are released from the composition within the first 10 min or 5 min of the dissolution test defined in claim 1.

7. A pharmaceutical composition according to any of the preceding claims, wherein at least about 70% of the one or more glucocorticoids are released from the composition within the first 15 min such as, e.g., within the first 10 min or 5 min of the dissolution test defined in claim 1.

8. A pharmaceutical composition according to any of the preceding claims, wherein at least about 80% of the one or more glucocorticoids are released from the composition within the first 15 min of the dissolution test defined in claim 1.

9. A pharmaceutical composition according to any of the preceding claims, wherein at least about 80% of the one or more glucocorticoids are released from the composition within the first 10 min of the dissolution test defined in claim 1.

10. A pharmaceutical composition according to any of the preceding claims, wherein at least about 90% of the one or more glucocorticoids are released from the composition within the first 15 min or within the first 10 min of the dissolution test defined in claim 1.

11. A pharmaceutical composition according to any of the preceding claims for administration to the systemic circulation via a mucosa.

12. A pharmaceutical composition according to claim 11, wherein the mucosa is selected from the mucosa in the oral cavity, the nasal cavity, the lung, the bronchia, the rectum, and the vagina.

13. A pharmaceutical composition according to claim 12, wherein the mucosa is the mucosa in the oral cavity.

14. A pharmaceutical composition according to any of the preceding claims designed for administration to the oral cavity.

15. A pharmaceutical composition according to any of the preceding claims in liquid, semi-solid or solid form.

16. A pharmaceutical composition according to any of the preceding claims in the form of a solid dosage form.

17. A pharmaceutical composition according to claim 35, wherein the solid dosage form is selected from the group consisting of granules, beads, pellets and powders.

18. A pharmaceutical composition according to any of the preceding claims in unit dosage form.

19. A pharmaceutical composition according to claim 18, wherein the unit dosage form is in the form of a tablet including a chewable tablet, a suckable tablet, an effervescent tablet, a sublingual tablet, a rapid-burst tablet, an immediate release tablet, a rapidly dissolvable tablet or the like.

20. A pharmaceutical composition according to any of claims 142-15 in the form of a spray, a wafer, a film, a gel, a hydrogel, a patch, a gingival patch, a bioadhesive patch, a sachet, a pulmonary, bronchial or respiratory inhaler including a powder inhaler, a suppository, a vagitory, a clysma, a solution or the like.

21. A pharmaceutical composition according to any of the preceding claims, wherein the total amount of the one or more glucocorticoids expressed as hydrocortisone is from about 1 to about 200 mg.

22. A pharmaceutical composition according to claim 21, wherein the total amount of the one or more glucocorticoids expressed as hydrocortisone is from about 1 to about 175 mg such as, e.g., from about 1 to about 150 mg, from about 1 to about 100, from about 1 to about 75 mg, from about 1 to about 70 mg, from about 1 to about 60 mg, from about 5 to about 50 mg, from about 5 to about 40 mg or from about 10 to about 30 mg.

23. A pharmaceutical composition according to any of the preceding claims, wherein the one or more glucocorticoids is selected from the group consisting of hydrocortisone, cortisone, prednisolone, prednisone, methylprednisone, triamcinolone, paramethasone, betamethasone, dexamethasone and fludrocortisone or mixtures thereof, including pharmaceutically acceptable esters, salts and complexes thereof.

24. A pharmaceutical composition according to claim 23, wherein the pharmaceutically acceptable salt is a phosphate, a succinate, a lysinate, an acetate, a cypionate, a valerate, a hemisuccinate, a butyrate or a trometamole salt.

25. A pharmaceutical composition according to claim 23 in unit dosage form, wherein the one or more glucocorticoids are cortisone or hydrocortisone including pharmaceutically acceptable esters, salts and complexes thereof in an amount corresponding to from about 1-200.

26. A pharmaceutical composition according to claim 23 in unit dosage form, wherein the one or more glucocorticoids are betamethasone including pharmaceutically acceptable esters, salts and complexes thereof in an amount corresponding to from about 1 to about 20 mg.

27. A pharmaceutical composition according to claim 23 in unit dosage form, wherein the one or more glucocorticoids are prednisolone including pharmaceutically acceptable esters, salts and complexes thereof in an amount corresponding to from about 1 to about 10 mg.

28. A pharmaceutical composition according to claim 23 in unit dosage form, wherein the one or more glucocorticoids are dexamethsone including pharmaceutically acceptable esters, salts and complexes thereof in an amount corresponding to from about 0.1 to about 2 mg.

29. A pharmaceutical composition according to claim 23 in unit dosage form, wherein the one or more glucocorticoids are fludrocortisone including pharmaceutically acceptable esters, salts and complexes thereof in an amount corresponding to from about 0.05 to about 5 mg.

30. A pharmaceutical composition according to claim 23 in unit dosage form, wherein the one or more glucocorticoids are prednisone including pharmaceutically acceptable esters, salts and complexes thereof in an amount corresponding to from about 10 to about 50 mg.

31. A pharmaceutical composition according to claim 23 in unit dosage form, wherein the one or more glucocorticoids are methylprednisolone including pharmaceutically acceptable esters, salts and complexes thereof in an amount corresponding to from about 2 to about 20 mg.

32. A pharmaceutical composition according to any of the preceding claims in the form of a film, patch, wafer, gel, sachet, gingival patch, lozenge or the like.

33. A pharmaceutical composition according to claim 32, wherein the composition comprises a pharmaceutically acceptable excipient selected from the group consisting

of an acrylic polymer including a derivative thereof, a cellulose derivative, modified starch, polyethylene oxide, chitosan, gelatin, sodium alginate, pectin, scleroglucan, xanthan gum, guar gum, or poly-co-(methyl vinyl ether-maleic anhydride), alone or in combinations thereof.

34. A pharmaceutical composition according to claim 33, wherein the cellulose derivative is selected from the group consisting of hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, sodium carboxymethyl cellulose, methyl cellulose, ethyl hydroxyethyl cellulose, carboxymethyl cellulose, microcrystalline cellulose, modified cellulose gum, or crosscaramellose.

35. A pharmaceutical composition according to any of the preceding claims further comprising one or more bio/mucoadhesion promoting agents.

36. A pharmaceutical composition according to claim 35, wherein the one or more bio/mucoadhesion promoting agents are present in concentration of from about 0.1 to about 25% w/w.

37. A pharmaceutical composition according to claim 35 or 36, wherein the one or more bio/mucoadhesion promoting agents are a polymer including a synthetic polymer, a natural polymer and a derivative thereof, and mixtures thereof.

38. A pharmaceutical composition according to claim 37, wherein the polymer is selected from a carbomer, a polyethylene oxide, a poly co-(methylvinyl ether/maleic anhydride, and mixtures thereof.

39. A pharmaceutical composition according to claim 37, wherein the polymer is a polysaccharide.

40. A pharmaceutical composition according to claim 40, wherein the polysaccharide is selected from the group consisting of gelatin, sodium alginate, pectin, scleroglucan, xanthan gum; guar gum, microcrystalline cellulose, crosscaramellose, hydroxypropyl cellulose, methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, ethyl hydroxyethyl cellulose, carboxymethyl cellulose, sodium carboxymethyl cellulose, moderately cross-linked starch, and chitosan.

41. A pharmaceutical composition according to any of the preceding claims further comprising a dissolution promoting agent.

42. A pharmaceutical composition according to claim 41, wherein the dissolution promoting agent is present in a concentration of from about 0.05 to about 5% w/w.

43. A pharmaceutical composition according to claim 41 or 42, wherein the dissolution promoting agent is selected from the group consisting of sodium lauryl sulphate, a polysorbate, a bile acid, a bile salt, a salt of cholic acid or cholanic acid, isopropyl myristate, methyl laurate, oleic acid, oleyl alcohol, glycerol monoleate, glycerol dioleate, glycerol trioleate, glycerol monostearate, glycerol monolaurate, propylene glycol monolaurate, sodium dodecyl sulfate, and a sorbitan ester.

44. A pharmaceutical composition according to any of the preceding claims, wherein the one or more glucocorticoids are present as microparticles or nanoparticles.

45. A pharmaceutical composition according to claim 44, wherein the mean particle size is 10 μm or less.

46. A pharmaceutical composition according to claim 44 or 45, wherein the micro- or nanoparticles are encapsulated.

47. A pharmaceutical composition according to claim 46, wherein the micro- or nanoparticles are encapsulated with a coating comprising a lechitin or a lechitin based compound.

48. A pharmaceutical composition according to any of the preceding claims further comprising a disintegrating agent.

49. A pharmaceutical composition according to claim 48, wherein the disintegrating agent is selected from the group consisting of cross-linked polyvinylpyrrolidone, carboxymethyl starch, natural starch, microcrystalline cellulose, and cellulose gum.

50. A pharmaceutical composition according to claim 48 or 49, wherein the disintegrating agent is present in a concentration of from about 0.5 to about 10% w/w.

51. A pharmaceutical composition according to any of the preceding claims further comprising a taste-masking agent.

52. A pharmaceutical composition according to claim 51, wherein the taste-masking agent is selected from the group consisting of menthol, peppermint, vanillin, a terpene based compound, or an artificial sweetener.

53. A pharmaceutical composition according to any of the preceding claims, wherein the one or more glucocorticoids are taste masked by incorporation into an inclusion complex by means of alpha-, beta-, or gamma-cyclodextrins, preferably by beta-cyclodextrins.

54. A pharmaceutical composition according to any of the preceding claims for buccal administration.

55. A pharmaceutical composition according to claim 54 in the form of a gel, a gum, a wafer, a thin-layer film, a patch, a gingival patch, a tablet, a sachet, a lozenge, a fast-dissolving tablet, a cream or an ointment.

56. A kit for treating a subject suffering from a disorder requiring acute glucocorticoid therapy comprising one or more containers for housing a pharmaceutical composition according to any of claims 1-55, and instructions for use thereof.

57. A kit according to claim 56, wherein the one or more containers are in the form of blisters or blister packs.

58. A method for treating a subject suffering from a disorder requiring acute glucocorticoid therapy, the method comprises administering via a mucosa of the subject an effective amount of one or more glucocorticoids to obtain a fast rise in the glucocorticoid serum level to at least 20% of C_{max} within 20 min after administration.

59. A method according to claim 58, wherein at least 40% of C_{max} is reached within 30 min after administration.

60. A method according to claim 58 or 59, wherein at least 75% of C_{max} is reached within 45 min after administration.

61. A method according to any of claims 58-60, wherein T_{max} is reached within 60 min after administration of the composition via a mucosa of the subject.

62. A method according to any of claims 58-61, wherein the disorder requiring acute glucocorticoid therapy is an acute adrenal crisis.

63. A method according to claim 62, wherein the acute adrenal crisis relates to a primary, secondary or tertiary adrenal insufficiency, an anaphylactic reaction, an Addison crisis, a status asthmaticus, a blood transfusion reaction, a brain edema, a severe allergic reaction, acute asthma, acute anaphylaxia, septic shock, acute bacterial meningitis, acute RSV (respiratory syncytial virus) infection with bronchiolitis in children, acute croup-children, mononucleosis with complications (airway obstruction, thrombocytopenia or haemolytical anaemia), or tonsillitis/peritonsillitis e.g. in children with airway obstruction.

64. A method according to any of claims 58-62, wherein the disorder requiring acute glucocorticoid therapy relates to an inflammatory disorder, an autoimmune disorder, or a medical disorder in which a glucocorticoid forms a part of the first line emergency medical treatment or intense short-time medical treatment.

65. A method according to any of claims 58-64, wherein the mucosa is selected from the mucosa in the oral cavity, the nasal cavity, the lung, the bronchia, the rectum and the vagina.

66. A method according to any of claims 58-65, wherein the mucosa is the mucosa in the oral cavity.

67. A method according to any of claims 58-66, wherein the effective amount of the one or more glucocorticoids expressed as hydrocortisone is from about 1 to about 200 mg.

68. A method according to claim 67, wherein the effective amount of the one or more glucocorticoids expressed as hydrocortisone is from about 1 to about 175 mg such as, e.g., from about 1 to about 150 mg, from about 1 to about 125 mg, from about 1 to about 100 mg, from about 1 to about 75 mg, from about 1 to about 70 mg, from about 1

to about 60 mg, from about 5 to about 50 mg, from about 5 to about 40 mg or from about 10 to about 30 mg.

69. A method according to any of claims 58-68, wherein the one or more glucocorticoids is selected from the group consisting of hydrocortisone, cortisone, prednisolone, prednisone, methylprednisone, triamcinolone, paramethasone, betamethasone, dexamethasone and fludrocortisone or mixtures thereof, including pharmaceutically acceptable esters, salts and complexes thereof.

70. A method according to claim 69, wherein the pharmaceutically acceptable salt is a phosphate, a succinate, a lysinate, an acetate, a cypionate, a valerate, a hemisuccinate, a butyrate or a trometamole salt.

71. A method according to any of claims 58-70, wherein the effective amount of the one or more glucocorticoid is contained in a pharmaceutical composition suitable for administration by the subject itself or by non-medically trained persons.

72. A method according to claim 71, wherein the composition is in a form that can be administered to the subject even if he is unconscious.

73. A method according to claim 71 or 72, wherein the composition is in a form that can be administered to the subject and have effect even if he is unable to swallow the composition.

74. A method according to any of claims 58-73, wherein the one or more glucocorticoids are cortisone or hydrocortisone including pharmaceutically acceptable esters, salts and complexes thereof and wherein the effective amount is in a range of from about 1 to about 100 mg.

75. A method according to any of claims 58-73 wherein the one or more glucocorticoids are betamethasone including pharmaceutically acceptable esters, salts and complexes thereof and wherein the effective amount is in a range of from about 1 to about 20 mg.

76. A method according to any of claims 58-73, wherein the one or more glucocorticoids are prednisolone including pharmaceutically acceptable esters, salts

and complexes thereof and wherein the effective amount is in a range of from about 1 to about 10 mg.

77. A method according to any of claims 58-73, wherein the one or more glucocorticoids are dexamethsone including pharmaceutically acceptable esters, salts and complexes and wherein the effective amount is in a range of from about 0.1 to about 2 mg.

78. A method according to any of claims 58-73, wherein the one or more glucocorticoids are fludrocortisone including pharmaceutically acceptable esters, salts and complexes thereof and wherein the effective amount is in a range of from about 0.05 to about 5 mg.

79. A method according to any of claims 58-73, wherein the one or more glucocorticoids are prednisone including pharmaceutically acceptable esters, salts and complexes thereof and wherein the effective amount is in a range of from about 10 to about 50 mg.

80. A method according to any of claims 58-73, wherein the one or more glucocorticoids are methylprednisolone including pharmaceutically acceptable esters, salts and complexes thereof and wherein the effective amount is in a range of from about 2 to about 20 mg.

81. A method according to any of claims 58-80, wherein the effective amount is administered in the form of a pharmaceutical composition as defined in any of claims 1-55.

82. A method according to any of claims 58-80, wherein the effective amount is administered in the form of a pharmaceutical kit as defined in claims 56 or 57.

83. Use of an amount of one or more glucocorticoids for the preparation of a pharmaceutical composition or kit as defined in any of claims 1-58 for the treatment of a disorder requiring acute glucocorticoid therapy by providing a fast rise in the glucocorticoid serum level to at least 20% of C_{max} within 20 min after administration via a mucosa.

84. Use according to claim 83, wherein at least 40% of C_{max} is reached within 30 min after administration.

85. Use according to claim 83 or 84, wherein at least 75% of C_{max} is reached within 45 min after administration.

86. Use according to any of claims 83-85, wherein T_{max} is reached within 60 min after administration of the composition via a mucosa of the subject.

87. Use according to any of claims 83-86, wherein an effective amount of the one or more glucocorticoid is contained in a pharmaceutical composition suitable for administration by the subject itself or by non-medically trained persons.

88. Use according to any of claims 83-87, wherein the composition is in a form that can be administered to the subject even if he is unconscious.

89. Use according to claim 87 or 88, wherein the composition is in a form that can be administered to the subject and have effect even if he is unable to swallow the composition.

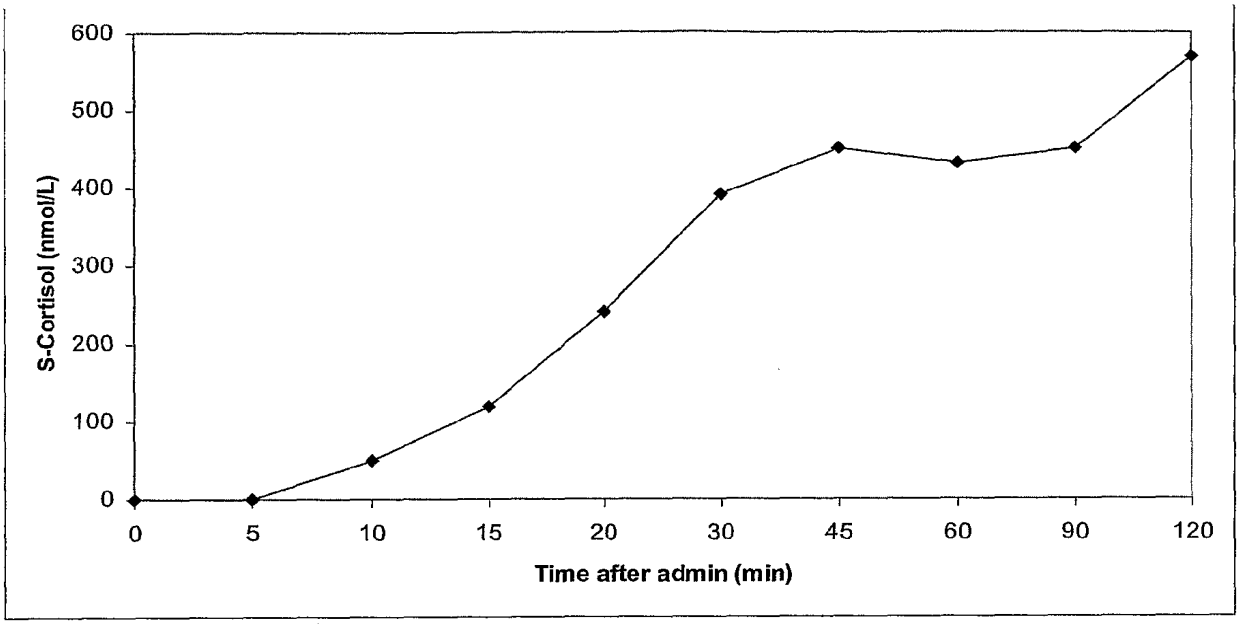
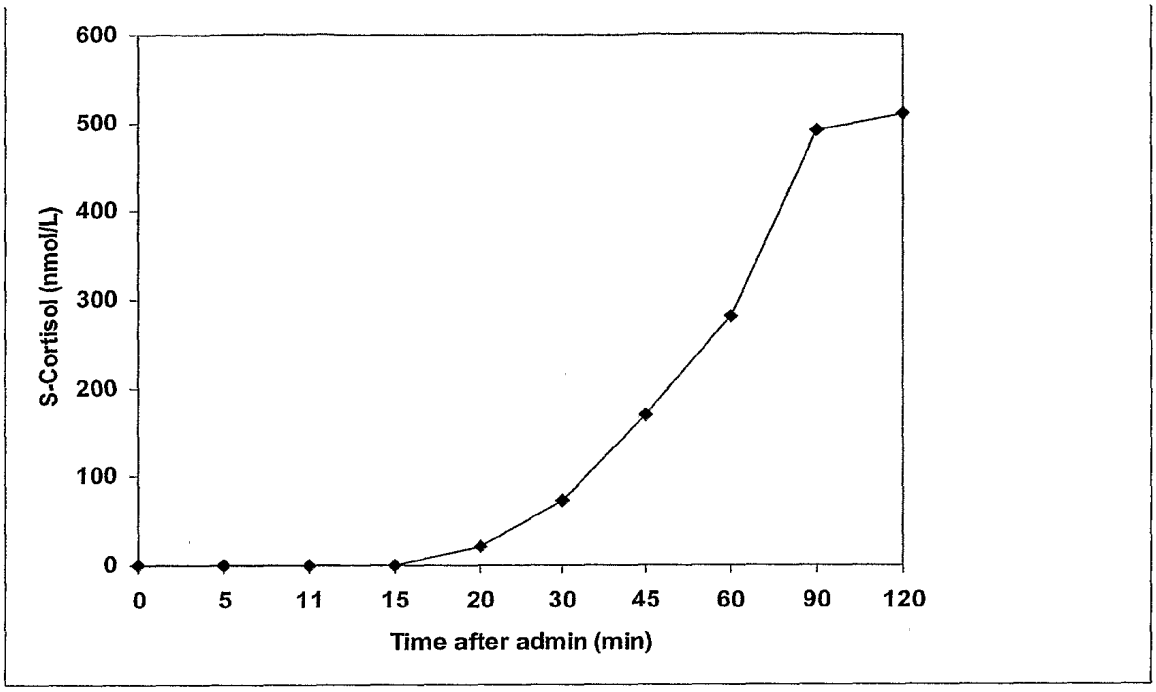

600
500
400
300
200
100
0
S-Cortisol (nmol/L)
0
5
10
15
20
30
45
60
90
120
Time after admin (min)

Fig. 1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500
400
300
200
100
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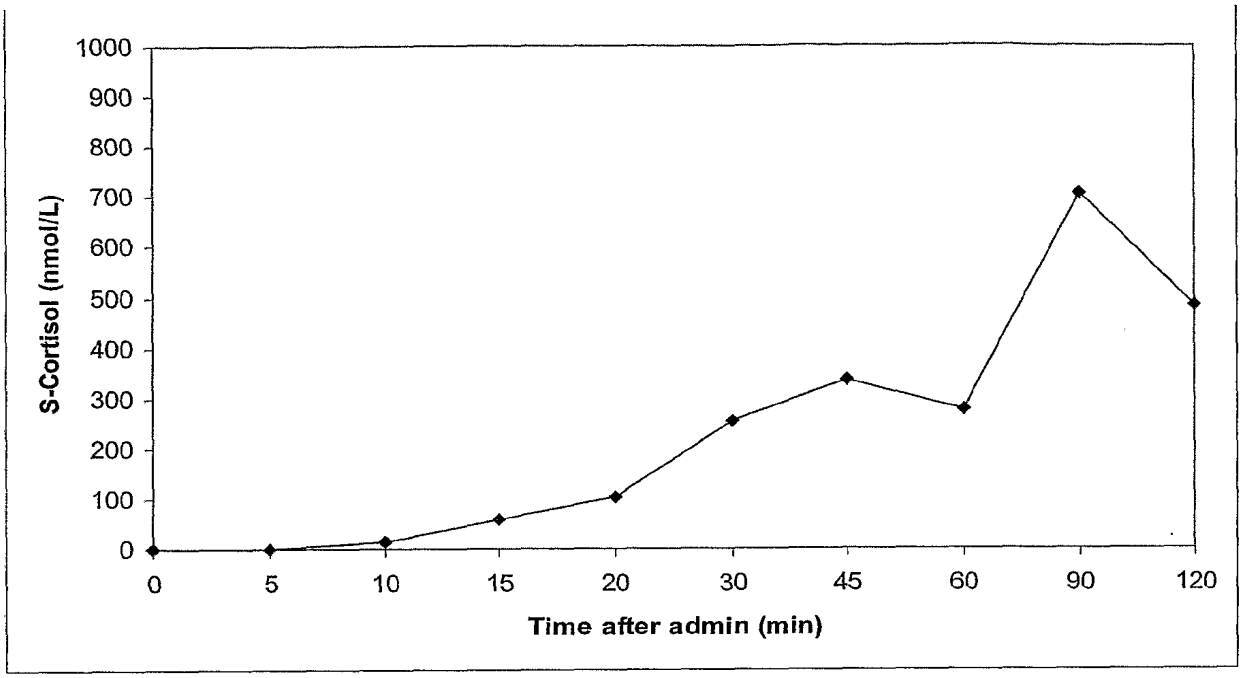
11
15
20
30
45
60
90
120
Time after admin (min)

Fig. 2


S-Cortisol (nmol/L)
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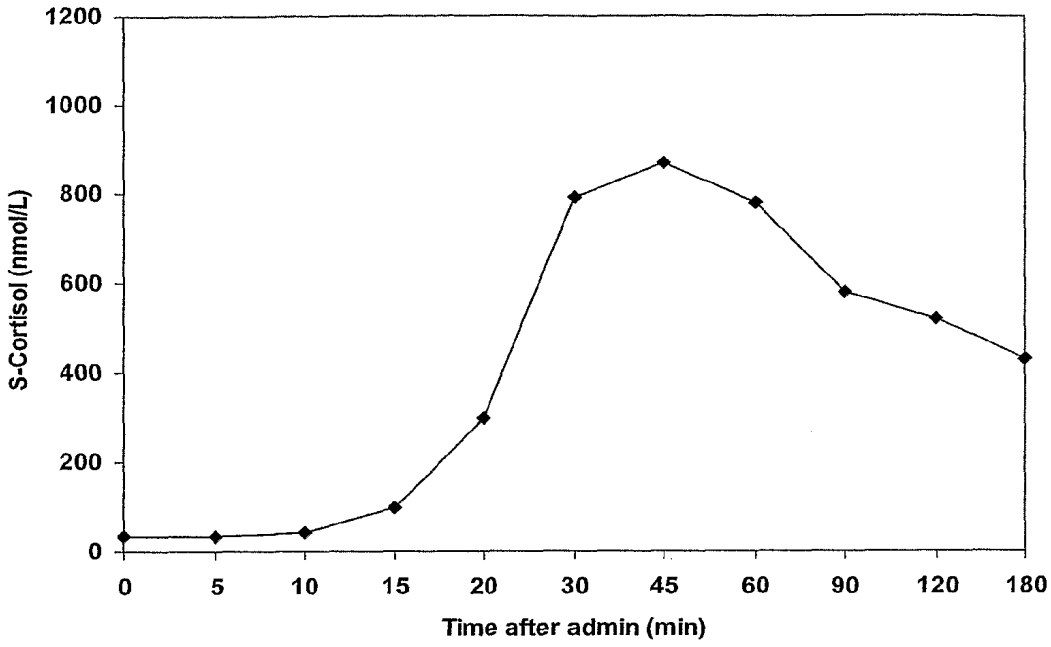
900
800
700
600
500
400
300
200
100
0
0
5
10
15
20
30
45
60
90
120
Time after admin (min)

Fig. 3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1000
800
600
400
200
0
S-Cortisol (nmol/L)
0
5
10
15
20
30
45
60
90
120
180
Time after admin (min)

Fig. 4

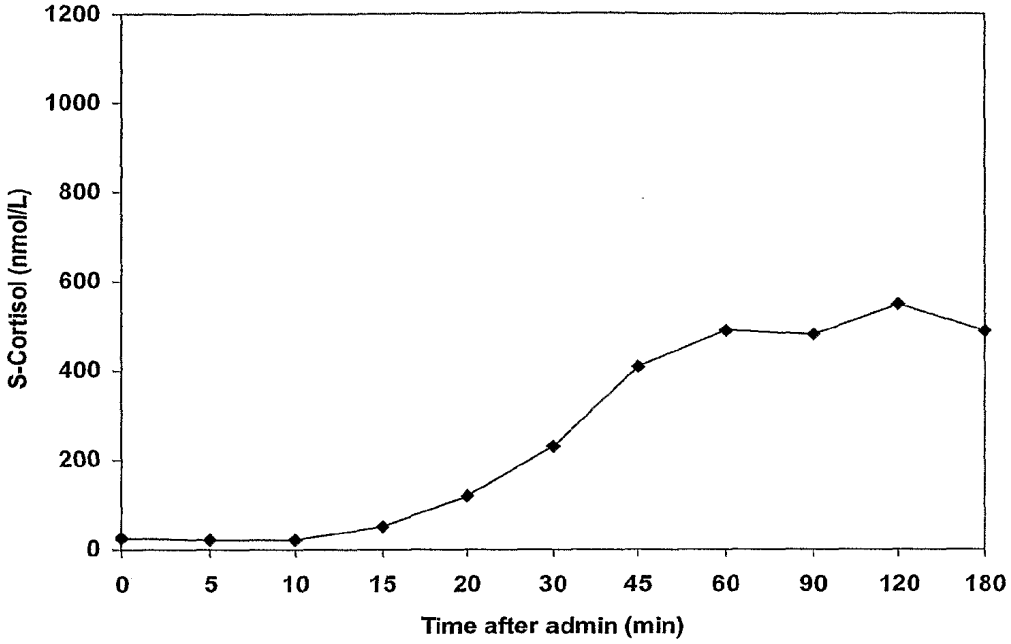

1200
1000
800
600
400
200
0
S-Cortisol (nmol/L)
0
5
10
15
20
30
45
60
90
120
180
Time after admin (min)

Fig. 5

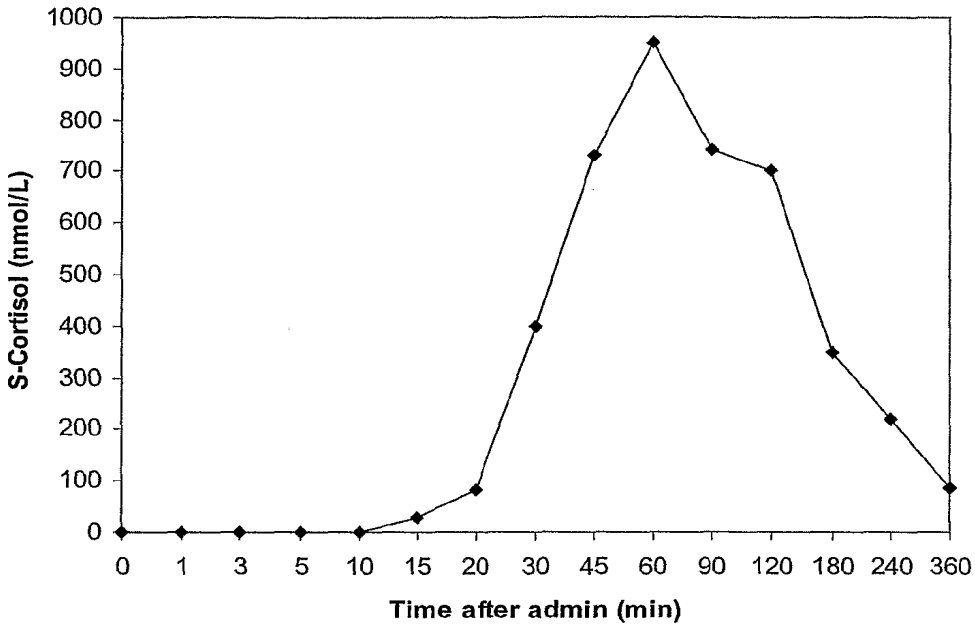

1000
900
800
700
600
500
400
300
200
100
0
S-Cortisol (nmol/L)
0 1 3 5 10 15 20 30 45 60 90 120 180 240 360
Time after admin (min)

Fig. 6

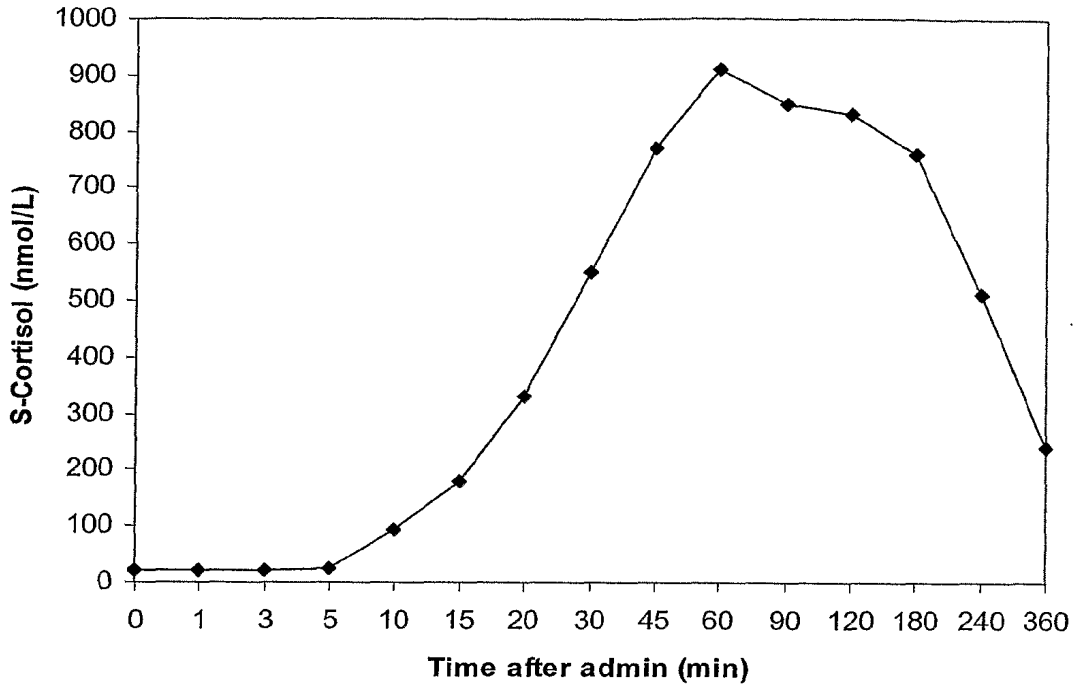
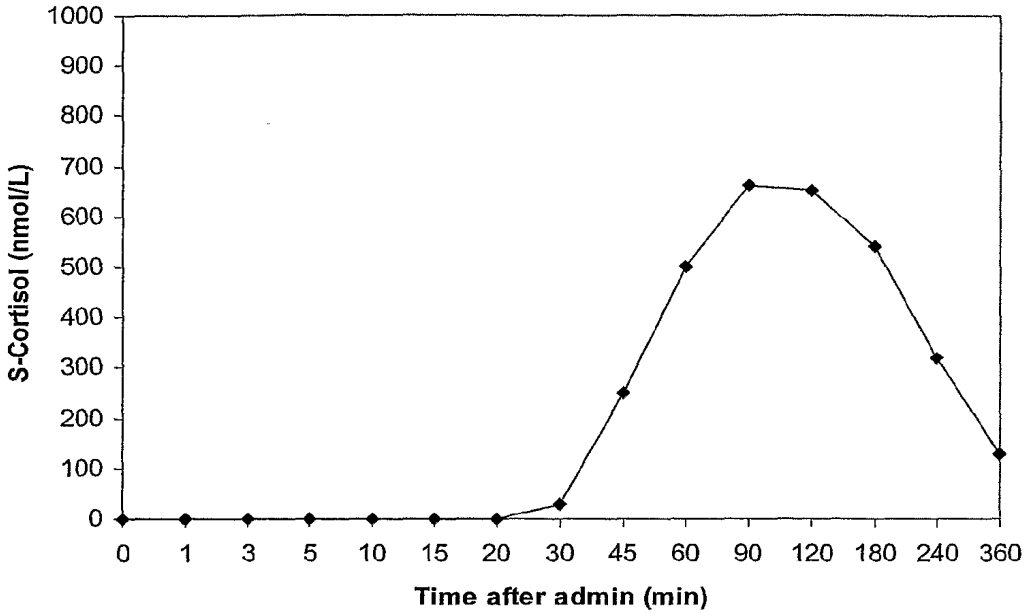

S-Cortisol (nmol/L)
1000
900
800
700
600
500
400
300
200
100
0
0 1 3 5 10 15 20 30 45 60 90 120 180 240 360
Time after admin (min)

Fig. 7

8/12


S-Cortisol (nmol/L)
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900
800
700
600
500
400
300
200
100
0
0 1 3 5 10 15 20 30 45 60 90 120 180 240 360
Time after admin (min)

Fig. 8

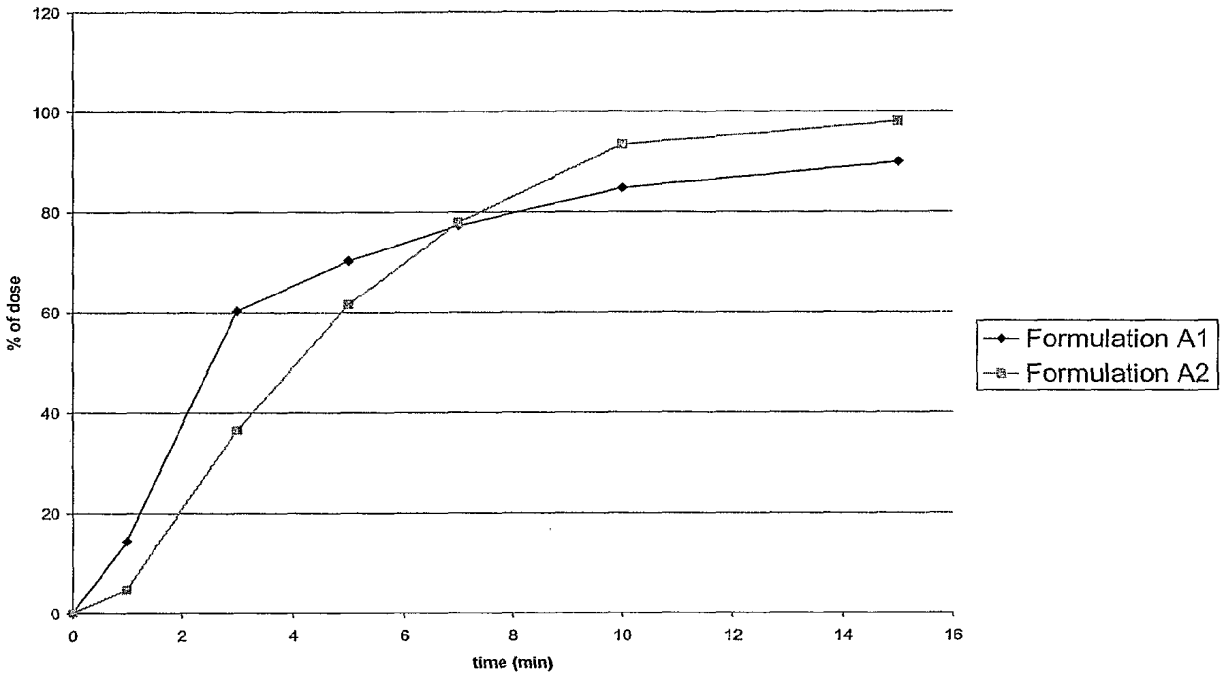
120
100
80
60
40
20
0
% of dose
0
2
4
6
8
10
12
14
16
time (min)
Formulation A1
Formulation A2

Fig. 9

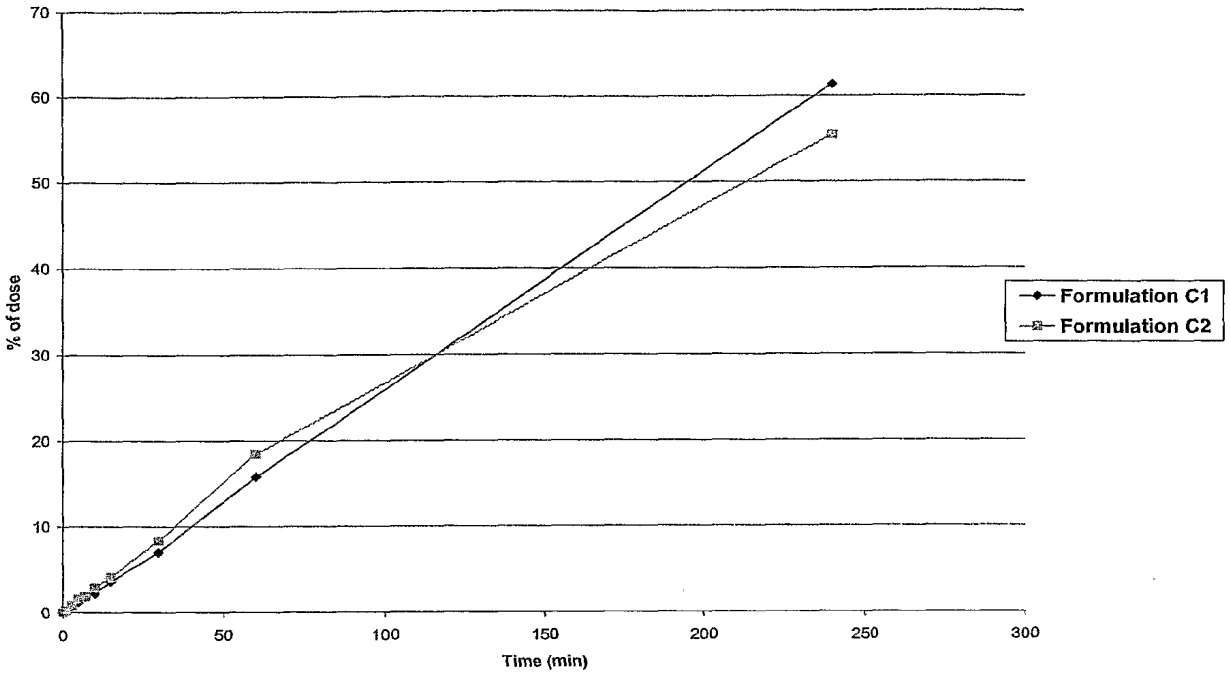
70
60
50
40
30
20
10
0
% of dose
0
50
100
150
200
250
300
Time (min)
Formulation C1
Formulation C2

Fig. 10

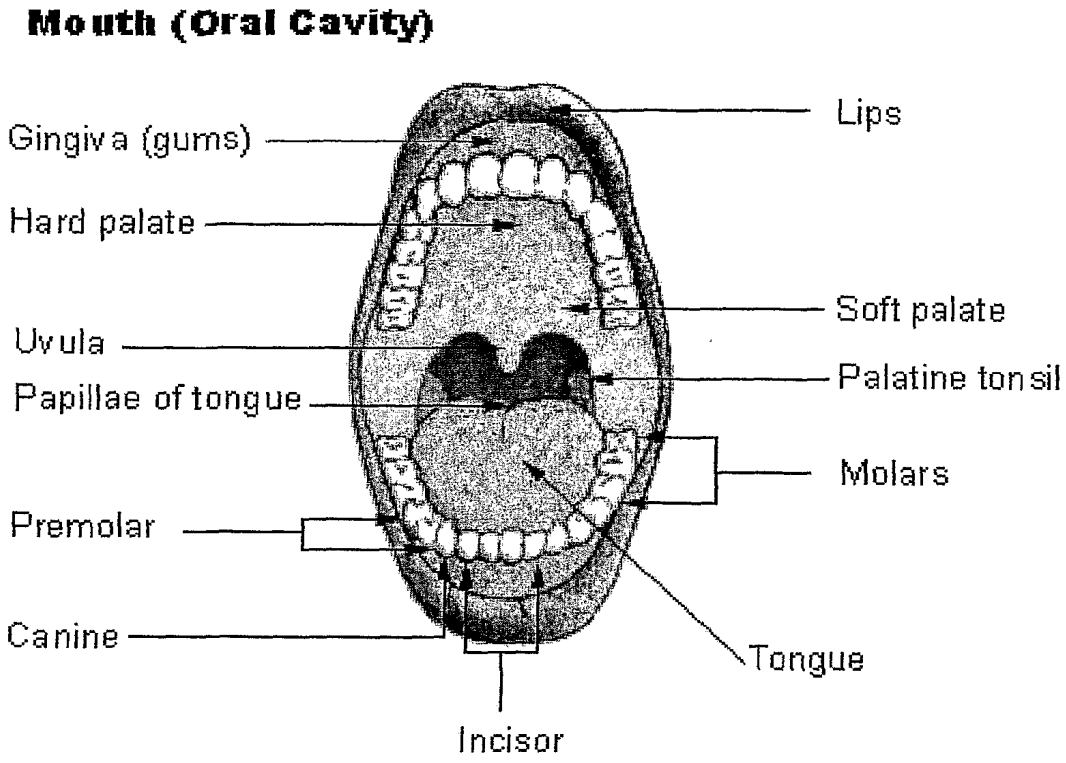
Mouth (Oral Cavity)
Gingiva (gums)
Hard palate
Uvula
Papillae of tongue
Premolar
Canine
Incisor
Lips
Soft palate
Palatine tonsil
Molars
Tongue

Fig. 11

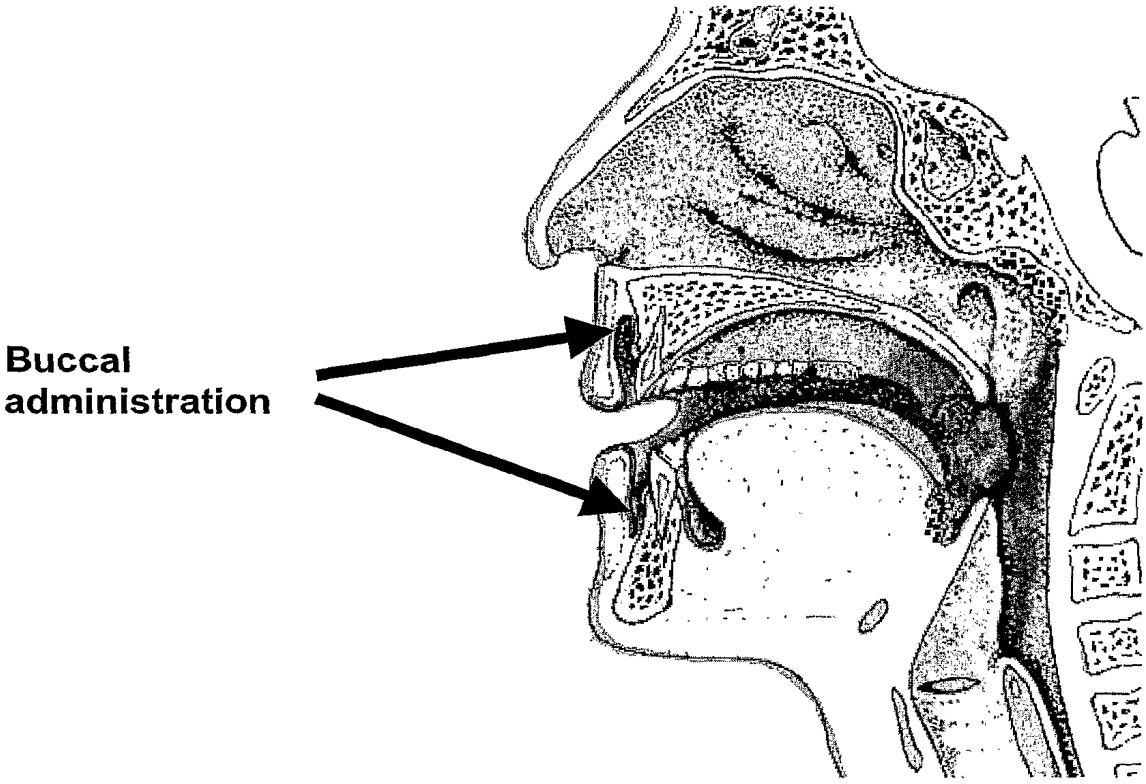

Fig. 12

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(54) Extrudable compositions for topical or transdermal drug delivery.

(57) An effective and convenient medicament delivery system comprising novel extrudable compositions. The preferred compositions of the invention contain a thermoplastic water-soluble polymer selected from the group consisting of hydroxypropyl cellulose and polyethylene oxide ; a water-soluble polymer derived from acrylic acid ; medicament ; and plasticizer. The compositions provide an effective medicament delivery system and are especially suitable for use with adhesive bandages.

EP 0 598 606 A1

BACKGROUND OF THE INVENTION

This invention relates to novel extrudable compositions for the topical application of medicaments to human or animal skin and, more particularly, to bandages containing such compositions. Adhesive bandages, wound dressings, and the like containing the novel compositions of the invention provide a superior wound care system.

Creams, ointments, solutions and powders are known to be useful for the topical application of various drugs to skin. However, the application of these materials typically is non-quantitative and it is difficult for the user to control the amount of drug delivered to the area to be treated. When such materials are used in conjunction with adhesive bandages or wound dressings, they frequently detackify (that is, result in a loss of adhesion) the adhesive portion of the bandage, thereby increasing the risk of contamination. In addition, such materials are messy and inconvenient to use, frequently soiling clothing and the like.

Various wound dressings and bandages for the topical application of medicaments are also known. For example, U.S Patent No. 4,616,644, issued October 14, 1986 in the name of Saferstein et al., describes an adhesive bandage wherein a thin coating of a high molecular weight polyethylene oxide is applied to the surface of the wound release cover of the bandage to stop bleeding faster.

U.S. Patent No. 4,880,416, issued November 14, 1989 in the name of Horiuchi et al. describes a dermal bandage comprised of a film-like adhesive material that comprises vinyl acetate polymer and a polycarboxylic acid or anhydride.

In EPO Application 0297828, Charkoudian et al. describes a bandage which is coated or impregnated with a soft, waxy, low melting composition containing a medicament. In example 1 a solution of polyethylene glycol and benzocaine is coated onto a nonwoven fabric of the type used in bandages. In example 2 Charkoudian et al. further describes impregnating a non-woven fabric with a methanol solution of polyvinyl pyrrolidone (PVP), polyethylene glycol and benzocaine, and letting the methanol evaporate. The resulting composition is extremely tacky and dissolves very slowly upon contact with wound exudate. Moreover, since the compositions have melting points below 40 °C, they cannot be subject to conventional ethylene oxide sterilization techniques.

In U.S. Patent No. 4,713,243, issued December 15, 1987, Schiraldi et al. describes a bioadhesive extruded film that is useful in intra-oral drug delivery. The thin film is comprised of a bioadhesive layer consisting essentially of 40-95 % by weight hydroxypropyl cellulose, 5-60 % of a homopolymer of ethylene oxide, 0-10 % of a water insoluble polymer, and 2-10 % of a plasticizer.

From the foregoing discussion, it will be seen that various compositions and devices useful for topically applying medicaments to the skin are known. However, such compositions have not been found to be entirely suitable when used by themselves or in connection with conventional adhesive bandages. For example, many compositions interfere with a bandage's functions to absorb wound exudate and adhere to the skin. Another problem is that upon dissolution many of these materials form a thin, free-flowing fluid having little structural integrity. As a result, the medicament is dispersed too quickly and readily spreads away from the area to be treated. Yet another problem is that many compositions of the prior art are not stable at higher temperatures and humidities. This property is crucial because the compositions may be stored for lengthy periods under less than ideal warehouse conditions. In addition, they must be able to withstand rigorous sterilization procedures.

Accordingly, it is an object of the present invention to provide a method for topically or transdermally delivering a medicament which comprises applying to the skin a novel, extrudable composition which, upon contact with body fluid, releases a controlled amount of medicament to the area to be treated.

It is another object of the invention to provide an extrudable composition for delivering a medicament to the skin which can be used alone or in conjunction with sterilized and/or adhesive bandages.

It is yet another object of the invention to provide a composition which does not readily dissolve to a free-flowing fluid upon contact with body fluids.

It is a further object of the invention to provide an extruded film that is an effective and convenient medicament delivery system.

SUMMARY OF THE INVENTION

The inventors have found that various extrudable compositions comprising:

(a) at least one thermoplastic water-soluble polymer;

(b) at least one water-soluble polymer derived from carboxylic acid;

(c) plasticizer; and

(d) at least one medicament,

can achieve the above objects and advantages.

The inventors have further found that extrudable compositions comprising, about 5-70 % by weight of (a); about 1-10 % of (b); about 10-80 % of (c); and about 0.01-10 % of (d), are particularly advantageous. In one preferred group of compositions, (a) comprises at least one polymer selected from the group consisting of hydroxypropyl cellulose and polyethylene oxide, (b) comprises at least one polymer derived from acrylic acid and (c) comprises at least one plasticizer selected from the group consisting of glycerine, propylene glycol and polyethylene glycol. The medicament comprises at least one, and preferably more, pharmaceutically acceptable therapeutic agents.

The compositions of this invention have the consistency of a non-flowing "ointment", as defined in The United States Pharmacopeia, The National Formulary (USP XXII, NF XVII), U. S. Pharmacopeial Convention, Inc., Rockville, MD, p. 1692 (1990), which is hereby incorporated by reference. After contact with body fluids, the composition dissolves into a matrix and releases the medicament, but it still possess good structural integrity.

The compositions of the invention can be placed directly on the skin as a free, extruded, single or multi-layered thin film. Alternatively, the films may be used in conjunction with a substrate like a bandage, wound dressing or blemish patch. For example, the absorbent pad material of a conventional bandage can be coated or at least partially impregnated with the composition, thereby providing a superior wound care product that rapidly delivers moisture-sensitive active ingredients to the area to be treated. Since the composition is extrudable, it can be formed into free films or coated on a substrate without the use of organic solvents.

In another preferred embodiment of the invention the novel extrudable compositions of the invention comprise:

(a) about 20-30% (by weight) of hydroxypropyl cellulose and about 0-10% of polyethylene oxide;

(b) about 1-10% by weight of a copolymer of acrylic acid and allyl sucrose;

(c) about 60-70% by weight of at least one plasticizer selected from the group consisting of glycerin and polyethylene glycol; and

(d) about 0.01-10% by weight of medicament.

The novel extrudable compositions of the present invention alleviate many of the above problems. For example, when used in connection with an adhesive bandage, they do not interfere with the bandage's absorption and adhesion functions. In addition, they may be stored for at least one week at 40 °C and 80% relative humidity without experiencing a significant weight loss (i.e., more than 10% by weight). Moreover, the compositions and their properties are not impaired by ethylene oxide sterilization at 170 °F, or E-beam or cobalt sterilization techniques. In addition, they are also sufficiently flexible so that they are comfortable to wear.

In another preferred embodiment of the invention, the extrudable compositions are used in conjunction with blemish patches to provide anti-acne medicament thereto.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a graph showing the relationship between viscosity and temperature for a typical composition of the present invention and a comparative composition.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed toward water-soluble films which rapidly dissolve in body fluids such as blood, perspiration, or wound exudate, and deliver active ingredients to a treatment site in a controlled manner.

In accordance with one embodiment of the present invention, the absorbent component of a bandage or wound dressing of known construction is coated or at least partially impregnated with the extrudable composition of the invention. Upon application to the injured area, the exudate from the wound or moisture from the skin dissolves the film, thereby converting it to a matrix having an ointment-like consistency and making the active ingredient available to treat the injury. Because of these ointment-like properties, the film is tacky and adheres to the skin.

As previously mentioned, the bandages or wound dressings which can be used in conjunction with the present invention comprise conventional adhesive or non-adhesive bandages or wound dressings of the medical or surgical type. Generally such bandages include a plastic film backing having attached thereto an absorbent pad portion. The absorbent pad material may be any of the woven or non-woven fabrics of natural or synthetic fibers heretofore employed as dressings, including for example, cotton, nylon or polyester. Suitable substrates further include woven or standard papers, and plastics. Preferred substrates include absorbent pad materials comprised of a rayon and polypropylene (10:90 weight ratio) spun bonded web, a knitted polyester fabric such as that used for DERMICEL taffeta tape manufactured by Johnson &Johnson Consumer Products,

Inc., Skillman, N.J., and a composite nonwoven fabric made of thin, breathable polyester/polyurethane laminate known as FABRELLE which is manufactured by Fabrite Industries, Woodbridge, N.J..

Suitable plastic film backings include highly plasticized polyvinyl chloride, polyurethane, polyolefins, ethylene vinyl acetate and block copolymers films such as HYTREL® copolyester ether elastomers available from E. I. DuPont, Wilmington, Delaware. These plastic films may or may not contain an adhesive, which may or may not be pressure sensitive.

Adhesive bandages further include one or more release tabs. Release tabs (such as silicone-coated release paper or other alternate materials which can be readily removed at the time of use), are applied so as to cover, in an overlaying manner, the entire adhesive side of an adhesive bandage.

In addition, each bandage can be packaged and sealed in an individual wrapper (which typically is made of glassine-paper or a similar bacterial barrier material). Each bandage is packaged before it undergoes ethylene oxide or irradiation sterilization so as to maintain sterility until the bandage is ready for use.

In another preferred embodiment of the invention, the extrudable compositions may be used in conjunction with blemish patches to treat acne. Generally such blemish patches resemble the conventional adhesive bandages described above, i.e., they comprise a plastic film or fabric backing, an absorbent pad, an adhesive, and one or more release tabs, with the extrudable composition laminated to the absorbent pad.

As an alternate configuration, the blemish patch may simply contain a layer of the extrudable composition laminated to the aforementioned absorbent pad material. The extrudable composition serves as the media for holding the anti-acne medicament as well as an adhesive for adhering the patch to the skin site. Preferably, the pad stock will have some flexibility so that it conforms to facial contours. The patch may also contain a plastic film on the side of the pad opposite to the layer of extrudable composition to control moisture vapor transmission through the patch. A thin polyurethane film will allow for high moisture vapor transmission, whereas a thin polyolefin film will result in low moisture vapor transmission through the patch. This configuration may also be used with other medicaments.

The thermoplastic, water-soluble 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 and copolymers. The term "thermoplastic" as used herein indicates that the polymers are adequately rigid at normal temperatures and under normal conditions of stress, but are capable of deformation under heat and pressure. The term "water-soluble" as used herein indicates that the thermoplastic polymers are soluble or swellable in aqueous or aqueous-based solutions. Hydroxypropyl cellulose has an added advantage; namely, it is also soluble in non-aqueous solvents like methanol.

The compositions of the invention comprise about 5-70% of thermoplastic, water-soluble polymer, preferably about 10-40%, more preferably about 10-30%, even more preferably about 20-30% and most preferably about 23-30%.

Preferably, the thermoplastic, water-soluble polymers of the invention consist essentially of hydroxypropyl cellulose and/or polyethylene oxide. Thus, the hydroxypropyl cellulose and polyethylene oxide polymers useful for this invention can be used singly or a mixture. If a mixture of hydroxypropyl cellulose and polyethylene oxide is used, preferably they are used in a ratio of between about 1:9 to about 9:1, by weight, more preferably between about 4:6 to about 4:0, even more preferably at ratio of about 4:1.

The hydroxypropyl cellulose ("HPC") useful for purposes of the present invention is commercially available from Aqualon, Inc. (Wilmington, DE) under the trade name KLUCEL®. Preferred grades include KLUCEL EF, with an average molecular weight of about 60,000 and having a viscosity of about 300-700 cps (Brookfield) in a 10 percent water solution, or KLUCEL LF, with a molecular weight of about 100,000 and having a viscosity of about 75-150 cps in a 5 percent water solution. In general, any HPC having a number average molecular weight above about 60,000 is useful for purposes of this invention.

The homopolymer of ethylene oxide useful for purposes of this invention has a number average molecular weight of between about 100,000 to 3,000,0000 or even higher. Although polyethylene oxide ("PEO") polymers having an average molecular weight of above 600,000 are useful for several embodiments of the invention, PEO having a number average molecular weight of less than about 600,000 is preferred, less than about 400,000 is more preferred, and between about 100,000 and 400,000 is even more preferred. Such polymers are commercially available from the Union Carbide Corporation under the trade name POLYOX. Preferred grades include POLYOX WSR-N-10, which has an average molecular weight of about 100,000 and POLYOX WSR-N8, which has an average molecular weight of about 200,000.

Small amounts of other (non-thermoplastic or thermoplastic) water-soluble polymers may be used as well, replacing a small portion of the water-soluble, thermoplastic polymers. Other polymers which are useful for the present invention include, for example, homopolymers and copolymers of carboxymethyl cellulose, hydroxyethyl cellulose, polyacrylamide, polyacrylic acid and its homologs, polyvinyl alcohol, polyvinyl pyrrolidone,

polyethylene amines, polymethacrylic acid, polyvinylamine, polymethacrylamide, polyvinylmethylether, and the like. Natural gums such as polysaccharides, alginates, carrageenan, guar gum, gum agar, gum arabic, gum ghatti, gum karaya, gum tragacanth, locust bean gum, pectins, starch and its derivatives, tamarind gum, and xanthan are also useful. The gums are used to adjust the hydrophilic/hydrophobic balance of the composition, which in turn affects the solubility of the medicament in the composition.

Small amounts of polymers derived from carboxylic acids (or from pharmaceutically acceptable salts thereof) provide increased flexibility and stability to the extrudable compositions of the invention. The carboxylic acid polymers useful for the invention include any such polymer having a number average molecular weight of above about 450,000. Preferably, the compositions of the invention comprise at least one such polymer in amounts of between about 1-10% (by weight), preferably between about 3-8%, and most preferably between about 5-7%.

Homopolymers and copolymers derived from acrylic acid are preferred. Copolymers comprised mainly of acrylic acid and allylsucrose, such as those commercially available from B.F. Goodrich under the trade name CARBOPOL, are even more preferred. For example, CARBOPOL 934P, having a molecular weight of about 3,000,000 is especially preferred. Other polymers that are useful for the invention include homopolymers and copolymers derived from methyl acrylate, methacrylic acid, methyl methacrylate or hydroxyethyl methacrylate, or their amide derivatives.

Suitable pharmaceutically acceptable salts of the carboxylic acid polymers include alkali metal salts such as sodium or potassium salts and ammonium salts. The degree of neutralization of salts is not limited. The pharmaceutically acceptable salts may have any molecular weight.

Any pharmaceutically acceptable medicament or pharmaceutical agent may be delivered by the drug delivery system of the present invention. Usable medicaments include those which are capable of withstanding the heats and pressures generated in the extrusion process involved in making the films of the present invention.

Preferred medicaments include:

anesthetics and/or analgesics such as benzocaine, lidocaine, dyclonine HCl, phenol, menthol, aspirin, phenacetin, acetaminophen, ibuprofen, potassium nitrate, and the like;

anti-inflammatories such as hydrocortisone acetate, triamcinolone acetonide, glycyrrhizinate, and the like;

antihistamines such as chlorpheniramine maleate, ephedrine HCl, diphenhydramine HCl, and the like;

antibiotics such as tetracycline, doxycycline hyclate, meclocyline, minocycline, bacitracin zinc, polymyxin B sulfate, neomycin sulfate, and the like;

fungistats such as nystatin, miconazole, ketoconazole, and the like;

anti-acne agents like salicylic acid; and

antiseptics such as benzylalkonium chloride; iodine, silver solfidiazine, chlorohexidine and salts thereof, cetylpyridinium chloride, and the like.

Medicaments that are not capable of withstanding the heats and pressure generated in the extrusion process are also of use in the present invention. Such medicaments can be applied to the extruded compositions using techniques that are well-known to those skilled in the art. For example, such medicaments may be dissolved in a solvent and coated onto the extruded compositions or films. As the solvent evaporates, it leaves behind the medicament. Anti-acne medicaments like retinoic acid and benzoyl peroxide can be utilized in the present invention in this manner.

The medicament should be added in a pharmaceutically effective amount, i.e., an amount sufficient to prevent, cure or treat a disease to which the pharmaceutical preparation of this invention is to be applied. The compositions of the invention typically comprise at least one medicament, and preferably more than one, in amounts ranging from between about 0.01 to 10%, by weight.

Plasticizers useful for purposes of the present invention include block copolymers of polyethyleneoxide and polypropyleneoxide such as PLURONIC® F 127 and TETRONIC® 1302; 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 MYVEROL®; mineral oils; vegetable oils such as castor oil, and the like. These plasticizers may be used singly or in any combination.

The purpose of the plasticizer is several fold; namely, to improve polymer melt processing by reducing polymer viscosity, to increase adhesion to the skin, to increase the dissolution rate in body fluids, and/or to impart flexibility to the final product. In addition, the plasticizer can impart "ointment-like" characteristics to the final product as defined by U.S.P. "Hydrophilic Ointments or Gels."

Compositions of the invention comprise between about 10-80% (by weight) of plasticizer, preferably between about 30-80%, more preferably between about 30-70%, and most preferably between about 60-70%.

Preferred plasticizers include propylene glycol or polyethylene glycol (PEG) polymers having a number

average molecular weight of from about 200 to 20,000. Although PEG polymers having higher average molecular weights are useful in the present invention, such polymers having an average molecular weight between 200 to 3500 are preferred. More preferred are PEG polymers having an average molecular weight of between 200 and 1500, such as CARBOWAX 600 (available from Union Carbide Corporation), which has an average molecular weight of about 600. Glycerin (especially Grade 916 USP, available from Emory), is also preferred plasticizer.

In one preferred embodiment of the invention, the extrudable compositions comprise, and preferably consist essentially of:

a. thermoplastic water-soluble polymer;

b. a water-soluble polymer derived from a carboxylic acid or a pharmaceutically acceptable salt thereof;

c. plasticizer; and

d. medicament.

The inventors have found that the advantages attained by the novel compositions are due to the unique formulations described herein.

Preferably the compositions of this embodiment comprise about 5-70% of (a), about 1-10% of (b), about 10-80% of (c), and about 0.01-10% of (d), by weight. More preferably, they comprise about 10-40% of (a), about 1-10 % of (b), about 30-80% of (c), and about 0.01-10% of (d). Even more preferably, they comprise about 20-30% of (a), about 3-8% of (b), about 30-70% of (c), and about 0.01-10% of (d). Most preferably, the compositions comprise about 23-30% of (a), about 5-7% of (b), about 60-70% of (c), and about 0.01-10% of (d).

In accordance with the teachings above and in another preferred embodiment, the extrudable compositions of the invention comprise about 10-30% of (a), about 1-10% (b), about 60-70% of (c), and about 0.01-10% of (d), by weight.

In yet another embodiment, the compositions of the invention comprise about 20-30% hydroxypropyl cellulose and about 0-10% polyethylene oxide, about 1-10% of a copolymer derived from acrylic acid and allyl sucrose, about 0.01-10% of said medicament, and about 60-70% of glycerin; by weight. Even more preferably, they comprise about 22-29% hydroxypropyl cellulose and about 4-7% polyethylene oxide, about 5-7% of said copolymer, about 0.01-10% of said medicament, and about 60-70% glycerin; by weight.

In yet another embodiment which has been found to be particularly suitable for blemish patches, the extrudable compositions of the invention comprise about 22-27% hydroxypropyl cellulose, about 5-7% of said acrylic acidallyl sucrose copolymer, about 0.01-10% medicament, and about 60-70% glycerin; by weight. Alternatively, such a composition may comprise about 10-15% hydroxypropyl cellulose and 15-20% polyethylene oxide, about 5-7% of said acrylic acid-allyl sucrose copolymer, about 0.01-10% medicament, and about 30-40% of glycerin and 30-40% polyethylene glycol; by weight.

The inventors have further found that for certain applications that are especially suitable for use with adhesive bandages, the carboxylic acid polymer may be left out of the extrudable composition altogether. In practicing this embodiment of the invention the extrudable composition comprises polyethylene oxide, plasticizer and medicament.

Preferably, the extrudable compositions of this embodiment comprise about 15-80% of polyethylene oxide and about 20-85% of plasticizer, by weight. More preferably they comprise about 25-70% of polyethylene oxide and about 30-75% of plasticizer, by weight. Even more preferably they comprise about 35-60% of polyethylene oxide and about 40-65% of plasticizer, by weight. Of course, about 0-10% (preferably 0.01-10%), by weight, of a medicament can replace the equivalent amount of any of the above ingredients. The preferred plasticizer for use in this composition is polyethylene glycol.

The extrudable compositions of the invention may be prepared by mixing the above ingredients in a variety of ways well-known to those skilled in the art. For example, the preweighed ingredients can be added to an intensive mixer such as a Brabender Prep Center or a Baker Perkins Blender and mixed at 80-95 °C, with or without solvent. Thus, the compositions can be prepared as hot melts. Alternatively, aqueous solvents or alcohols (like methanol) can be used.

The resultant blend can be cast at elevated temperatures, at say, about 50 to 140°C. Alternatively, the blend can be extruded using a single or twin extruder, or pelletized. If extruded, film thicknesses may vary from "thin" films of about 1.0 mil to "thick" films of about 20 mils or greater, the thickness depending on the intended use of the product. The film can also be extrusion coated onto a variety of substrates as discussed above and then subjected to heat and pressure to form a laminate. Temperatures on the order of 21°-130°C and contact pressures of up to 40 pounds per linear inch are suitable for forming the laminate. Additional films or insoluble ingredients, such as a water-insoluble medicaments, may be coated or laminated onto the resultant product.

When used in connection with an absorbent pad, the compositions of the invention may be at least partially impregnated into the absorbent pad using any technique well-known to those skilled in the art. Alternatively,

the film or composition can be applied adjacent to the body facing surface of the absorbent pad by the use of elevated temperatures and pressures. In the latter embodiment, the film or composition is distinct or discernable from the underlying absorbent pad.

Moisture sensitive or water-insoluble active ingredients also can be blended into the compositions of the invention without degradation or separation from the solid components, since the remaining components of the extrudable composition are frequently soluble in aqueous and non-aqueous solvents and are also useable as hot melts.

In addition to the polymers and plasticizers, minor amounts of other non-essential but customary ingredients will often be used if desired, e.g., antioxidants, foamers, neutralizing agents, stabilizing agents, fillers, preservatives, flavors, and colorants. For example, the extrudable composition can be modified to impart more or less tack contain a color, or to produce a scent to heighten the sensory cue to the user that the product is working. Another modification includes adding fumed silica to improve absorption and stability of the compositions. The fumed silica is generally added in an amount ranging from about 0.01 to about 5% by weight of the total composition. As another example, sodium bicarbonate and/or citric acid can be added to the compositions to enable them to foam upon contact with moisture. The pH of the extrudable composition is also generally controlled within the range of about 3 to 8.

This invention will now be illustrated in greater detail by reference to the following examples, but it should be understood that they are not intended to limit the present invention. In these examples, all the parts, percents and ratios are by weight unless otherwise indicated.

EXAMPLE 1

An ointment film was formed by adding 100 gms of polyethylene oxide (POLYOX N-10) to 200 gms of polyethylene glycol (CARBOWAX 600) in a Brabender heated at 80 °C. The components were blended for five minutes to fully plasticize the polyethylene oxide. Then, 26 gms of copolymer of acrylic acid and allyl sucrose (CARBOPOL 934P), was slowly added to the blend and mixed for an additional 30 minutes. The resultant ointment was extrusion coated onto unitized pad stock to form a flexible, aesthetically pleasing film.

EXAMPLE 2

Various antibiotics and antiseptics were added to the composition of Example 1 at the concentrations shown below. The resulting compositions were then coated onto pad stock to form a film layer.

Sample	Antibiotic/Antiseptic	Concentration
A	Bacitracin Zinc[1]	500 units/gm
	Neomycin Sulfate[2]	3.5 mg/mg
	Polymyxin B Sulfate[3]	10,000 units/gm
B	Neomycin Sulfate[2]	3.5 mg/mg
	Polymyxin B Sulfate[3]	10,000 units/gm
C	Benzalkonium Chloride	0.13 (% w/w)

[1]Activity = 71000 U/gm
[2]Activity = 0.7 gm/gm
[3]Activity = 7700 U/gm

Samples A, B and C were not sterilized.
Additional samples were prepared as follows:
Sample D = Sample A ethylene oxide sterilized at 165°F (with moisture).

Sample E = The film sample of Example 1 without antibiotics/antiseptics or sterilization.

Sample F = NEOSPORIN Maximum Strength Ointment (Burroughs-Welcome Co.) coated onto filter paper.

Sample G = Untreated filter paper.

Sample A-G were then tested to determine their antimicrobial activity using the zone of inhibition method. Agar base layers were poured into petri dishes and allowed to solidify. The base layers were then covered with a seeded (inoculated) agar layer. The seeded agar layer contained three test microorganisms Staphylococcus epidermidis, Micrococcus luteus and Bordetella bronchiseptica (evaluated separately) as recommended in the USP Pharmacopeia XXII for testing neomycin, bacitracin and polymyxin, respectively.

Pieces of each of the Samples (8 sq. mm) were placed active side down on each seeded agar plate (6 squares were evaluated per test organism). The samples were incubated at 35°C for 18 hours. The clear zones of inhibition were measured and are reported below as the average of the six zones:

Clear Zone in Millimeters			
Sample	M. luteus	S. epidermidis	B. bronchiseptica
A	11.7	11.0	11.7
B	0.0	11.2	11.7
C	17.2	16.0	4.0
D	5.8	10.5	10.7
E	0.0	0.0	0.0
F	10.5	14.2	7.5
G	0.0	0.0	0.0

The above results demonstrate that the compositions of the present invention (Samples A-D) exhibit good antimicrobial activity.

EXAMPLE 3

Approximately 0.5% (by weight) of fumed silica (CABOSIL M-5) was added to the composition of Example 1. The fumed silica is added to moisture-sensitive active-containing films to absorb moisture and improve the stability of the films.

EXAMPLE 4

Approximately 100 gms of sodium bicarbonate and 50 gms of citric acid were added to the ointment blend of Example 1 (after the addition of the copolymer of acrylic acid and ally sucrose) and the blend was mixed for an additional 10 minutes. The resulting film foamed effervescently upon contact with water.

EXAMPLE 5

Blemish Patch

Two extrudable compositions were prepared. Both vehicles were anhydrous, hydrophilic blends made from the following raw materials:

	Low Tack Vehicle	High Tack Vehicle
Acrylic Acid - Ally Sucrose Copolymer (CARBOPOL 934P)	5.6%	6.2%
Polyethylene Glycol (CARBOWAX 600)	32.3%	0
GLYCERIN (USP 99.5%)	32.3%	67.0%
Hydroxypropyl Cellulose (KLUCEL EF)	11.1%	24.8%
Polyethylene Oxide (POLYOX N-10)	16.7%	0
Salicyclic Acid	2.0%	2.0%

Mixing was performed in a Baker-Perkins Blender at a screw speed of 30 RPM, blade speed of 36 RPM, at 80 °C for about 30 minutes. The polyethylene glycol and/or glycerin were premixed and then added to the mixing bowl of the blender. The hydroxypropyl cellulose, acrylic acid-allyl sucrose, copolymer and polyethylene oxide (low tack only) were also premixed in a "V" blender for about three and a half minutes. After approximately two-three minutes, the premixed powders were added at once to the mixing bowl. The viscosity of the blend quickly increased and began generating sheer force. The blend was masticated for about twenty-five minutes and then salicylic acid was added.

Pelletizing the Ointment

After mixing for about thirty minutes (total mixing time), the blend was extruded as a rod directly into the pelletizer. (Prior to reaching the pelletizer, a cooling stage may be added to ensure a solidified ointment.) The pellets had a diameter of approximately 1/4" or less.

Extruding the Ointment

A Killian extruder was used for extrusion. Initial settings were as follows:

ZONE 1	ZONE 2	ZONE 3	ZONE 4	DIE
150 °F	160 °F	175 °F	180 °F	200 °F

SCREW SPEED	LINE SPEED
50 RPM	21 FT/MIN

The extruded film was laminated to two substrates; clear unitized pad stock used in BAND-AID® brand adhesive bandages and flexible fabric. (The roll may require a silicone release sheet as a carrier paper.) No finishing was required.

EXAMPLE 6

Rheological Data

Figure 1 is a graph showing the relationship between viscosity and temperature of a composition of the present invention (Composition A) and a composition from EP Application No. 0297828 to Charkondian et al. (Composition B). The viscosity is reported in poises.

Composition A was prepared and then extruded into a film. Composition B was prepared in accordance with Example 2 of EP Application No. 0297828, except that benzocaine was omitted, and the viscosity was measured after the methanol solvent was removed.

Composition A (weight %)

Acrylic Acid-Allyl Sucrose Copolymer - 6.42%
(CARBOPOL 934P)
Hydroxypropyl Cellulose - 25.7%
(KLUCEL EF NF)
Glycerine - 65.78%
Potassium Hydroxide (dry) - 2.0%
Fumed Silica (CABOSIL M-5) - 0.1%
Dye - trace amount

Composition B

Polyvinylpyrrolidone - 40 gms.
Polyethylene Glycol 400 - 60 gms.
Methanol - 125 ml.

The viscosity of Compositions A and B was measured on a Rheometrics RDS-7700 parallel plate rheometer at 10 rad./sec. The resulting data is shown on Figure 1. Since the composition of the present invention is more viscous, it will be more resistant to flow than the composition of EP Appln. No. 0297828. This is an important property of the composition of the present invention, since it is not desirable to have the film and resulting medicament flow from the bandage or the traumatized area of the skin to which it is applied.

EXAMPLE 7

An additional extrudable composition suitable for use in a blemish pad was prepared using procedures similar to those described in Example 5. The composition contained (weight%) :

Glycerine - 53%
Acrylic Acid - Ally Sucrose Copolymer
(CARBOPOL 934P) - 6%
Hydroxypropyl Cellulose
(KLUCEL EF NF) - 26%
Fumed Silica (CARBOSIL M-5) - 1%
Salicylic Acid - 2%
Na-Ca Salt of Polyvinyl Menthyl Ether
Maleic Anhydride (GANTREZ MS-955) - 12%

EXAMPLE 8

A composition was prepared by blending 28% polyethylene oxide (POLYOX N-80) (having an average molecular weight of about 200,000) with 72% polyethylene glycol (CARBOWAX 600), in a Brabender mixer for one hour at 80 °C. The blend was coated onto release paper and laminated at 60 °C onto unitized pad stock. The resultant films had thicknesses of between 1 to 3 ounces/yd^2. The films did not interfere with the conventional absorption of the pad stock, and did not flake or peel.

EXAMPLE 9

Blends of polyethylene glycol (PEG) (number average molecular weight of between 200-1450) and polyethylene oxide (PEO) (number average molecular weight of approximately 100,000) having the proportions shown below were prepared and laminated onto unitized pad stock using procedures similar to those described in Example 8.

Sample	PEG	PEO (% w/w)
A	51	49
B	62.5	37.5
C	25	75
D	83.3	16.7
E	5	95
F	86	14

The films were evaluated for their flexibility, dissolution rate and stability at elevated temperatures and humidity. Samples A and B were preferred because they exhibited good flexibility and dissolution rates. Samples C and D had acceptable properties, and Samples E and F were found to have unacceptable properties.

EXAMPLE 10

When the medicament is heat or pressure sensitive, composition of the invention can be blended without medicament, and extrusion coated onto a substrate. Then, the medicament can be deposited onto the film using any technique well-known to those skilled in the art. The following is an example of this technique.

Layer 1 have the composition shown below was blended and extrusion coated onto flexible fabric using procedures similar to those described in Example 5.

Layer 1	**wt %**
Acrylic Acid - Allyl Sucrose Copolymer (CARBOPOL 934P)	6.5
Glycerin (Emory 916 USP)	54.5
Hydroxypropyl Cellulose (KLUCEL JF EF)	26.0
Fumed Silica (Cabosil M-5)	1.0
Na-Ca Salt of a Copolymer of Polyvinyl Menthyl Ether and Maleic Anhydride (GANTREZ MS-955)	12.0

A solution of benzoyl peroxide was prepared by mixing the composition shown below with an equal amount (by weight) of acetone. This solution was then coated onto Layer 1. Layer 2 was dried and the acetone was allowed to evaporate, which resulted in a tacky benzoyl peroxide-containing layer laminated to Layer 1. The resulting structure is suitable for use as a blemish patch.

Layer 2	wt %
Benzoyl Peroxide	10.0
Dimethylaminoethyl Methacrylate	65.0
Triacetine	25.0

Additional solvents may be added to enhance solubility. However, any solvent used must have a low boiling point and high vapor pressure to ensure that critically high temperatures are not reached during the drying step.

EXAMPLE 11

Examples of Multilayered Films

A single-layered film containing the medicament "A" is made in accordance with the present invention, and is extruded onto a substrate. A second extruded film containing medicament "B" is then extruded onto the first layer. Thus, the "B-containing" film is in contact with the skin and "B" is the first medicament that comes in contact with the inflamed skin or wound. For example, the B-containing film may contain lidocaine for pain relief and the A-containing film may contain hydrocortisone for reducing inflammation. Additional film laminates containing many separate drug layers and different medication strategies can be constructed.

Diffusion of the "bioactive-type" drugs typically occurs at skin temperature, e.g., 33 to 35 °C. In order to minimize transfer or co-mingling of drugs between separate film layers, the compositions can be stored under cold conditions (say, for example, at approximately 4 °C) and brought to room temperature when needed.

Various modifications can be made to the above-described embodiment without departing from the spirit and scope of the present invention.

Claims

1. A composition comprising:
   a. thermoplastic water-soluble polymer;
   b. a water-soluble polymer derived from a carboxylic acid or a pharmaceutically acceptable salt thereof; and
   c. plasticizer.

2. The composition of claim 1 further comprising:
   d. medicament.

3. The composition of claim 2 comprising about 5-70% of (a), about 1-10% of (b), about 10-80% of (c), and about 0.01-10% of (d), by weight.

4. The composition of claim 2 comprising about 10-40% of (a), about 1-10% of (b), about 30-80% of (c), and about 0.01-10% of (d), by weight.

5. The composition of claim 2 comprising about 23-30% of (a), about 5-7% of (b), about 60-70% of (c), and about 0.01-10% of (d), by weight.

6. The composition of claim 2 wherein (a) comprises at least one polymer selected from the group consisting of hydroxypropyl cellulose and polyethylene oxide.

7. The composition of claim 6 wherein said polyethylene oxide has a number average molecular weight of greater than about 600,000.

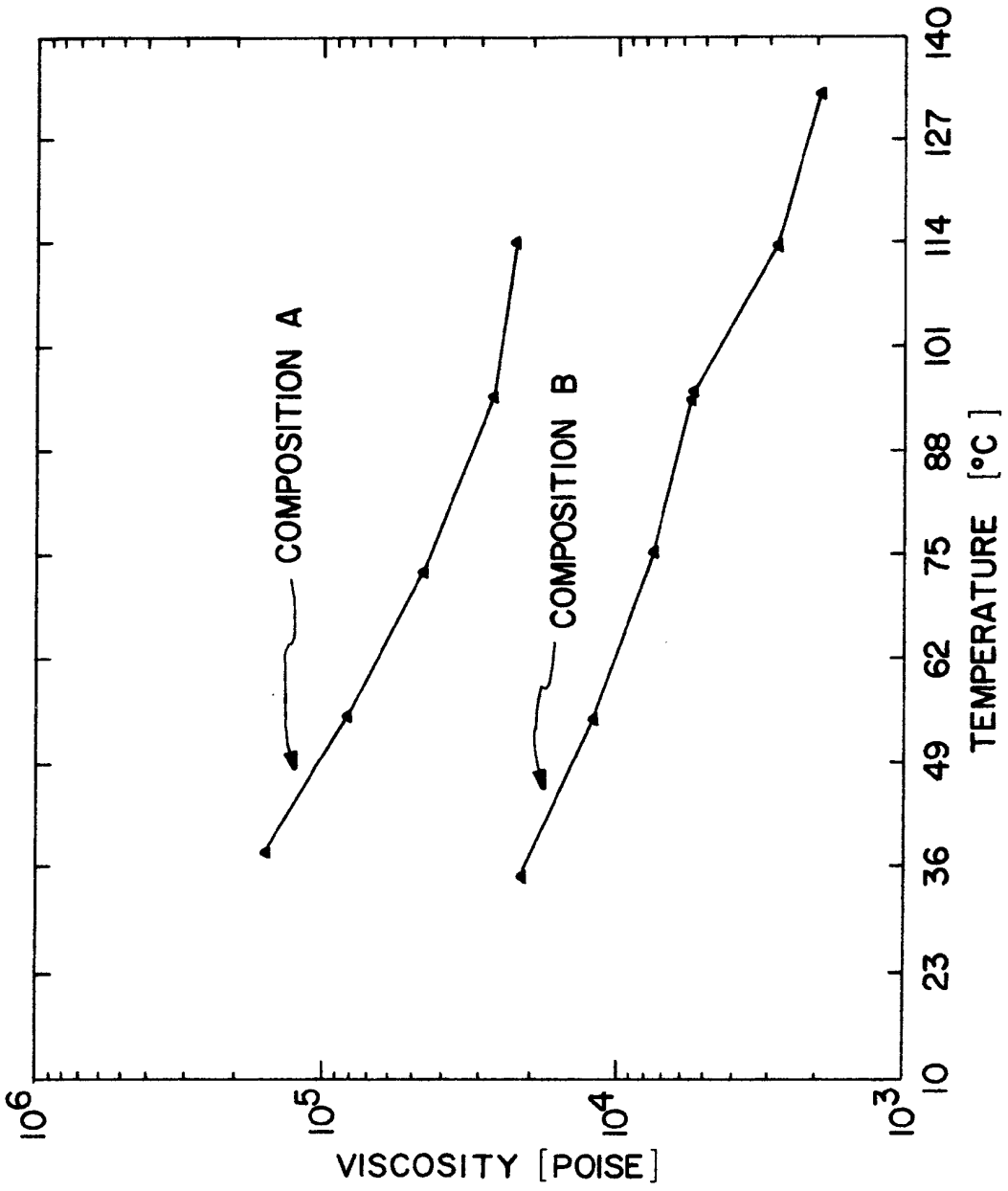
8. The composition of claim 6 wherein said polyethylene oxide has a number average molecular weight of less than about 600,000.

9. The composition of claim 6 wherein said polyethylene oxide has a number average molecular weight of

between about 100,000 and 400,000.

10. The composition of claim 6 wherein said hydroxypropyl cellulose has a number average molecular weight greater than about 60,000.

FIG.1


COMPOSITION A
COMPOSITION B
VISCOSITY [POISE]
10^6
10^5
10^4
10^3
TEMPERATURE [°C]
10
23
36
49
62
75
88
101
114
127
140

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 93 30 9172

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.5)
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D,Y	US-E-RE33093 (MICHAEL T. SCHIRALDEI ET AL.) & US-A-4 713 243 (MICHAEL T. SCHIRALDI ET AL.)	1-10	
P,Y	EP-A-0 551 626 (LEK) * claims *	1-10	
A	EP-A-0 386 960 (AMERICAN CYANAMID COMPANY) * claims *	1	
A	US-A-4 303 066 (MARK J. D'ANDREA) * abstract *	1	

TECHNICAL FIELDS SEARCHED (Int.Cl.5)

A61L

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	10 February 1994	ESPINOSA, M

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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EPO FORM 1503 03.82 (P04C01)

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	11775484
	Filing Date	2007-07-10
	First Named Inventor	Robert K. Yang
	Art Unit	1615
	Examiner Name	Unassigned
	Attorney Docket Number	1199-4B CIP

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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
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CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ None

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Andrew H. Berks, Reg. No. 36,089/	Date (YYYY-MM-DD)	2008-01-29
Name/Print	Andrew H. Berks	Registration Number	36089

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9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Acknowledgement Receipt

EFS ID:	2782531
Application Number:	11775484
International Application Number:	
Confirmation Number:	5059
Title of Invention:	UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS
First Named Inventor/Applicant Name:	Robert K. Yang
Customer Number:	23869
Filer:	Andrew Henry Berks/Barbara Thomas
Filer Authorized By:	Andrew Henry Berks
Attorney Docket Number:	1199-4B CIP
Receipt Date:	29-JAN-2008
Filing Date:	10-JUL-2007
Time Stamp:	15:14:18
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes) /Message Digest	Multi Part /.zip	Pages (if appl.)
1	Information Disclosure Statement (IDS) Filed	1199-4B_CIP_IDS2.pdf	12384203 d329a9c2db12fc58858a4ea4c9edd86dbe344b81	no	9

Warnings:	
Information:	

2	Foreign Reference	WO09215289A1.pdf	2708703 81787667d640edac405d1bd440f1ec8857c7c3fd	no	62
Warnings:					
Information:					
3	Foreign Reference	WO09505416A2.pdf	3314755 7df764cb4acb162cda19b6aec69d95ce08ec89fc	no	79
Warnings:					
Information:					
4	Foreign Reference	WO09518046A1.pdf	1771914 67d6836cdb0660dff4fbbdbb9e476a5487b2a8a8	no	44
Warnings:					
Information:					
5	Foreign Reference	WO03030882A1.pdf	3468456 8f85202ab23b4d8297ed315e6b4c3ecad7deae2a	no	77
Warnings:					
Information:					
6	Foreign Reference	WO03030883A1.pdf	3495280 5baea410922b241f8f9c793740402dad01a255e8	no	66
Warnings:					
Information:					
7	Foreign Reference	WO2005102287.pdf	2171625 c45129d979c558dbc4b349e80cced3497af6a88f	no	56
Warnings:					
Information:					
8	Foreign Reference	EP00598606A1.pdf	757025 df12c2c2c1dd57028f8f24397652ea9c20e15ed7	no	15
Warnings:					
Information:					
9	NPL Documents	Article-Lazaridou_et_al.pdf	1040475 d7cf9497dd8a02956e7f42a9c57174df2aef7623	no	12
Warnings:					
Information:					
10	NPL Documents	Article-Polyethylenglykole.pdf	95950 2ca2cf9dacb941aa3594d37057afad88a897dbbd	no	2
Warnings:					
Information:					

11	NPL Documents	Article-Repka-Bioadhesive.pdf	821731 83f1a5cfe7cc8dbdef7937a303dee6980ac283ca	no	12
Warnings:					
Information:					
12	NPL Documents	Article-Repka-Vitamin_E.pdf	529225 cbb6e7065d42c273f2c0706006a3f51c6b64dc37	no	8
Warnings:					
Information:					
13	Information Disclosure Statement (IDS) Filed	1199-4B_CIP_IDS3.pdf	5544883 1ed253fea14b60194ccbfac5fc7521ea71e81a03	no	6
Warnings:					
Information:					
			Total Files Size (in bytes):	38104225	

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National Stage of an International Application under 35 U.S.C. 371
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New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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APPLICATION NUMBER	FILING OR 371(c) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
11/775,484	07/10/2007	Robert K. Yang	1199-4B CIP

CONFIRMATION NO. 5059

23869
HOFFMANN & BARON, LLP
6900 JERICHO TURNPIKE
SYOSSET, NY11791

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

Publication No. US-2008-0044454-A1
Publication Date: 02/21/2008

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Office of Public Records. The Office of Public Records can be reached by telephone at (703) 308-9726 or (800) 972-6382, by facsimile at (703) 305-8759, by mail addressed to the United States Patent and Trademark Office, Office of Public Records, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently http://pair.uspto.gov/. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Pre-Grant Publication Division, 703-605-4283

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): Yang et al.	Examiner: Melissa Mercier
Application No.: 11/775,484	Group Art Unit: 1615
Filed: July 10, 2007	Docket: 1199-4B CIP
For: UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS	Dated: July 7, 2010

Confirmation No. 5059

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT AND RESPONSE TO RESTRICTION REQUIREMENT

Sir:

In response to the Restriction Requirement dated June 7, 2010, a response to which is due by July 7, 2010, the Applicant responds as follows:

Amendments to the claims begin on page 2 of this submission.

Remarks begin on page 10 of this submission.

Amendments to the Claims

This listing of claims shall replace all previous listings of claims:

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

5. (Original) The drug delivery composition of claim 1, wherein the taste-masking agent is a polymer.

6. (Original) The drug delivery composition of claim 1, wherein the taste-masking agent is a water-soluble polymer.

7. (Original) The drug delivery composition of claim 6, wherein said water-soluble polymer has an average molecular weight of equal to or greater than about 40,000.

8. (Original) The drug delivery composition of claim 1, wherein the 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.

9. (Original) The drug delivery composition of claim 1, wherein the uniformity is determined by the presence of no more than a 10% by weight of drug variance throughout said matrix.

10. (Original) The drug delivery composition of claim 9, wherein said drug variance is less than 5% by weight.

11. (Original) The drug delivery composition of claim 9, wherein said drug variance is less than 2% by weight.

12. (Original) The drug delivery composition of claim 9, wherein said drug variance is less than 0.5% by weight.

13. (Original) The drug delivery composition of claim 1, wherein the coated particulate bioeffecting agent has a shape selected from the group consisting of spherically shaped particles, ellipsoidally shaped particles, irregularly shaped particles, and combinations thereof.

14. (Original) The drug delivery composition of claim 1, wherein said taste-masking agent is present in the amount of about 15-80% by weight of the particle.

15. (Original) The drug delivery composition of claim 1, wherein said taste-masking agent is present in the amount of about 20-60% by weight of the particle.

16. (Original) The drug delivery composition of claim 1, wherein said taste-masking agent is present in the amount of about 25-35% by weight of the particle.

17. (Original) The drug delivery 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.

18. (Currently Amended) A thin film drug delivery composition comprising:

(a) an edible water-soluble film forming matrix comprising at least one water-soluble polymer comprising polyethylene oxide alone or in combination with a hydrophilic cellulosic polymer; and

(b) a coated particulate active component uniformly stationed therein;

wherein the coating on the particulate active component is a taste-masking ~~and/or controlled-release~~ agent, and

wherein the active component is uniformly distributed in the film composition.

19. (Original) The drug delivery composition of claim 18, wherein said thin film drug delivery composition is extruded.

20. (Currently Amended) The drug delivery composition of claim 18, wherein the taste-masking ~~and/or controlled-release~~ agent is a thin film coating over the particulate active component.

21. (Currently Amended) The drug delivery composition of claim 18, wherein the taste-masking ~~and/or controlled release~~ agent is a water-soluble polymer.

22. (Original) The drug delivery composition of claim 18, wherein the composition is free of added plasticizers, surfactants, or polyalcohols.

23. (Original) The drug delivery composition of claim 18, wherein the at least one water-soluble polymer comprises about 20% to about 100% by weight polyethylene oxide.

24. (Original) The drug delivery composition of claim 18, wherein the at least one water-soluble polymer comprises a hydrophilic cellulosic polymer in a ratio of up to about 4:1 with polyethylene oxide.

25. (Withdrawn) 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.

26. (Withdrawn) A method of preparing a thin film drug delivery vehicle comprising:

(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 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.

27. (Withdrawn) The method of claim 26, wherein said drying includes applying heat to the bottom of said carrier surface.

28. (Withdrawn) The method of claim 26, wherein said pharmaceutically active agent / taste-masking agent complex comprises a particulate active agent and a thin film coating of said taste-masking agent over said particulate active agent.

29. (Withdrawn) A method of preparing a thin film drug delivery vehicle having a substantially uniform distribution of components comprising:

(a) forming a masterbatch pre-mix of an edible water-soluble polymer component and water;

(b) feeding a predetermined amount of the premix to at least one mixer;

(c) adding to the at least one mixer a predetermined amount of a taste-masked active component comprising a particulate active component and a taste masking agent coating the particulate active component;

(d) mixing the premix and the taste-masked active component in the at least one mixer to form a uniform matrix;

(e) forming a wet film from the matrix;

(f) rapidly forming a visco-elastic film by applying hot air currents to the bottom side of the wet film with substantially no top air flow; and

(g) drying the visco-elastic film to form a self-supporting edible film.

30. (Withdrawn) The method of claim 29, wherein the wet film is fed onto a substrate having a top and a bottom side, and the wet film forms a visco-elastic film by applying hot air currents to the bottom side of the substrate while minimizing air flow on the top side of the film.

31. (Withdrawn) The method of claim 29, wherein the taste-masked active component is stable for a sufficient time prior to drying for the visco-elastic film to form a self-supporting edible film.

32. (Withdrawn) The method of claim 29, wherein the temperature at which the film is dried does not exceed 100° C.

33. (Withdrawn) The method of claim 29, wherein the temperature at which the film is dried does not exceed 80° C.

34. (Withdrawn) A process for making a self-supporting, edible film having a substantially uniform distribution of components comprising:

(a) forming a premix of an edible water-soluble polymer component containing polyethylene oxide and optionally one or more additional polymers;

(b) blending into the premix a taste-masked active component comprising a particulate active component coated with a taste masking agent, to form a uniform matrix;

(c) extruding a film from the matrix; and

(d) cooling the film to form a self-supporting edible film.

35. (New) The drug delivery composition of claim 1, wherein the taste-masking agent is selected from the group consisting of 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.

36. (New) The drug delivery composition of claim 1, wherein said bioeffecting agent is selected from the group consisting of 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.

Remarks

The Examiner has required restriction of the pending claims. Claims 1-34 are pending. The Examiner requires election between the following Groups pursuant 35 U.S.C § 121, as follows:

Group I:	Claims 1-17 drawn to a drug delivery composition, classified in class 424, subclass 439;
Group II:	Claims 18-24, drawn to a thin film drug delivery composition, classified in class 424, subclass 484;
Group III:	Claim 25, drawn to a drug delivery vehicle, classified in class 424, subclass 484;
Group IV:	Claims 26-28, drawn to a method of preparing a thin film drug delivery vehicle, classified in class 514, subclass 400+;
Group V:	Claims 29-33, drawn to a method of preparing a thin film vehicle having a substantially uniform distribution of components, classified in class 514, subclass 400+; and
Group VI:	Claim 34, drawn to a method of preparing a self supporting, edible film having a substantially uniform distribution of components, classified in class 514, subclass 400+.

The Examiner alleged that the various groups were unrelated for various reasons. In particular, with respect to Groups I and II (which, coincidentally are in the same class), the Examiner stated that the coating of Group II can have either a taste masking or controlled release agent. Further, the Examiner alleged that the film in Group II is not required to be flow able.

The Applicant has amended the independent claim of Group II (claim 18) to recite that the coating on the particulate active component is a taste-masking agent. It is further noted that the independent claim of Group I (claim 1) does not recite a flowable film, rather it recites a flowable film forming matrix, which is "capable of being dried without loss of uniformity in the

stationing of said particulate bioeffecting agent therein." One of ordinary skill in the art would understand that a film-forming matrix is used to form the final film composition. Claims 1 and 18 (and those dependent thereon) are directed to film compositions.

Given the present amendment to claim 18, it is respectfully requested that claims 1-17 and claims 18-24 be maintained and examined together. There is no added burden on the Examiner to search these two groups.

In view of the requirement for restriction, the Applicant elects to prosecute the claims of Group I, including claims 1-17. In light of the amendments submitted herein, the Applicant respectfully requests that the amended claims 18-24 be considered along with claims 1-17. It is further noted that the requirement for restriction has been made, at least in part, between product claims and method claims, and that the Applicant has elected claims directed to the product. Should these claims be allowable, the Applicant will seek to rejoin those method claims that recite the same limitations of the allowed product claims.

The Applicant makes this election without prejudice to seeking rejoinder of the withdrawn claims or to filing one or more divisional applications directed to any non-elected groups. The Applicant further makes the amendments herein without prejudice to filing one or more divisional applications seeking claims directed to the now-canceled language of the claims of Group II.

New claims 35-36 have been added, which are dependent upon claim 1 and further define the scope of the invention. In particular, claim 35 defines the taste masking agent of claim 1, and claim 36 further defines the bioeffective agent of claim 1. Support for these amendments may be found, for example, at paragraphs [0107] and [0132] of the application as filed. No new matter is introduced through this amendment. These claims are part of Group I, and are thus elected herein.

Fees due with two new dependent claims are due with this submission, and the

Commissioner is authorized to charge payment of these fees to Deposit Account No. 08-2461. No other fees are due. However, if any additional fee should be due, the Commissioner is hereby authorized to charge payment of any fees associated with this communication to Deposit Account No. 08-2461. Such authorization includes authorization to charge fees for extensions of time, if any, under 37 C.F.R § 1.17 and also should be treated as a constructive petition for an extension of time in this reply or any future reply pursuant to 37 C.F.R. § 1.136.

In view of the documents submitted herewith, Applicant respectively urges that the application is in condition for examination. Please direct any questions regarding this submission to Applicant's undersigned agent.

Respectfully submitted,

/Jon A. Chiodo/
Jon A. Chiodo
Registration No. 52,739
Attorney for Applicants

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Electronic Patent Application Fee Transmittal

Application Number:	11775484
Filing Date:	10-Jul-2007
Title of Invention:	UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS
First Named Inventor/Applicant Name:	Robert K. Yang
Filer:	Jon Anthony Chiodo/Shannon Farischon
Attorney Docket Number:	1199-4B CIP

Filed as Small Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Claims in excess of 20	2202	2	26	52
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**52**

Electronic Acknowledgement Receipt

EFS ID:	7966875
Application Number:	11775484
International Application Number:	
Confirmation Number:	5059
Title of Invention:	UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS
First Named Inventor/Applicant Name:	Robert K. Yang
Customer Number:	23869
Filer:	Jon Anthony Chiodo/Shannon Farischon
Filer Authorized By:	Jon Anthony Chiodo
Attorney Docket Number:	1199-4B CIP
Receipt Date:	07-JUL-2010
Filing Date:	10-JUL-2007
Time Stamp:	14:33:19
Application Type:	Utility under 35 USC 111(a)

Payment information:

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Payment Type	Deposit Account
Payment was successfully received in RAM	$52
RAM confirmation Number	810
Deposit Account	082461
Authorized User	

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Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		1199_4B_CIP_Amendment_Reponse_Restriction_Requirement_07072010.pdf	96281 b4acfa01831c7c8490d1fbd56447f742e3e0908e	yes	12

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Response to Election / Restriction Filed	1	1
	Claims	2	9
	Applicant Arguments/Remarks Made in an Amendment	10	12

Warnings:

Information:

2	Fee Worksheet (PTO-875)	fee-info.pdf	30429 11b6ef83aa2cc4b3c818a4f3b3e10082b7137386	no	2

Warnings:

Information:

Total Files Size (in bytes):	126710

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☒ To be Mailed
11/775,484	07/10/2007	

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY ☒ RATE ($)	SMALL ENTITY ☒ FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	07/07/2010	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 36	Minus	** 34	= 2	X $26 =	52	OR	X $ =	
	Independent (37 CFR 1.16(h))	* 6	Minus	***6	= 0	X $110 =	0	OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE	52	OR	TOTAL ADD'L FEE	

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)	OR	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/KATRINA HARLING/

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/775,484	07/10/2007	Robert K. Yang	1199-4B CIP	5059

23869 7590 09/09/2010
HOFFMANN & BARON, LLP
6900 JERICHO TURNPIKE
SYOSSET, NY 11791

EXAMINER	
MERCIER, MELISSA S	
ART UNIT	PAPER NUMBER
1615	
MAIL DATE	DELIVERY MODE
09/09/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	11/775,484	YANG ET AL.	
	Examiner	Art Unit	
	MELISSA S. MERCIER	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) *25-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24,35 and 36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1-29-08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election of Group I, comprising claims 1-17 in the reply filed on July 7, 2010 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Additionally in view of Applicants arguments and amendment to claim 18, Group II, comprising claims 18-24 have been rejoined with Group I.

Therefore, claims 1-24 and newly presented claims 35 and 36 are under prosecution in this application. Claims 25-34 are withdrawn as reading on non elected groups.

Priority

Applicant's claim of priority date of October 12, 2001 is present in the filing of Provisional Application 60/328,868.

Information Disclosure Statement

Receipt of the three Information Disclosure Statements filed on January 29, 2008 is acknowledged. Signed copies are attached to this office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-17 and 35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claim 1, Applicant has not particularly pointed out how the combined particulate and taste masking agents can have a particle size of 200 microns or less when they are intimately associated with each other. It is the understanding of the Examiner that an intimate admixture is a mixture and not a coated particle. Therefore, Applicant has not pointed out if both the particulate bioeffecting agent and the taste masking agent have the claimed particle size or if the particle size is only applicable when the taste making agent is coated on the particulate bioeffecting agent.

Regarding claim 35, the phrase "such as" and “including” renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-5, 8-12, 14-19, 22, and 35-36 are rejected under 35 U.S.C. 102(e) as being anticipated by Bess et al. (US Patent 7,067,116).

Bess discloses fast dissolving orally consumable solid film containing a taste masking agent and a pharmaceutically active agent at weight ratio of dissolving 1:3 to 3:1 (Title). The films include a water soluble film forming polymer and a taste masked pharmaceutically active agent (abstract).

Examples of water soluble film forming polymers include pullulan, HPMC, hydroxyethyl cellulose, hydropropyl cellulose, PVP, carboxymethyl cellulose PVA, sodium alginate, PEG, xanthan gum, for example (column 5, lines 1-16).

The active agents include antimicrobial agents, NSAIDS, anti-tussives, decongestants, anti-histamines, expectorants, anti-diarrheals, PPI's, CNS depressants and stimulants (columns 2 and 3).

The taste masking agent is an ion exchange resin includes synthetic polymer of acrylic acid, methacrylic acid, sulfonated styrene, and sulfonated divinylbenzene or partially synthetic polymers of modified celluloses and dextrans (column 4, lines 1-24). Less preferred embodiments partially taste masking agents of magnesium trisilicate and polymers such as Eudragit E and/or cellulosics, such as ethylcellulose (column 4, lines 60-67).

The active agents adsorbed to the ion exchange resin is in the range from about 25-75% by weight of the pharmaceutically active agent/resin adsorption complex, thereby meeting the limitations of claims 14-15. The recitation of adsorption complex would necessarily result in a thin film coating over portions of the agent.

The pharmaceutically active agent/resin adsorption complex can also be coated in the range from about 40 to about 70% w/w pharmaceutically active agents/resin complex. Variation in the amount of coating and/or the use of coating/uncoated complex mixtures can be employed to selectively modify the dissolution profile (column 11, lines 43-53).

The particle size of the coated and uncoated pharmaceutically active agent/resin adsorption complex is about 60-200 microns (column 11, lines 54-58).

Plasticizers, surfactants, and polyalcohol's are optional ingredients; therefore, they are not required by Bess in order for the film to perform as disclosed.

The films can additionally include polyethylene oxide compound (column 8, line 15-18).

Regarding claim 19, Bess discloses his formulations are cast on a suitable substrate and dried to form a film (column 8, lines 47-48); however, this is considered a product by process limitation. Applicant is directed to MPEP 2112 which discloses "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985).

Since the methods of preparing the films disclosed in the reference recite numerous mixing steps of the same structural elements as recited in the instant claims,

it is the position of the Examiner that absent of showing of evidence to the contrary, the films would inherently possess the same uniformity as recited in instant claims 9-12.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-12, 17, and 35-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al. (WO 00/42992) in view of Ghana et al (US Patent 5,653,993).

Chen discloses a water soluble hydrocolloid; mucosal surface coated forming film, having an effective dose of an active agent (page 3, lines 30-33).

The hydrocolloid includes a polymer selected from the group consisting of natural, semi-natural and synthetic biopolymers (page 4, lines 1-3).

The active agents is selected from the group consisting of therapeutic agents, dietary supplements, and hygiene aids, for example sildenafil citrate, nicotine, hydromorphone, oxybutynine, or estradiol (page 4, lines 7-10). The active agent can be encapsulated in a material that is different than the hydrocolloid. Encapsulation is additionally utilized to achieve masking of taste of active agents that are bitter (page 9, lines 13-15).

The hydrocolloid is a water soluble non gelling natural polysaccharide, polypeptide or protein (page 14, lines 12-31).

The films can be cast or extruded (page 15-16).

Chen does not disclose the particle size of the encapsulated active agents.

Ghanta discloses the preparation of taste masked microcapsules. The encapsulating material is cellulose acetate phthalate and gelatin (abstract).

The average/mean microcapsule diameter ranges from about 25 to about 600 microns (column 3, lines 59-62).

The gelatin used can be of any origin so long as it is of pharmaceutical grade. The gelatin, for example, can have a number average molecular weight of about 27,000 to 70,000 (column 4, lines 43-47).

It would have been within the skill of the ordinary practitioner to have used the particle size disclosed by Ghanta in order to make the encapsulated active agents utilized by Chen since both references discloses the particles are suitable for taste masking and Ghanta discloses they do not form agglomerates (column 3, lines 33-35), thereby allowing for a more uniform distribution.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have selected the particle size of the microcapsules in Chen since Ghanta discloses in order to make wider use of NSAIDs while substantially eliminating the bitter taste, aftertaste and adverse mouth feel and make these drugs more pleasant upon taking them orally, there has long been desired a way to insure delivery of these drugs in their desired concentrations while avoiding their extremely bitter taste, lingering aftertaste and adverse mouth feel effects referred to above connected with their ingestion orally, thereby encouraging patient compliance.

Claims 1-4, 9-13, 17-20, and 22-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schiraldi et al. (US Patent 4,713,243) in view of Grass et al. (US Patent 3,237,596).

Schiraldi discloses a bioadhesive extruded single or multilayered thin film having a water soluble or swellable polymer matrix, bioadhesive layer consists essentially of 40-95% by weight of a hydroxypropyl cellulose, 5-60% of a homopolymer of ethylene oxide, 0-10% of a water-insoluble polymer such as ethyl cellulose, propyl cellulose, polyethylene and polypropylene, and 2-10% of a plasticizer, said film having incorporated therein a medicament, such as anesthetics, analgesics, anticaries agents, anti-inflammatories, antihistamines, antibiotics, antibacterials, fungistats, etc (abstract).

Schiraldi does not disclose the medicament being coated with a taste masking polymer having a particle size of 200 microns or less.

Grass discloses a method of coating discrete solids. The solids have a particle size of about 5 to about 200 microns (column 1, lines 10-15). Spherical particles of acetaminophen coated with 12-hydroxystearyl alcohol are disclosed in the Examples.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have employed the method of coating medicaments as disclosed by Grass for incorporation into the films disclosed by Schiraldi in order to achieve the taste masking, sustained dissolution, enteric properties, improved stability, delayed interaction, wettability, and improved flow properties of the active agent for incorporation into drug formulation.

Claims 18-21 and 23-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schiraldi et al. (US Patent 4,713,243) in view of Thakur et al. (US 2004/0156901).

The teaching of Schiraldi are discussed above and applied in the same manner.

Schiraldi does not disclose the medicament being coated with a taste masking water soluble polymer

Thakur discloses particulate cores of active agents coated with a taste masking polymer, preferably cellulose acetate (paragraph 0034), which is a water soluble polymer.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have used coated active agents, as discussed by Thakur in

order to provide dosage forms in which pharmaceutical agents with unappealing tastes can be masked and allow for increased patient compliance.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MELISSA S. MERCIER whose telephone number is (571)272-9039. The examiner can normally be reached on 8:00am-4:30pm Mon through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert A. Wax can be reached on (571) 272-0623. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Melissa S Mercier/
Examiner, Art Unit 1615

/Carlos A. Azpuru/
Primary Examiner, Art Unit 1617

Notice of References Cited	Application/Control No. 11/775,484	Applicant(s)/Patent Under Reexamination YANG ET AL.	
	Examiner MELISSA S. MERCIER	Art Unit 1615	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-7,067,116	06-2006	Bess et al.	424/78.1
*	B	US-5,653,993	08-1997	Ghanta et al.	424/440
*	C	US-4,713,243	12-1987	Schiraldi et al.	424/676
*	D	US-3,237,596	03-1966	GRASS JR GEORGE M et al.	118/62
*	E	US-2004/0156901	08-2004	Thakur et al.	424/471
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
*	N	WO0042992	07-2000	WO	Chen	A61K 9/70
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	11775484	YANG ET AL.
	Examiner	Art Unit
	MELISSA S MERCIER	1615

SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
East-see attached	9-6-10	MMercier
Palm inventor search	9-6-10	MMercier

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner

/MELISSA S MERCIER/ Examiner.Art Unit 1615	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(Not for submission under 37 CFR 1.99)

Application Number	11775484
Filing Date	2007-07-10
First Named Inventor	Robert K. Yang
Art Unit	1615
Examiner Name	Unassigned
Attorney Docket Number	1199-4B CIP

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	4569837		1986-02-11	Suzuki et al.	
	2	4593053		1986-06-03	Jevne	
	3	4608249		1986-08-26	Otsuka et al.	
	4	4615697		1986-10-07	Robinson	
	5	4623394		1986-11-18	Nakamura et al.	
	6	4652060		1987-03-24	Miyake	
	7	4659714		1987-04-21	Watt-Smith	
	8	4675009		1987-07-23	Hymes et al.	

/Melissa Mercier/ (09/03/2010)

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /MM/

Receipt date: 01/29/2008	Application Number	11775484	11775484 - GAU: 1615
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**	Filing Date	2007-07-10	
	First Named Inventor	Robert K. Yang	
	Art Unit	1615	
	Examiner Name	Unassigned	
	Attorney Docket Number	1199-4B CIP	

	9	4695465		1987-09-22	Kigasawa et al.	
	10	4704119		1987-11-03	Shaw et al.	
	11	4713239		1987-12-15	Babaian et al.	
	12	4713243		1987-12-15	Schiraldi et al.	
	13	4722761		1988-02-02	Cartmell et al.	
	14	4740365		1988-04-26	Yukimatsu et al.	
	15	4748022		1988-05-31	Busciglio	
	16	4765983		1988-08-23	Takayanagi et al.	
	17	4772470		1988-09-20	Inoue et al.	
	18	4777046		1988-10-11	Iwakura et al.	
	19	4789667		1988-12-06	Makino et al.	

/Melissa Mercier/ (09/03/2010)

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /MM/

Receipt date: 01/29/2008	Application Number	11775484	11775484 - GAU: 1615
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**	Filing Date	2007-07-10	
	First Named Inventor	Robert K. Yang	
	Art Unit	1615	
	Examiner Name	Unassigned	
	Attorney Docket Number	1199-4B CIP	

	20	4849246		1989-07-18	Schmidt	
	21	4860754		1989-08-29	Sharik et al.	
	22	4876092		1989-10-24	Mizobuchi et al.	
	23	4876970		1989-10-31	Bolduc	
	24	4888354		1989-12-19	Chang et al.	
	25	4894232		1990-01-16	Reul et al.	
	26	4900552		1990-02-13	Sanvordeker et al.	
	27	4900554		1990-02-13	Yanagibashi et al.	
	28	4900556		1990-02-13	Wheatley et al.	
	29	4910247		1990-03-20	Haldar et al.	
	30	4915950		1990-04-10	Miranda et al.	

/Melissa Mercier/ (09/03/2010)

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /MM/

	31	4925670		1990-05-15	Schmidt	
	32	4927634		1990-05-22	Sorrentino et al.	
	33	4927636		1990-05-22	Hijiya et al.	
	34	4937078		1990-06-26	Mezei et al.	
	35	4940587		1990-07-10	Jenkens et al.	
	36	4948580		1990-08-14	Browning	
	37	4958580		1990-09-25	Asaba et al.	
	38	4978531		1990-12-18	Keiko et al.	
	39	4981693		1991-01-01	Higashi et al.	
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Receipt date: 01/29/2008	Application Number	11775484	11775484 - GAU: 1615
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**	Filing Date	2007-07-10	
	First Named Inventor	Robert K. Yang	
	Art Unit	1615	
	Examiner Name	Unassigned	
	Attorney Docket Number	1199-4B CIP	

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	48	5166233		1992-11-24	Kuroya	
	49	5186938		1993-02-16	Sablotsky et al.	
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	3	199518046	WO		1995-07-06			☐
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Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	Lazaridou et al.; Thermophysical properties of chitosan, chitosan-starch and chitosan-pullulan films near the glass transition; Carbohydrate Polymers, Applied Science Publishers, Ltd; Barking, GB, Vol. 48, No. 2, May 1, 2002, pp. 170-190	☐
	2	XP-002298105; Polyethylenglykole; Internet: www.roempp.com; 09/20/2004	☐
	3	Repka et al.; Influence of Vitamin E. TPGS on the properties of hydrophilic films produced by hot-melt extrusion; International Journal of Pharmaceutics; Vol. 202, pp 63-70; 2000	☐
	4	Repka et al.; Bioadhesive properties of hydroxypropylcellulose topical films produced by hot-melt extrusion; Journal of Controlled Release; Vol. 70; pp 341-351; 2001	☐

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EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	96	edible SAME film AND (active drug medicant medicament) SAME (particle particulate) AND micron	USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/09/05 10:47
L2	291	edible SAME film AND (active drug medicant medicament) SAME (particle particulate) AND micron	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/09/05 11:02
L3	308	edible SAME film AND (active drug medicant medicament) SAME (particle particulate) AND (coat encapsulate)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/09/05 13:23
L4	177	"4713243"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/09/05 13:28
L5	52	"6284264"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/09/05 13:46
L6	47	"5393528"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/09/05 13:49
L7	17	"1110546"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/09/05 13:52

EAST Search History (Prior Art)

L8	19068	film AND (active drug medicant medicament) SAME particle adj1 size	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/09/05 13:53
L9	5583	film AND (active drug medicant medicament) SAME particle adj1 size SAME (coat coating coated encapsulate encapsulated)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/09/05 13:54
L10	89	edible WITH film AND (active drug medicant medicament) SAME particle adj1 size SAME (coat coating coated encapsulate encapsulated)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/09/05 13:55
L11	45	"4849246"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/09/05 14:02
L12	3	"0514691"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/09/05 14:09
L13	0	"0514691A"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/09/05 14:10
L14	0	"EP0514691"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/09/05 14:10
L15	37	taste adj1 masking SAME (active drug medicant medicament) SAME particle adj1 size	USPAT	OR	ON	2010/09/05 14:20

EAST Search History (Prior Art)

L16	19	taste adj1 masking SAME (active drug medicant medicament) SAME particle adj1 size AND film	USPAT	OR	ON	2010/09/05 14:24
L17	37	taste adj1 masking SAME (active drug medicant medicament) SAME particle adj1 size	USPAT	OR	ON	2010/09/05 14:29
L18	21	taste adj1 masking SAME (drugactive drug medicant medicament) SAME particle adj1 size	USPAT	OR	ON	2010/09/05 14:35
L19	37	taste adj1 masking SAME (drug active drug medicant medicament) SAME particle adj1 size	USPAT	OR	ON	2010/09/05 14:35
L20	159	taste adj1 masking SAME (drug active drug medicant medicament) SAME particle adj1 size	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/09/05 14:35
L21	45	"5215755"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/09/05 15:14
L22	47	taste adj1 masking SAME (drug active drug medicant medicament) SAME particle adj1 size AND spherical	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/09/05 15:41

INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(Not for submission under 37 CFR 1.99)

Application Number	11775484
Filing Date	2007-07-10
First Named Inventor	Robert K. Yang
Art Unit	1615
Examiner Name	Unassigned
Attorney Docket Number	1199-4B CIP

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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	0307537		1884-11-04	Foulks	
	2	0688446		1901-12-10	Stempel	
	3	2142537		1939-01-03	Tisza	
	4	2277038		1942-03-24	Curtis	
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	Attorney Docket Number	1199-4B CIP	

	9	3444858		1969-05-20	Russell	
	10	3536809		1970-10-27	Applezweig	
	11	3551556		1970-12-29	Kliment et al.	
	12	3598122		1971-08-10	Zaffaroni	
	13	3632740		1972-01-04	Robinson et al.	
	14	3640741		1972-02-08	Etes	
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	16	3731683		1973-05-08	Zaffaroni	
	17	3753732		1973-08-21	Boroshok	
	18	3814095		1974-06-04	Lubens	
	19	3892905		1975-07-01	Albert	

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	20	3911099		1975-10-07	DeFoney et al.	
	21	3972995		1976-08-03	Tsuk et al.	
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	23	3998215		1976-12-21	Anderson et al.	
	24	4029757		1977-06-14	Mlodozeniec et al.	
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	26	4031200		1977-06-21	Reif	
	27	4123592		1978-10-31	Rainer et al.	
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	29	4136145		1979-01-23	Fuchs et al.	
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	31	4139627		1979-02-13	Lane et al.	
	32	4226848		1980-10-07	Nagai et al.	
	33	4251400		1981-02-17	Columbus	
	34	4292299		1981-09-28	Suzuki et al.	
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	37	4307075		1981-12-22	Martin	
	38	4325855		1982-04-20	Dickmann	
	39	4373036		1983-02-08	Chang et al.	
	40	4406708		1983-09-27	Hesselgren	
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	43	4460562		1984-07-17	Keith et al.	
	44	4466973		1984-08-21	Rennie	
	45	4503070		1985-03-05	Eby	
	46	4515162		1985-05-07	Katsuhiro	
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	48	4529601		1985-07-16	Broberg et al.	
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	50	4562020		1985-12-31	Hijiya et al.	

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	6	0250187	EP		1993-09-29			☐
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	15	5629003		1997-05-13	Horstmann et al.	
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	20	6177096		2001-01-23	Zerbe et al.	
	21	6153210		2000-11-28	Roberts et al.	
	22	6231957		2001-05-15	Zerbe et al.	
	23	6284264		2001-09-04	Zerbe et al.	
	24	6375963		2002-04-23	Repka et al.	
	25	RE33093		1989-10-17	Schiraldi et al.	
	26	4631837		1986-12-30	Magoon	
	27	6072100		2000-06-06	Mooney et al.	

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	1	20020127254		2002-09-12	Fotinos et al.	

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Yang et al.	Examiner:	Melissa Mercier
Application No.:	11/775,484	Group Art Unit:	1615
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Confirmation No.	5059	Dated:	December 9, 2010

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

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Dated: December 9, 2010

Signature: /Marcy Mancuso/

AMENDMENT AND RESPONSE PURSUANT TO 37 C.F.R. §1.111

Sir:

In response to the Office Action dated September 9, 2010, a response to which is due by December 9, 2010, the Applicant responds as follows:

Amendments to the claims begin on page 2 of this submission.

Remarks begin on page 10 of this submission.

Amendments to the Claims

This listing of claims shall replace all previous listings of claims:

1. (Currently Amended) 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; and wherein the uniformity is determined by the composition having a variation of drug content of less than 10% per film unit.

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

5. (Original) The drug delivery composition of claim 1, wherein the taste-masking agent is a polymer.

6. (Original) The drug delivery composition of claim 1, wherein the taste-masking agent is a water-soluble polymer.

7. (Original) The drug delivery composition of claim 6, wherein said water-soluble polymer has an average molecular weight of equal to or greater than about 40,000.

8. (Original) The drug delivery composition of claim 1, wherein the 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.

9. (Cancelled)

10. (Currently amended) The drug delivery composition of claim ~~9~~ 1, wherein said ~~drug variance~~ variation of drug content is less than 5% by weight per film unit.

11. (Currently amended) The drug delivery composition of claim ~~9~~ 1, wherein said ~~drug variance~~ variation of drug content is less than 2% by weight per film unit.

12. (Currently amended) The drug delivery composition of claim ~~9~~ 1, wherein said ~~drug variance~~ variation of drug content is less than 0.5% by weight per film unit.

13. (Original) The drug delivery composition of claim 1, wherein the coated particulate bioeffecting agent has a shape selected from the group consisting of spherically shaped particles, ellipsoidally shaped particles, irregularly shaped particles, and combinations thereof.

14. (Original) The drug delivery composition of claim 1, wherein said taste-masking agent is present in the amount of about 15-80% by weight of the particle.

15. (Original) The drug delivery composition of claim 1, wherein said taste-masking agent is present in the amount of about 20-60% by weight of the particle.

16. (Original) The drug delivery composition of claim 1, wherein said taste-masking agent is present in the amount of about 25-35% by weight of the particle.

17. (Original) The drug delivery 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.

18. (Currently Amended) A thin film drug delivery composition comprising:

(a) an edible water-soluble film forming matrix comprising at least one water-soluble polymer comprising polyethylene oxide alone or in combination with a hydrophilic cellulosic polymer; and

(b) a coated particulate active component uniformly stationed therein;

wherein the coating on the particulate active component is a taste-masking agent, and

wherein the active component is uniformly distributed in the film composition; and wherein the uniformity is determined by the composition having a variation of drug content of less than 10% per film unit.

19. (Original) The drug delivery composition of claim 18, wherein said thin film drug delivery composition is extruded.

20. (Previously presented) The drug delivery composition of claim 18, wherein the taste-masking agent is a thin film coating over the particulate active component.

21. (Previously presented) The drug delivery composition of claim 18, wherein the taste-masking agent is a water-soluble polymer.

22. (Original) The drug delivery composition of claim 18, wherein the composition is free of added plasticizers, surfactants, or polyalcohols.

23. (Original) The drug delivery composition of claim 18, wherein the at least one water-soluble polymer comprises about 20% to about 100% by weight polyethylene oxide.

24. (Original) The drug delivery composition of claim 18, wherein the at least one water-soluble polymer comprises a hydrophilic cellulosic polymer in a ratio of up to about 4:1 with polyethylene oxide.

25. (Withdrawn) 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.

26. (Withdrawn) A method of preparing a thin film drug delivery vehicle comprising:

(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 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.

27. (Withdrawn) The method of claim 26, wherein said drying includes applying heat to the bottom of said carrier surface.

28. (Withdrawn) The method of claim 26, wherein said pharmaceutically active agent / taste-masking agent complex comprises a particulate active agent and a thin film coating of said taste-masking agent over said particulate active agent.

29. (Withdrawn) A method of preparing a thin film drug delivery vehicle having a substantially uniform distribution of components comprising:

(a) forming a masterbatch pre-mix of an edible water-soluble polymer component and water;

(b) feeding a predetermined amount of the premix to at least one mixer;

(c) adding to the at least one mixer a predetermined amount of a taste-masked active component comprising a particulate active component and a taste masking agent coating the particulate active component;

(d) mixing the premix and the taste-masked active component in the at least one mixer to form a uniform matrix;

(e) forming a wet film from the matrix;

(f) rapidly forming a visco-elastic film by applying hot air currents to the bottom side of the wet film with substantially no top air flow; and

(g) drying the visco-elastic film to form a self-supporting edible film.

30. (Withdrawn) The method of claim 29, wherein the wet film is fed onto a substrate having a top and a bottom side, and the wet film forms a visco-elastic film by applying hot air currents to the bottom side of the substrate while minimizing air flow on the top side of the film.

31. (Withdrawn) The method of claim 29, wherein the taste-masked active component is stable for a sufficient time prior to drying for the visco-elastic film to form a self-supporting edible film.

32. (Withdrawn) The method of claim 29, wherein the temperature at which the film is dried does not exceed 100° C.

33. (Withdrawn) The method of claim 29, wherein the temperature at which the film is dried does not exceed 80° C.

34. (Withdrawn) A process for making a self-supporting, edible film having a substantially uniform distribution of components comprising:

(a) forming a premix of an edible water-soluble polymer component containing polyethylene oxide and optionally one or more additional polymers;

(b) blending into the premix a taste-masked active component comprising a particulate active component coated with a taste masking agent, to form a uniform matrix;

(c) extruding a film from the matrix; and

(d) cooling the film to form a self-supporting edible film.

35. (Currently amended) The drug delivery composition of claim 1, wherein the taste-masking agent is selected from the group consisting of 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.

36. (Previously presented) The drug delivery composition of claim 1, wherein said bioeffecting agent is selected from the group consisting of 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.

Remarks

Claims 1-8 and 10-36 are pending in this application. Claims 25-34 have been withdrawn from consideration by the Examiner. By this Amendment, claim 9 is cancelled and claims 1, 10, 11, 12, 18, and 35 are amended. Support for the amendments to the claims may be found, for example, in the original claims, and the specification. No new matter is added.

In view of the foregoing amendments and following remarks, reconsideration and allowance are respectfully requested.

I. Rejection under 35 U.S.C. §112, Second Paragraph

The Office Action rejects claims 1-17 and 35 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In particular, the Examiner asserts that "Applicant has not particularly pointed out how the combined particulate and taste masking agents can have a particle size of 200 microns or less when they are intimately associated with each other." Moreover, the Examiner asserts that "Applicant has not pointed out if both the particulate bioeffecting agent and the taste masking agent have the claimed particle size or if the particle size is only applicable when the taste masking agent is coated on the particulate bioeffecting agent." *See* Office Action, page 3, second paragraph.

Applicants respectfully disagree with the Examiner and traverse the rejection. Claim 1 clearly recites that "the **combined particulate and taste-masking agent** have a particle size of 200 microns." Accordingly, it would be clear to one skilled in the art that, regardless of whether the combined particulate bioeffecting agent is intimately associated with the taste masking agent or whether the particulate bioeffecting is coated with the taste masking agent, it is the

combination of the particulate bioeffecting agent and the taste masking agent that has a particle size of 200 microns. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

The Examiner also rejects claim 35 for containing the terms "such as" and "including." Without conceding the propriety of the rejections, claim 35 is amended to more clearly recite various novel features of the claimed invention, with particular attention to the Examiner's comments. Specifically, claim 35 is amended to delete the terms "such as" and "including," thereby obviating the rejection. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

II. Rejection Under 35 U.S.C. §102

The Office Action rejects claims 1-5, 8-12, 14-19, 22, and 35-36 under 35 U.S.C. §102(e) as being anticipated by U.S. Patent No. 7,067,116 to Bess et al. ("Bess"). Applicants respectfully traverse the rejection.

It is well settled that a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *See* MPEP §2131.

Independent claims 1 and 18 require that "the active component is uniformly distributed in the film composition; and wherein the uniformity is determined by the composition having a variation of drug content of less than 10% per film unit." Bess does not teach or suggest such a feature.

At most Bess teaches that its process involves "adding the oil mixture to the hydrated polymer gel and mixing until uniform; deaerating the film until air bubbles are removed, casting

the uniform mixture on a suitable substrate; and drying the cast mixture to form a film." *See* column 12, lines 13-17.

The instant specification teaches that the ability to achieve the uniformity of content within the claimed range is directly related to Applicants' drying technique. *See* for example paragraphs [0068] and [0069]. Nowhere does Bess teach or suggest the difficulties of achieving uniformity of content in cast films, nor steps or processes to overcome the inherent difficulties in doing so.

Moreover, claim 18 requires "the coating on the particulate active component is a taste-masking agent." Bess fails to teach or suggest such a feature.

Although Bess discloses a presence of a coating, nowhere does Bess teach or suggest a coating that is a taste-masking agent, as claimed.

The Examiner asserts that "the recitation of adsorption complex would necessarily result in a thin film coating over portions of the agent." *See* Office Action, page 4, last paragraph. Applicants respectfully disagree. Although, Bess discloses the taste masking agent as an ion exchange resin, the ion exchange resin does not necessarily form a coating. At most, Bess teaches that "The ratio of the pharmaceutically active agent adsorbate to ion exchange resin adsorbent in the adsorption complex is about 1:3 to about 3:1, preferably about 1:2 to about 2:1, most preferably about 1:1. The only limit to using ratios in excess of 1:3 is an economic and aesthetic one." *See* column 9, lines 55-60. Nowhere does Bess teach or suggest a taste-masking coating, as required by claim 18 and Bess fails to teach or suggest "the active component is uniformly distributed in the film composition; and wherein the uniformity is determined by the composition having a variation of drug content of less than 10% per film unit," as required by claims 1 and 18.

Accordingly Bess does not anticipate independent claims 1 and 18. Claims 2-5, 8-12, 14-17, 19, 22, and 35-36 variously depend from claims 1 and 18 and, thus, also are not anticipated by Bess. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

III. Rejections Under 35 U.S.C. §103

A. Chen in view of Ghana

The Office Action rejects claims 1–12, 17, and 35-36 under 35 U.S.C. §103(a) over PCT Publication No. WO 00/42992 to Chen et al. ("Chen") in view of U.S. Patent No. 5,653,993 to Ghana et al. ("Ghana"). Applicants respectfully traverse the rejection.

Chen is cited for its alleged disclosure of water soluble hydrocolloid, mucosal coating, an effective dose of agent. The Examiner acknowledges that Chen fails to teach or suggest the particle size of the encapsulated active agents. *See* Office Action, page 7, line 12. Nevertheless, the Examiner cites Ghana as allegedly curing the deficiencies of Chen.

By this Amendment, independent claim 1 is amended to recite that "the active component is uniformly distributed in the film composition; and wherein the uniformity is determined by the composition having a variation of drug content of less than 10% per film unit." Chen and Ghana, whether considered independently or combined, fail to teach or suggest such features.

Neither Chen nor Ghana disclose the difficulties of achieving uniformity of content in cast films, nor steps or processes to overcome the inherent difficulties in doing so. Thus, the Examiner has not provided any rationale to modify Chen or Ghana in order to arrive at the presently claimed invention.

The claimed invention is directed to solving the problems associated with achieving a taste-masked drug which is uniformly distributed throughout a film, such that individual dosage units cut from the film will have the same amount of drug in them and will be pleasant tasting.

There are several problems addressed by the present invention. One such problem is the delivery of bad-tasting actives in a dosage form which inherently exposes a high degree of the active to the taste buds. This is because most films are relatively thin by nature with planar surfaces and such the active is readily exposed to the taste buds as the film is dissolved. Thus, in view of the relatively large surface area of exposure, determining the proper size of the taste-masked particles was an important finding. Drug delivery films are not only relatively thin, but often dimensionally small. Thus, the smaller particles allow for a more uniform distribution to be readily achieved. Particles which are too large may self aggregate and cause a loss of uniformity of drug content per unit volume of film. Particles which are too large will also require more taste-masking material to effectively cover the active. Additionally, particles larger than 200 microns will present a gritty mouth feel and may be thicker than the film per se.

In short, the claimed invention solves the problems associated with effective delivery of a uniform amount of taste masked drug in a film dosage unit.

In particular, self aggregation or conglomeration of particles leads to **non-uniformity** of distribution of the drug in the film. The failure to achieve a high degree of accuracy with respect to the amount of active ingredient in dosage cut from the film can be harmful to the patient and may not meet the stringent governmental or agency standards relating to variation of active in dosage forms.

Self aggregation in film containing a pharmaceutical active increases the probability of perception of an unpleasant tasting film, as well as destroys the uniformity of the pharmaceutical agent in the film.

The claimed invention introduces a composition and processes as a solution that overcomes the above-mentioned problems.

Such a solution includes specific features such as particle size; maintaining the uniform distribution of active components by locking-in or substantially preventing migration of the active components within the visco-elastic film and resulting film product; and particular taste-masking agents.

Although Chen discloses the use of taste-modifying agents in a film dosage form, Chen 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. Therefore, Chen does not recognize the problem to be solved by the claimed invention, i.e. attaining low adjuvant content, high-taste-masked pharmaceutical active content films which have enhanced flexibility, structural integrity and **uniformity** (emphasis added). *See* page 3, lines 20-22.

Uniformity is important in oral film products, particularly products intended for delivery of pharmaceutical actives such that regulatory approval of the product may be obtained. As further explained on page 22 of the present application, the films prepared in accordance with the present invention have a "high degree of uniformity of the components of the film [which] makes them particularly well suited for incorporating pharmaceuticals". (lines 26-29). Specifically, the film products have:

> 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.
>
> (page 38, lines 16-20).

In contrast, Chen fails to teach or suggest and has absolutely no appreciation for the need to achieve dried films that are uniform in content.

As further evidence that Chen completely fails to appreciate uniformity, Chen merely discloses conventional hot air oven drying. Chen describes that the film is "dried under aeration at a temperature between 40-100°C so as to avoid destabilizing the agents contained within the formulation." (page 15, lines 28-29). Chen, however, does not disclose or even contemplate using the specific controlled, bottom-drying methods presently claimed. The only means of drying disclosed in the cited reference is the method of drying that the present application specifically seeks to avoid (uncontrolled air drying).

Ghana is cited for its alleged disclosure of a diameter ranges from about 25 to 600 microns. Ghana is directed to preparation of individual taste-masked microcapsules. Nowhere does Ghana teach or suggest film that is uniform in content, as required by the claims. Therefore, Ghana fails to cure the deficiencies of Chen. Therefore, Chen and Ghana, whether considered independent or combines fails to teach that "the active component is uniformly distributed in the film composition; and wherein the uniformity is determined by the composition having a variation of drug content of less than 10% per film unit."

Moreover, the Supreme Court addressed the standard for obviousness in its decision of *KSR International Co. v. Teleflex Inc.*, et al., 550 U.S. 389; 127 S.Ct. 1727; 167 L.Ed.2d 705; 82 U.S.P.Q.2d 1385 (2007). In order for an examiner to establish a prima facie case of obviousness

after KSR, some degree of predictability is necessary. (82 U.S.P.Q.2d at 1395-97). *Takeda Chemical Industries Ltd. V. Alphapharm Pty. Ltd.*, 83 USPQ.2d 1169 (Fed. Cir. 2007) is a post KSR decision in which the Federal Circuit articulated standards for establishing non-obviousness which again includes predictability of success. (83 USPQ.2d at 1176-79). Further, Section 2143.02 (II) of the MPEP states that "Obviousness does not require absolute predictability, however, at least some degree of predictability is required."

Clearly, the disclosure of Chen and Ghana does not provide sufficient predictability or expectation to support a prima facie case of obviousness as it fails to disclose, teach or suggest the drug delivery composition of the present invention.

Accordingly, the Examiner has not presented a prima facie case of obviousness as the examiner fails to present, inter alia, any evidence that the drug delivery composition contains the elements and properties, as claimed, nor has the Examiner presented any rationale to modify the cited references to arrive at the claimed composition.

Thus, claim 1 would not have been rendered obvious by Chen and Ghana. Claims 2–12, 17, and 35-36 depend from claim 1 and, thus, also would not have been rendered obvious by Chen and Ghana. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

B. Schiraldi in view of Grass

The Office Action rejects claims 1–4, 9-13, 17-20, and 22-23 under 35 U.S.C. §103(a) over U.S. Patent No. 4,713,243 to Schiraldi et al. ("Schiraldi") in view of U.S. Patent No. U.S. Patent No. 3,237,596 to Grass et al. ("Grass"). Applicants respectfully traverse the rejection.

The Examiner acknowledges that Schiraldi does not teach all the limitations provided by the claims, but alleges that Grass remedies the deficiencies of Schiraldi. The Examiner asserts that Grass teaches a method of coating discrete solids that have a particle size of 5 to 200 microns thus is easily combinable with Schiraldi. Applicants respectfully disagree.

Applicants wish to remind the Examiner of the "*Basic Requirements of a Prima Facie Case of Obviousness*", which can be found in M.P.E.P. §2143. According to these requirements, the following are necessary to establish a prima facie case of obviousness: (1) a reference or combination of references must provide some suggestion or motivation to modify the reference or to combine the teachings; (2) there must be a reasonable expectation of success; and (3) there must be a teaching or suggestion of all claim limitations.

Schiraldi is directed to a bioadhesive extruded film. Schiraldi describes a process for obtaining their bioadhesive extruded films. The components are all described as "powders" that are blended and then extruded by passing them through heated stainless steel rollers. Nowhere in Schiraldi is it disclosed or suggested that the components are uniformly distributed throughout the final end product. As the Examiner notes, the components are merely blended together.

The Examiner has not provided any teaching to suggest that the extruded film of the present invention is uniform. Nothing in the reference suggests that simply blending components guarantees uniformity. Furthermore, a liquid plasticizer is added to the powder blend during the blending process. According to Schiraldi, 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."

Thus, the films of Schiraldi must be extruded, and Schiraldi teaches away from a casted film product. "The film of the present invention has the advantage of being an extruded film,

rather than a cast film." (Schiraldi, col. 3, ll. 64-65). Accordingly, one of skill in the art would not find that the components utilized by Schiraldi would provide a casted film.

Grass is cited for its alleged disclosure of the particle size of about 5 to about 200 microns. Grass is directed to a method of coating discrete solids having a particular particle size. Nowhere does Grass teach or suggest film that is uniform in content, as required by the claims. Therefore, Grass fails to cure the deficiencies of Schiraldi.

Moreover, there is no rationale suggested in Schrialdi that the extruded film should be modified to be a casted film. Furthermore, there is no rationale suggested by Grass that its method can be used in a casted film product. In addition, there is no level of predictability in the teaching of Schiraldi that their components could be used in a casted film. There is also no level of predictability in the teachings of Grass that their formulations would be useful in a casted film product.

There is no rationale in Schiraldi or Grass to modify their teachings, in order to arrive at the claimed invention. Furthermore, there is no predictability in the teachings of Schiraldi or Grass to lead one of skill in the art to arrive at the present invention with any expectation of success. Moreover, the combination of Schiraldi and Grass does not teach all the claim limitations.

Therefore, independent claims 1 and 18 would not have been rendered obvious by Schiraldi and Grass. Claims 2–4, 9-13, 17, 19, 20, 22, and 23 variously depend from claims 1 and 18 and, thus, also would not have been rendered obvious by Schiraldi and Grass. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

C. Schiraldi in view of Thakur

The Office Action rejects claims 18-21 and 23-24 under 35 U.S.C. §103(a) over Schiraldi in view of U.S. Patent No. U.S. Publication No. 2004/0156901 to Thakur e al. ("Thakur").

The Examiner acknowledges that Schiraldi fails to teach or suggest that the medicament is coated with a taste-masking water soluble polymer. *See* Office Action, page 9, 3rd paragraph. Nevertheless, the Examiner cites Thakur as allegedly curing Schiraldi's deficiencies. Applicants respectfully traverse the rejection.

For at least the reasons mentioned above, Schiraldi fails to teach or suggest all the features of claims 1 and 18. Thakur is cited for its alleged teaching particulate cores of actives agents coated with taste-masking polymer. Thakur's disclosure is directed to "a solid dosage formulation of topiramate intended primarily for use by pediatric patients, or for patients who have difficulty swallowing tablets." *See* Abstract. Nowhere does Thakur teach or suggest film that is uniform in content, as required by the claims. Therefore, Thakur fails to cure the deficiencies of Schiraldi. Therefore, Schiraldi and Thakur, whether considered independent or combines fails to teach that "the active component is uniformly distributed in the film composition; and wherein the uniformity is determined by the composition having a variation of drug content of less than 10% per film unit."

Moreover, similar to the arguments stated above in regards to Grass, there is no rationale in Schiraldi or Thakur to modify their teachings. Furthermore, there is no predictability in the teachings of Schiraldi or Thakur to lead one of skill in the art to arrive at the present invention with any expectation of success. Moreover, the combination of Schiraldi and Thakur does not teach all the claim limitations. Applicants therefore respectfully request reconsideration and withdrawal of the Section 103 rejection based thereon.

IV. Conclusion

In view of the foregoing, it is respectfully submitted that this application is in condition for allowance. Favorable reconsideration and prompt allowance of the application are earnestly solicited.

Should the Examiner believe that anything further would be desirable in order to place this application in even better condition for allowance, the Examiner is invited to contact the undersigned at the telephone number set forth below.

Respectfully submitted,

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Application Number:	11775484
International Application Number:	
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Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		Amendment_and_Response.pdf	164555 13388a2192b087f5d60f0afeaf619d79714a0d45	yes	21

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New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
11/775,484	07/10/2007	

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY ☒ RATE ($)	SMALL ENTITY ☒ FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT 12/09/2010

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 35	Minus	** 36	= 0	X $26 =	0	OR	X $ =	
Independent (37 CFR 1.16(h))	* 6	Minus	***6	= 0	X $110 =	0	OR	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE	0	OR	TOTAL ADD'L FEE	

AMENDMENT

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/AMANDA FORD/

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	11775484
Filing Date	2007-07-10
First Named Inventor	Robert K. Yang
Art Unit	1615
Examiner Name	Mercier, Melissa S.
Attorney Docket Number	1199-4 B CIP

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	3007848		1961-11-07	J.H. Stroop	
	2	4478658		1984-10-23	Wittwer	
	3	5044761		1991-09-03	Yuhki et al.	
	4	5605696		1997-02-25	Eury et al.	
	5	5733575		1998-03-31	Mehra et al.	
	6	5800832		1998-09-01	Tapolsky et al.	
	7	5806284		1998-09-15	Gifford	
	8	5881476		1999-03-16	Strobush et al.	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	11775484
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	First Named Inventor	Robert K. Yang
	Art Unit	1615
	Examiner Name	Mercier, Melissa S.
	Attorney Docket Number	1199-4 B CIP

	9	6660292	B2	2003-12-09	Zerbe et al.	
	10	6800239	B2	2004-10-05	Horstmann et al.	
	11	6824829	B2	2004-11-30	Berry et al.	
	12	7005142	B2	2006-02-28	Leon et al.	
	13	7579019	B2	2009-08-25	Tapolsky et al.	

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U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20050048102	A1	2005-03-03	Tapolsky et al.	
	2	20070148097	A1	2007-06-28	Finn et al.	

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FOREIGN PATENT DOCUMENTS Remove

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] ¡	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	11775484
	Filing Date	2007-07-10
	First Named Inventor	Robert K. Yang
	Art Unit	1615
	Examiner Name	Mercier, Melissa S.
	Attorney Docket Number	1199-4 B CIP

	1	1 510 999	GB		1978-05-17	Schering Aktiengesellschaft		☐
	2	WO 03/030881	WO	A1	2003-04-17	Kosmos Pharma		☐
	3	WO 2008/011194	WO	A2	2008-01-24	Biodelivery Sciences International, Inc.		☐

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Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1		☐

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EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	11775484
	Filing Date	2007-07-10
	First Named Inventor	Robert K. Yang
	Art Unit	1615
	Examiner Name	Mercier, Melissa S.
	Attorney Docket Number	1199-4 B CIP

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☒ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ None

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Julie Tabarovsky, Reg. No. 60,808/	Date (YYYY-MM-DD)	2010-12-15
Name/Print	Julie Tabarovsky	Registration Number	60,808

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**