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:

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

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.

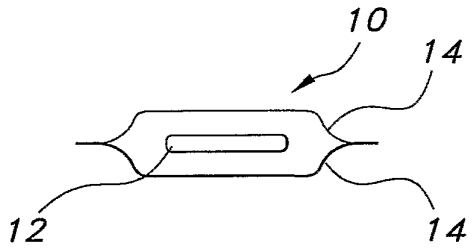

FIG. 1

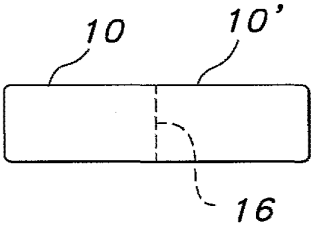

FIG. 2

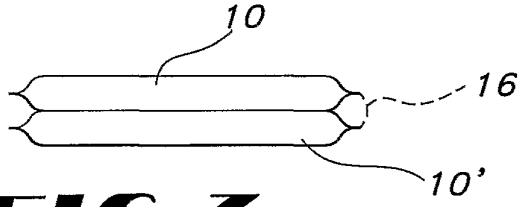

FIG. 3

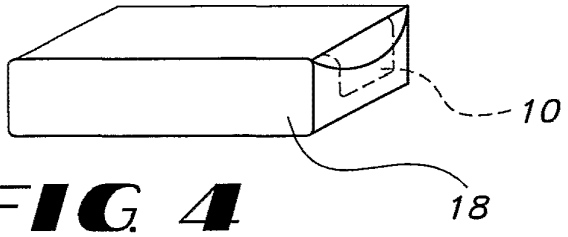

FIG. 4

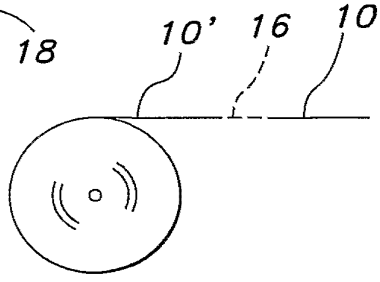

FIG. 5

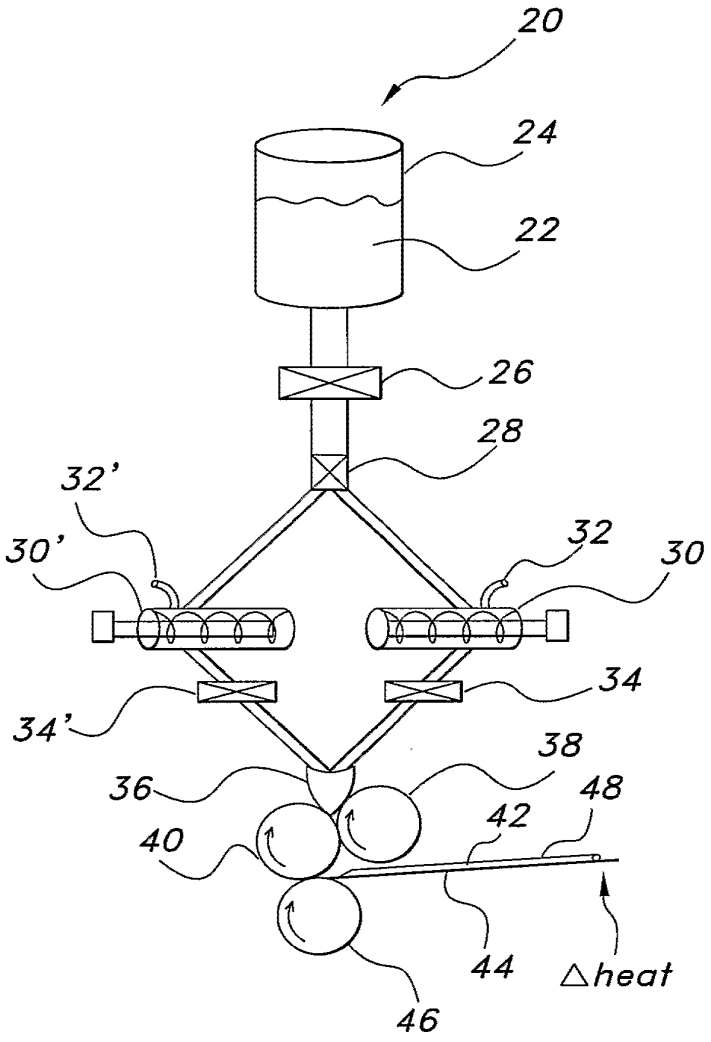

FIG. 6

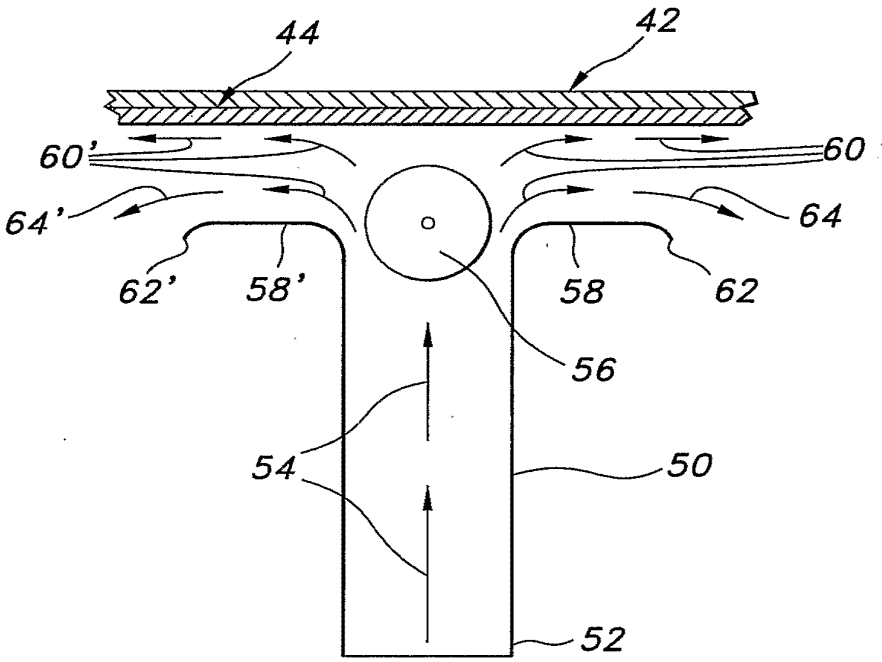

FIG. 7

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

"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

INTERNATIONAL SEARCH REPORT

Inte ıal Application No
PCT/US 02/32594

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
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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

national application No.
PCT/US 02/32594

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

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

2. ☒ Claims Nos.: 1-79 (in part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-79 (in part)

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

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

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

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte al Application No
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PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL SEARCHING AUTHORITY

To:
Scola, Daniel A. Jr.
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ETATS-UNIS D'AMERIQUE

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference 1199-82 PCT	Date of mailing *(day/month/year)* 11 April 2011 (11-04-2011)
International application No. PCT/US2010/044488	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
Applicant Reckitt Benckiser Healthcare (UK) Limited	International filing date *(day/month/year)* 5 August 2010 (05-08-2010)

1. [X] The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the International Search Report.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Fascimile No.: (41-22) 338.82.70

   For more detailed instructions, see *PCT Applicant's Guide*, International Phase, paragraphs 9.004 - 9.011.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. [ ] **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   [ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

   [ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. Following the expiration of 30 months from the priority date, these comments will also be made available to the public.

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before completion of the technical preparations for international publication (Rules 90*bis*.1 and 90*bis*.3).

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

Name and mailing address of the International Searching Authority	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040 Fax: (+31-70) 340-3016	LóPEZ NAVARRO, Angela Tel: +49 (0)89 2399-6027

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
1199-82 PCT		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US2010/044488	05/08/2010	07/08/2009
Applicant		
Reckitt Benckiser Healthcare (UK) Limited		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language,** the international search was carried out on the basis of:
      [X] the international application in the language in which it was filed
      [ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. [ ] This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [ ] **Certain claims were found unsearchable** (See Box No. II)

3. [ ] **Unity of invention is lacking** (see Box No III)

4. With regard to the **title,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings,**
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      [ ] as suggested by the applicant
      [ ] as selected by this Authority, because the applicant failed to suggest a figure
      [ ] as selected by this Authority, because this figure better characterizes the invention
   b. [ ] none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/044488

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/00 A61K31/485

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	"SUBOXONE Subligualtabletten" In: Verlag Rote Liste Service GmbH: "ROTE LISTE 2008" 2008, Verlag Rote Liste Service GmbH , Frankfurt/Main , XP002624986page 39018, the whole document	1-31
X	EP 1 897 543 A1 (EURO CELTIQUE SA [LU]) 12 March 2008 (2008-03-12) paragraphs [0016] - [0024], [0 31], [0039] - [0043], [0047] - [0053], [0056], [0057], [0060], [0061], [0079], [0082], [0093], [0100]; claims 1-10	1-31

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family 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
25 February 2011	11/04/2011

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, Fax: (+31-70) 340-3016	Toulacis, C

2

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/044488

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GB 2 447 016 A (RECKITT BENCKISER HEALTHCARE [GB]) 3 September 2008 (2008-09-03) the whole document	1-31
A	US 2005/192309 A1 (PALERMO PHILIP J [US] ET AL) 1 September 2005 (2005-09-01) the whole document	1-31
A	WO 03/030883 A1 (KOSMOS PHARMA [US]; FUISZ RICHARD C [US]; YANG ROBERT K [US]; MYERS GA) 17 April 2003 (2003-04-17) the whole document	1-31

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2010/044488

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 1897543 A1	12-03-2008	AU 2007291245 A1	06-03-2008
		CA 2661759 A1	06-03-2008
		DE 202006018608 U1	10-05-2007
		EP 2059243 A1	20-05-2009
		WO 2008025791 A1	06-03-2008
		JP 2010501628 T	21-01-2010
		US 2010087470 A1	08-04-2010
GB 2447016 A	03-09-2008	AR 065579 A1	17-06-2009
		AU 2008220574 A1	04-09-2008
		CA 2678582 A1	04-09-2008
		CL 6062008 A1	03-10-2008
		CN 101626766 A	13-01-2010
		EP 2129380 A1	09-12-2009
		WO 2008104738 A1	04-09-2008
		JP 2010520186 T	10-06-2010
		KR 20090117891 A	13-11-2009
		PE 01682009 A1	19-03-2009
		US 2011046172 A1	24-02-2011
		ZA 200905664 A	27-10-2010
US 2005192309 A1	01-09-2005	NONE	
WO 03030883 A1	17-04-2003	CA 2473970 A1	17-04-2003
		EP 1458367 A1	22-09-2004
		JP 2005536443 T	02-12-2005

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Applicant's or agent's file reference see form PCT/ISA/220 1197-80 PCT	Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet) APRIL 11, 2011 **FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2010/044488	05.08.2010	07.08.2009

International Patent Classification (IPC) or both national classification and IPC
INV. A61K9/00 A61K31/485

Applicant
Reckitt Benckiser Healthcare (UK) Limited

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Toulacis, C Telephone No. +49 89 2399-8638

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:

   a. (means)

      ☐ on paper

      ☐ in electronic form

   b. (time)

      ☐ in the international application as filed

      ☐ together with the international application in electronic form

      ☐ subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-31
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-31
Industrial applicability (IA)	Yes:	Claims	1-31
	No:	Claims	

2. Citations and explanations

see separate sheet

V

Reference is made to the following documents:

D1= Verlag Rrote Liste Service GmbH: "SUBOXONE Subligualtabletten" In: Verlag Rote Liste Service GmbH: "ROTE LISTE 2008", 2008, Verlag Rote Liste Service GmbH, Frankfurt/Main, XP002624986, page 39018,

D2 = EP 1 897 543 A1 (EURO CELTIQUE SA [LU]) 12 March 2008 (2008-03-12)

D3 = WO 03/030883 A1 (KOSMOS PHARMA [US]; FUISZ RICHARD C [US]; YANG ROBERT K [US]; MYERS GA) 17 April 2003 (2003-04-17)

Claims 1-31

(N)

The subject-matter of claims 1-31 is novel over document D1 and D2 either due to the defined dosage form being a **film** or to the presence of a **buffer.**

In context with novelty it is pointed out that the expressions:

i) "... in an amount to provide a local pH of said composition of a value sufficient to optimize absorption of said buprenorphine" (claims 1, 17, 24)

ii) "... in an amount sufficient to inhibit the absorption of said naloxone when administered orally" (claim 11)

iii) "... a buffer capacity sufficient to maintain the ionization of naloxone during the time which said composition is in the oral cavity of a user"

iv) "... having a bioequivalent release profile as a tablet containing about 2 times the amount of buprenorphine or a pharmaceutically acceptable salt thereof." (claim 26),

do not imply any delimiting technical feature to the claimed subject-matter, since they characterise the invention by indication of the result to be achieved and are considered to be unclear (Art. 6 PCT).

Characterisation of the invention or one of its features by indication of the result to be achieved is not permissible unless the invention can only be defined in such terms and if the result is one which can be directly and positively verified by tests or procedures adequately specified in the description and involving nothing more than trial and error (cf. Guidelines for Examination, chapter III, 4.7 PCT).

These prerequisite conditions are, however, not fulfilled in the present case.

In the present case it is possible to define the subject-matter in more concrete terms; i.e. a defined pH.

(IS)

The object of the present application is to provide an orally dissolvable **film** that provides the desired absorption levels of the agonist and antagonist, while providing an adhesive effect in the mouth, rendering it difficult to remove once placed in the mouth, thereby making abuse of the agonist difficult (description of the present application page 2, lines 12-15).

Said object has been achived by using a polymer carrier matrix and forming an orally dissolvable film comprising the active ingredients of the sublingual tablet, marketed under the the trade name Suboxone®.

The Applicant provided comparative data showing that the absorption and the in vivo absorption data of the presently claimed sublingual film compositions and the sublingual tablet, marketed under the the trade name Suboxone®, are bioequivalent (see Tables 1-12).

Said results however, are considered to be expected by the person skilled in the art being aware of documents D1 and D2.

The sublingual tablets disclosed in document D1 comprise already the pair agonist/ antagonist (Buprenorphine-HCl/Naloxon-HCL) in the presently claimed amounts and the buffer citric acid / sodium citrate as presently claimed, providing already the desired results with regard to absorption and in vivo absorption of the active agents.

Thus, the only problem which has been solved is the transformation of the sublingual tablet Suboxone® into a sublingual film by using a polymeric carrier matrix.

Besides the fact that said transformation is considered to lie within the merits of the person skilled in the art without the exercise of inventive skill, document D2 does clearly teach said transformation (see D2; particularly paragraphs 60, 82, 93, 100).

According to the description only a certain pH combined with a certain buffer/ Naloxone ratio, provided results wich can be regarded as surprising.

Said features however, are not reflected in the present claims (see description; page 30, lines 12-15).

(IA) The industrial applicability is beyond any doubt.

Possible steps after receipt of the international search report (ISR) and written opinion of the International Searching Authority (WO-ISA)

General information	For all international applications filed on or after 01/01/2004 the competent ISA will establish an ISR. It is accompanied by the WO-ISA. Unlike the former written opinion of the IPEA (Rule 66.2 PCT), the WO-ISA is not meant to be responded to, but to be taken into consideration for further procedural steps. This document explains about the possibilities.
Amending claims under Art. 19 PCT	Within 2 months after the date of mailing of the ISR and the WO-ISA the applicant may file amended claims under Art. 19 PCT directly with the International Bureau of WIPO. The PCT reform of 2004 did not change this procedure. For further information please see Rule 46 PCT as well as form PCT/ISA/220 and the corresponding Notes to form PCT/ISA/220.
Filing a demand for international preliminary examination	In principle, the WO-ISA will be considered as the written opinion of the IPEA. This should, in many cases, make it unnecessary to file a demand for international preliminary examination. If the applicant nevertheless wishes to file a demand this must be done before expiry of 3 months after the date of mailing of the ISR/WO-ISA or 22 months after priority date, whichever expires later (Rule 54bis PCT). Amendments under Art. 34 PCT can be filed with the IPEA as before, normally at the same time as filing the demand (Rule 66.1 (b) PCT). If a demand for international preliminary examination is filed and no comments/amendments have been received the WO-ISA will be transformed by the IPEA into an IPRP (International Preliminary Report on Patentability) which would merely reflect the content of the WO-ISA. The demand can still be withdrawn (Art. 37 PCT).
Filing informal comments	After receipt of the ISR/WO-ISA the applicant may file informal comments on the WO-ISA directly with the International Bureau of WIPO. These will be communicated to the designated Offices together with the IPRP (International Preliminary Report on Patentability) at 30 months from the priority date. Please also refer to the next box.
End of the international phase	At the end of the international phase the International Bureau of WIPO will transform the WO-ISA or, if a demand was filed, the written opinion of the IPEA into the IPRP, which will then be transmitted together with possible informal comments to the designated Offices. The IPRP replaces the former IPER (international preliminary examination report).
Relevant PCT Rules and more information	Rule 43 PCT, Rule 43bis PCT, Rule 44 PCT, Rule 44bis PCT, PCT Newsletter 12/2003, OJ 11/2003, OJ 12/2003

XS CPRTENFRDE

BNSDOCID: <XS_____2006100103CF_I_>

Electronic Acknowledgement Receipt

EFS ID:	10352126
Application Number:	12537571
International Application Number:	
Confirmation Number:	5630
Title of Invention:	SUBLINGUAL AND BUCCAL FILM COMPOSITIONS
First Named Inventor/Applicant Name:	Garry L. Myers
Customer Number:	23869
Filer:	Jon Anthony Chiodo/Shannon Farischon
Filer Authorized By:	Jon Anthony Chiodo
Attorney Docket Number:	1199-82
Receipt Date:	21-JUN-2011
Filing Date:	07-AUG-2009
Time Stamp:	15:03:29
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) Form (SB08)	1199-82_IDS_STMT.pdf	807207 9fe9efc3f89e76c508a00ee09851d1df4da14c4d	no	19

Warnings:	
Information:	

This is not an USPTO supplied IDS fillable form					
2	Foreign Reference	DE2432925B2.pdf	391222 31b03fb8dd7b622286ae98b8b707f50370bfec53	no	6
Warnings:					
Information:					
3	Foreign Reference	DE2449865B2.pdf	273837 9094d15aa43d70ed8b36f51e834340053e143eeb	no	4
Warnings:					
Information:					
4	Foreign Reference	DE_3630603_w_English_Abstract.pdf	473031 a7c3616705649ce2d27193e90daeff412c71c437	no	6
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5	Foreign Reference	EP219762B1.pdf	691680 00180352a813744e991932d9e3b5fa43304cc54d	no	7
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Information:					
6	Foreign Reference	WO1991005540A1w_EnglishAbstract.pdf	623170 7fa940607619873a33efa12e4a8fb3de32abc5739	no	17
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7	Foreign Reference	EP0259749_w_English_Abstract.pdf	650101 5049296592640 14fddc8c722a4bd152e580f3b81	no	9
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8	Foreign Reference	EP200508.pdf	1586877 04d8ad292a54efc60d618a556f1fdf2415c3ddb3	no	26
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9	Foreign Reference	EP241178B1.pdf	713150 fd17806c2ff368a0de58c08e59b95cab5b894761	no	10
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10	Foreign Reference	WO1992015289A1.pdf	2708176 5ddd4574609d04e5cbb015b7d4617775d09661c9	no	62

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11	Foreign Reference	EP273069B1.pdf	950334 3957a122586025b03626d828e441a173c7f67d6b	no	14
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12	Foreign Reference	EP250187B1.pdf	788153 1d91a65ea276cb4606f5473e8d59f709d8bf4623	no	16
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13	Foreign Reference	EP0452446_w_English_Abstract.pdf	382212 64e9bdb364d3afc978b303e96fd3c5fc0536589c	no	6
Warnings:					
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14	Foreign Reference	EP381194B1.pdf	670081 811e68e8acf2352eb3e1f546592caa1d3717d7c1	no	9
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15	Foreign Reference	EP440462B1.pdf	700084 8fa5c8ac0d19b6525fa9e102d96e71cb90f9c9e4	no	13
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Information:					
16	Foreign Reference	WO1995005416A2A3.pdf	3478844 9fabf07120134421f793390edd3fd234709496c4	no	83
Warnings:					
Information:					
17	Foreign Reference	WO1995018046A1.pdf	1772429 ce750b5be32dada91f49dfa95f274655ebb01177	no	44
Warnings:					
Information:					
18	Foreign Reference	EP514691B1.pdf	408495 f12f400e62a4ed0b2d0669a84776274f84ad0b44	no	7
Warnings:					
Information:					
19	Foreign Reference	WO2000018365A2A3.pdf	2476690 a08eea64e625daa98dbed4f58db893d9e9c1f0	no	67

Warnings:					
Information:					
20	Foreign Reference	WO2000042992A2A3.pdf	1834840 c5a77377b828ce000b8341978b6b6119f4c4fc6c	no	49
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21	Foreign Reference	EP1110546A1.pdf	249442 a8307fe72a90ba74d9231cca3fa26da463531b81	no	15
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Information:					
22	Foreign Reference	WO2001070194A1.pdf	1701055 8526842f676005a9819842f76afb36599cc02ce8	no	41
Warnings:					
Information:					
23	Foreign Reference	WO2001091721A2A3.pdf	1174759 6eeebb9ef6524084ad46a3f0dd229658450a3de2	no	26
Warnings:					
Information:					
24	Foreign Reference	WO2008011194.pdf	2726713 613b5ffd421695cb22802db80f3339199b56d175	no	53
Warnings:					
Information:					
25	Foreign Reference	EP_0949925_w_english_abstract.pdf	569533 f0bbb504aa7230b4c24a6356f08ac9fade5d0c8c	no	7
Warnings:					
Information:					
26	Foreign Reference	EP1897543A1.pdf	152277 f9383de9292afe49e378a034484237c17fa958b2	no	12
Warnings:					
Information:					
27	Foreign Reference	GB2_447_016.pdf	1015317 5fec89c363a04268b027c9898b8f99ecffceacd2	no	27
Warnings:					
Information:					
28	Foreign Reference	WO2003030883A1.pdf	3494494 62a2556527b1212323da5441c165abdf[illegible]799a5	no	66

Warnings:					
Information:					
29	Non Patent Literature	Polymeric_Films_Article.pdf	656405 7fddc5908d2b28a1b43ccfc229a3c3f7bbe86be8	no	11
Warnings:					
Information:					
30	Non Patent Literature	Bodmeier_Article.pdf	681354 dacac3a30651640316697677 7efe926b909dc027	no	6
Warnings:					
Information:					
31	Non Patent Literature	Suboxone_Subligualtabletten.pdf	218682 336e4c8cd824819673fb761694adafbbf016e95d	no	1
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32	Non Patent Literature	ISR_PCTUS2010044488.pdf	250451 1d8e95a5a44fe5ed481388210fd518809c2139e1	no	5
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33	Non Patent Literature	Written_Opinion_PCTUS2010044488.pdf	567421 5fe7fd49a6089317597ab124aecf731b6bce7e4b	no	6
Warnings:					
Information:					
		Total Files Size (in bytes):	35838516		

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.

<u>New Applications Under 35 U.S.C. 111</u>
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	12537571
Filing Date	2009-08-07
First Named Inventor	Garry L. Myers
Art Unit	1633
Examiner Name	Joseph T. Woitach
Attorney Docket Number	1199-82

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	1	3007848		1961-11-07	J.H. Stroop	
	2	5605696		1997-02-25	Eury et al.	
	3	7579019	B2	2009-08-07	Tapolsky et al.	
	4	5806284		1998-09-15	Gifford	
	5	6072100		2000-06-06	Mooney et al.	
	6	6375963	B1	2002-04-23	Repka et al.	
	7	6800329	B2	2004-10-05	Horstmann et al.	
	8	6824829	B2	2004-11-30	Berry et al.	

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	1	20030107149	A1	2003-06-12	Yang et al.	
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	3	20040191302	A1	2004-09-30	Davidson	
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	1	0598606	EP	B1	1999-06-30	Johnson & Johnson Consumer Products, Inc.		☐

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	Application Number	12537571
	Filing Date	2009-08-07
	First Named Inventor	Garry L. Myers
	Art Unit	1633
	Examiner Name	Joseph T. Woitach
	Attorney Docket Number	1199-82

	2	0949925	EP	B1	1999-10-20	Lohmann Therapie Syst Lts.	English Abstract	☐
	3	62126950	JP		1987-06-09	Toshihiko et al.	English Abstract	☐
	4	02265444	JP		1990-10-30	Toshiaki et al.	English Abstract	☐
	5	05147140	JP		1993-06-15	Hirofumi et al.	English Abstract	☐
	6	07322812	JP		1995-12-12	Tomoyoshi et al.	English Abstract	☐
	7	2001279100	JP		2001-10-10	Masahiro	English Abstract	☐
	8	03/030882	WO	A1	2003-04-17	Kosmos Pharma		☐

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	1	Lazaridou et al., "Thermophysical proprties of chitosan, chitosan-starch and chitosan-pullulan films near the glass transition," Carbohydrate Polymers 48: 179-190 (2002).	☐
	2	Repka et al., "Bioadhesive Properties of hydroxypropylcellulose topical films produced by hot melt extrusion," Journal of Controlled Release, 70: 341-351 (2001).	☐

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	Attorney Docket Number	1199-82

	3	Repka et al., "Influence of Vitamin E TPGS on the properties of hydrophilic films produced by hot melt extrusion", International Journal of Pharmaceutics 202: 63-70 (2000).	☐

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	Examiner Name	Joseph T. Woitach
	Attorney Docket Number	1199-82

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).

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

Signature	/Jon A. Chiodo, Reg. No. 52,739/	Date (YYYY-MM-DD)	2011-03-15
Name/Print	Jon A. Chiodo	Registration Number	52739

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FLAT MEDICAMENT PREPARATION FOR THE APPLICATION AND RELEASE OF BUPRENORPHINE OR A PHARMACOLOGICALLY COMPARABLE SUBSTANCE IN THE BUCCAL CAVITY, AND METHOD OF PRODUCING THE SAME

Publication number: EP0949925 (A2)
Publication date: 1999-10-20
Inventor(s): CREMER KARSTEN [DE]; LUESSEN HENRIK [DE] +
Applicant(s): LOHMANN THERAPIE SYST LTS [DE] +
Classification:
- international: ***A61K31/485; A61K9/00; A61K9/20; A61K9/70; A61P25/04;*** (IPC1-7): A61K31/485; A61K9/70
- European: A61K31/485; A61K9/00M18D; A61K9/20K; A61K9/70; A61K31/485
Application number: EP19970952767 19971114
Priority number(s): DE19961052188 19961216; WO1997EP06369 19971114

Also published as:
EP0949925 (B1)
DE19652188 (A1)
DE19652188 (C2)
PT949925 (E)
NO992907 (A)
more >>

Cited documents:
EP0219762 (B1)
US4673679 (A)
FR2514642 (A1)
XP000361365 (A)

Abstract not available for EP 0949925 (A2)
Abstract of corresponding document: **DE 19652188 (A1)**

The invention concerns a solid medicament preparation which can decompose in aqueous media and has a flat-, foil-, paper- or wafer-type presentation for the application and release of active substances in the buccal cavity. The invention is characterized in that it contains buprenorphine, an active substance which is pharmacologically comparable thereto, or a therapeutically suitable salt of buprenorphine or of the pharmacologically comparable active substance.

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 949 925 B1

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PCT/EP1997/006369

(87) Internationale Veröffentlichungsnummer:
WO 1998/026780 (25.06.1998 Gazette 1998/25)

(54) **FLACHE ARZNEIZUBEREITUNG ZUR APPLIKATION UND FREISETZUNG VON BUPRENORPHIN ODER EINER PHARMAKOLOGISCH VERGLEICHBAREN SUBSTANZ IN DER MUNDHÖHLE UND VERFAHREN ZU IHRER HERSTELLUNG**

FLAT MEDICAMENT PREPARATION FOR THE APPLICATION AND RELEASE OF BUPRENORPHINE OR A PHARMACOLOGICALLY COMPARABLE SUBSTANCE IN THE BUCCAL CAVITY, AND METHOD OF PRODUCING THE SAME

PREPARATION MEDICAMENTEUSE PLATE POUR ADMINISTRER OU LIBERER, DANS LA CAVITE BUCCALE, DE LA BUPRENORPHINE OU UNE SUBSTANCE COMPARABLE SUR LE PLAN PHARMACOLOGIQUE ET PROCEDE PERMETTANT DE LA PREPARER

(84) Benannte Vertragsstaaten:
AT BE CH DE DK ES FI FR GB GR IE IT LI LU NL PT SE
Benannte Erstreckungsstaaten:
SI

(30) Priorität: **16.12.1996 DE 19652188**

(43) Veröffentlichungstag der Anmeldung:
20.10.1999 Patentblatt 1999/42

(73) Patentinhaber: **LTS LOHMANN Therapie-Systeme AG**
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Bussardweg 10
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(56) Entgegenhaltungen:
EP-A- 0 219 762 **FR-A- 2 514 642**
US-A- 4 673 679

- **J.P. CASSIDY ET AL.: "controlled buccal delivery of buprenorphine" JOURNAL OF CONTROLLED RELEASE, Bd. 25, Nr. 1/2, 27.Mai 1993, AMSTERDAM (NL), Seiten 21-29, XP000361365**

EP 0 949 925 B1

Printed by Jouve, 75001 PARIS (FR)

Beschreibung

[0001] Vorliegende Erfindung betrifft eine Arneizubereitung zur Applikation von Buprenorphin oder pharmakologisch vergleichbaren Wirkstoffen im Bereich der Mundhöhle bzw. der Mundschleimhaut. Sie betrifft insbesondere eine Zubereitung, die flach und als folien-, papier- oder oblatenartige Darreichungsform ausgestaltet ist.

[0002] Flache Wirkstoffträger wurden bereits für verschiedene Zwecke entwickelt und hergestellt. Als grundlegend für diese Darreichungsform kann die DE-OS 27 46 414 angesehen werden, die ein folienartiges Band aus Wirkstoff, Bindemittel und weiteren Hilfsstoffen beschreibt, bei dem aufgrund homogenen Dikke, Dichte und Breite ein direkter Zusammenhang zwischen einer Längeneinheit des Bandes und der darin enthaltenen Wirkstoffdosis besteht. Die Vorteile der kontinuierlichen Dosierbarkeit wurden auch von anderen Anmeldern erkannt und in speziellen Einzelvarianten beschrieben. So beschreibt DE-PS 36 30 603 ein flächiges Trägermaterial z.B. in Form eines Trennpapieres mit einer wirkstoffhaltigen Beschichtung, wobei letztere nach Vorzerteilung in Dosiereinheiten vom Trägermaterial dosisweise abziehbar ist.

[0003] Die Praktikabilität des flachen Formates im allgemeinen sowie die Vorteile bei der Herstellung der Darreichungsform und bei der Dosierung unter ihrer Anwendung wurden im Stand der Technik erkannt. Darüber hinaus lassen sich weitere Vorteile solcher Darreichungsformen ableiten, wie etwa die Bedruckbarkeit einer relativ großen Fläche auf der Arzneiform im Verhältnis zu ihrem Gewicht, womit die Einnahmesicherheit erhöht werden kann, wie auch die Möglichkeit der diskreten Einnahme, ohne daß Flüssigkeit zur Verfügung steht.

[0004] Trotz dieser klaren Vorteile haben sich solche Darreichungsformen bisher kaum durchgesetzt. Offensichtlich reicht für viele Hersteller von Pharmazeutika der Nutzen gegenüber konventionellen Darreichungsformen nicht aus, um Produkte dieser Art mit den gebräuchlichen Wirkstoffen zu entwickeln und deren arzneimittelrechtliche Zulassung zu betreiben. Darüber hinaus können vorhandene Produktionsmaschinen und existierendes Knowhow für diese neuartigen Produkte nicht genutzt werden; ein hoher Investitionsbedari: würde entstehen. Trotz der oben beschriebenen Vorteile von flächen- film- oder papierartigen Darreichungsformen ist der therapeutische und/oder wirtschaftliche Nutzen bei der Verabreichung von gängigen, auch peroral applizierbaren Wirkstoffen im Vergleich zu konventionellen Tabletten anscheinend nicht so groß, daß er die Kosten der Umstellung auf diese Darreichungsformen rechtfertigen würde.

[0005] Zu den Wirkstoffen, dies sich nur wenig für eine perorale Verabreichung eignen, zählt das in der Schmerztherapie seit Jahren erfolgreich eingesetzte Opiat Buprenorphin. Nach peroraler Applikation ist es kaum bioverfügbar, d. h. erscheint nur in einem sehr geringen Ausmaß von wenigen Prozent der eingenommenen Dosis im Blutkreislauf (McQuay & Moore, in: Buprenorphine, Hrsg. Cowan & Lewis, New York 1995). Der Grund für die mangelnde Bioverfügbarkeit liegt vermutlich im weitgehenden Abbau der Substanz während der ersten Leberpassage nach der gastrointestinalen Resorption ("First-pass Effekt"). Eine Möglichkeit, den First-pass-Effekt bei der oralen Verabreichung zu umgehen, besteht darin, den Wirkstoff bereits an der Mundschleimhaut zur Resorption zu bringen. Wirkstoff, welcher hier ins Blut übertritt, muß nicht als erstes das Pfortadersystem und damit in konzentrierter Form die den Wirkstoff metabolisierende Leber passieren, um in den zentralen Körperkreislauf zu gelangen. Voraussetzung für eine buccale oder sublinguale Applikation ist jedoch die ausreichende Permeabilität der oralen Mucosa für den Wirkstoff unter Berücksichtigung der notwendigen Dosis. Die Permeabilität wiederum hängt in hohem Maße von den physikochemischen Eigenschaften des Wirkstoffs ab. Da Buprenorphin in sehr geringen Dosen wirksam ist und außerdem die erforderlichen physikochemischen Charakteristika besitzt, ist die buccale oder sublinguale Applikation sehr attraktiv.

[0006] In der Zeitschrift "Journal of Controlled Release", Bd. 25, Nr. 1/2, 1993, werden nicht zerfallsfähige polymere Systeme zur buccalen Anwendung von Buprenorphin beschrieben, die mit einer für den Wirkstoff nicht permeablen Schicht abgedeckt wurden, so daß eine gerichtete Freisetzung des Wirkstoffs möglich und der Verlust von Wirkstoff durch Schlucken vermindert wurde. Die wirkstoffundurchlässige Schicht wurde dabei mit Hilfe eines randständig aufgebrachten Klebers in der Mundhöhle in Position gehalten und das System wurde nach mehreren Stunden wieder aus der Mundhöhle entfernt.

[0007] Die US Patentschrift US 4 673 679 offenbart eine pharmazeutische Zubereitung zur buccalen und sublingualen Verabreichung von Opiaten und Opiatantagonisten in Form von im wässrigen Medium der Mundhöhle zerfallsfähigen Pflastern. Die zur buccalen Anwendung offenbarten Pflaster enthalten u. a. den mukoadhäsiven Hilfsstoff Carbopol 934P sowie ersterifizierte Derivate von Nalbuphin als "prodrugs".

[0008] Tatsächlich befinden sich - zumindest in Deutschland - neben den injektabilen Darreichungsformen keine peroralen, sondern nur sog. Sublingualtabletten mit Buprenorphin im Handel (Temgesic® sublingual). Diese Tabletten würdigen zwar - wenn auch vorwiegend durch die Einnahmevorschrift, denn nur diese, nicht die Tablette an sich, legt die sublinguale Gabe nahe - die Tatsache, daß eine sublinguale Applikation des Wirkstoffes der peroralen vorzuziehen ist; sie bieten jedoch ein für den Anwendungszweck mit erhetblichen Nachteilen behaftetes Vehikel. Hierzu gehört zunächst die nicht unbeträchtliche Zerfallzeit, die bei gepreßten Tabletten selbst unter günstigen Voraussetzungen mindestens einige Minuten beträgt, bei den im Handel er-

hältlichen Buprenorphin-Tabletten in der Regel etwa 5 bis 10 Minuten. Für Patienten mit starken, akuten Schmerzen bedeutet diese Zerfallzeit eine unerwünschte Verzögerung des Wirkstoffeintritts, bei einer Substitutions- oder Entwöhnungstherapie dagegen eine zeitliche Belastung des medizinischen Personals, welches die bestimmungsgemäße Verwendung der Tabletten überwachen und eine mißbräuchliche Wiederentnahme der unzerfallenen Tabletten aus dem Mund verhindern muß. Weitere Nachteile der Tablette sind das Fremdkörpergefühl im Mund während der Zerfallzeit, aber auch die große Variabilität beim Ausmaß der sublingualen Absorption, die dadurch verursacht wird, daß der Wirkstoff beim oder nach dem Zerfall der Tablette überwiegend keinen direkten Kontakt zur Mundschleimhaut hat, sondern in den Speichel freigesetzt wird; der Speichel kann sich aber mehr und weniger zufällig über eine sehr variable Zeit in der Mundhöhle befinden, bevor er geschluckt wird.

[0009] Aufgabe der vorliegenden Erfindung ist daher die Schaffung von Arzneizubereitungen auf der Basis von und mit den allgemeinen Vorteilen von flachen, film- oder papierartigen Wirkstoffträgern, welche durch die Kombination mit einem speziellen Wirkstoff noch zusätzliche therapeutische und/oder wirtschaftliche Vorteile gegenüber Arzneizubereitungen desselben Wirkstoffes auf der Basis konventioneller Darreichungsformen wie etwa Tabletten aufweist. Darüber hinaus ist es ebenso die Aufgabe der Erfindung, eine Applikationsform für Buprenorphin bereitzustellen, die den Wirkstoff in der Mundhöhle freisetzt, ohne die im Stand der Technik beschriebenen Nachteile zu besitzen.

[0010] Die Aufgabe wird entsprechend den Merkmalen des Anspruchs 1 dadurch gelöst, dass eine im wässrigen Medium der Mundhöhle zerfallsfähige oblatenförmige Arzneizubereitung mit einer mukoadhäsiven, als Wirkstoff Buprenorphin oder eine therapeutisch vergleichbare Wirksubstanz enthaltende Schicht auf der Basis von wasserlöslichen filmbildenden Polymeren bereitgestellt wird, die eine der mucoadhäsiven Fläche entgegengesetzte nicht-mucoadhäsive Außenschicht mit geringerer Permeabilität für den Wirkstoff aufweist.

[0011] Eine Arzneizubereitung nach Anspruch 1 ist, wie im folgenden dargelegt werden soll, einer konventionellen Darreichungsform zur Verabreichung von Buprenorphin sowohl unter wirtschaftlichen als auch unter therapeutischen Gesichtspunkten weit überlegen und eignet sich insbesondere einerseits zur Analgesie bei starken Schmerzzuständen, andererseits zur Therapie der Opiat oder Cocainabhängigkeit im Sinne einer Substitutionstherapie oder eines Entwöhnungsprogrammes.

[0012] Die Arzneizubereitung nach Anspruch 1 kann bei der Applikation direkt mit der Mundschleimhaut in Kontakt gebracht werden. Durch die flächige Ausgestaltung befindet sich sofort nach der Applikation etwa die Hälfte der ohnehin großen Oberfläche der Darreichungsform unmittelbar auf der Mucosa. Das freigesetzte Buprenorphin findet also für den Eintritt in den Körper zwei besonders günstige Faktoren vor, nämlich eine kurze Diffusionsstrecke und eine große Diffusionsfläche. Hierdurch wird der Anteil an Buprenorphin herabgesetzt, der verschluckt wird, was bei vielen anderen Wirkstoffen nicht sonderlich problematisch wäre. Bei Buprenorphin jedoch ist das Verschlucken von Wirkstoff möglichst zu vermeiden oder herabzusetzen, da verschlucktes Buprenorphin aus den dargelegten Gründen unwirksam bleibt. Bereits bei der einfachsten erfindungsgemäßen Ausgestaltung und mit einer Zerfallzeit von wenigen Minuten nach Applikation oder nach dem Einbringen in wässrige Medien wird sich daher die Überlegenheit eines buprehorphinhaltigen Films gegenüber einer buprenorphinhaltigen Tablette zeigen.

[0013] Ein verbesserter Kontakt der erfindungsgemäßen Arzneizubereitung mit der Mundschleimhaut läßt sich durch die Auswahl der Hilfsstoffe herbeiführen. Von bestimmten pharmazeutisch gebräuchlichen, oral applizierbaren Hilfsstoffen ist bekannt, daß sie schleimhauthaftende Eigenschaften besitzen. Beispiele für solche mucoadhäsiven Substanzen sind Polyacrylsäure, Carboxymethylcellulose, Traganth, Alginsäure, Gelatine, Hydroxymethylcellulose,Methylcellulose und Gummi Arabicum. Darüber hinaus ist von verschiedenen nicht mucoadhäsiven Stoffen bekannt, daß sie in bestimmten Mischungsverhältnissen ebenfalls mucoadhäsive Eigenschaften ausbilden. Ein Beispiel für ein solches Gemisch ist Glycerinmonooleat/ Wasser im Verhältnis 84: 16 (Engström et. aL., Pharm. Tech. Eur. 7 [1995], Nr. 2, S. 14-17).

[0014] Durch den zwei oder mehrschichtigen Aufbau der Darreichungsform der erfindungsgemäßen Arzneizubereitung kann vermieden werden, daß die Zubereitung verschiedene Schleimhautpartien miteinander verklebt, was zu erheblichen Missempfindungen führen würde. Außerdem kann bei einem solchen Aufbau, bei dem die nicht mukoadhäsive Schicht eine relativ geringere Permeabilität gegenüber dem Wirkstoff als die mukoadhäsive Schicht besitzt, vermieden werden, dass durch die Freisetzung in den Speichel der Mundhöhle statt zur Schleimhaut Wirkstoffverluste eintreten.

[0015] Erfindungsgemäße Arzneizuberoitungen sind auch solche, die neben dem Wirkstoff Buprenorphin oder einem diesem pharmakologisch vergleichbaren Wirkstoff noch einen oder mehrere weitere Wirkstoffe enthalten. Eine solche Zubereitung kann in mehrfacher Hinsicht vorteilhaft sein. Zum einen ist es eine anerkannte Methode zur Behandlung mehrerer gleichzeitig auftretender Symptome oder Zustände, eine fixe Wirkstoffkombination in einem Medikament zu verabreichen. Hierzu lassen sich beliebige, therapeutisch sinnvolle Wirkstoffe in die erfindungsgemäße Zubereitung einarbeiten. Zum anderen ist die erfindungsgemäße Kombination eines Opiatwirkstoffes mit einer anderen Substanz, welche die spezifischen Risiken einer Opiatverabreichung reduzieren kann, besonders sinnvoll und vorteilhaft. So lassen sich beispielsweise - gegebe-

nenfalls partielle- Opiatantagonisten wie etwa Nalbuphin, Naloxon oder Naltrexon mit dem Opiatwirkstoff kombinieren, was zur Folge hat, daß die Sucht- bzw. Gewöhnungsgefahr durch die wiederholte Verabreichung der Zubereitung dadurch verringert wird, daß sich die Dosis nicht steigern läßt, ohne gleichzeitig eine Steigerung des antagonistischen Effektes in Kauf zu nehmen. Von der Wahl eines geeigneten Antagonisten sowie des Dosisverhältnisses in der Zubereitung wird der Erfolg dieser Strategie abhängen.

[0016] Wenn auch Buprenorphin - gegebenenfalls in Form eines seiner therapeutisch akzeptablen Salze - der am meisten bevorzugte Wirkstoff ist, betrifft die Erfindung auch solche Wirkstoffe, die dem Buprenorphin pharmakologisch ähnlich oder vergleichbar sind, da die beschriebenen Vorteile der Erfindung, wenn auch in unterschiedlichem Ausmaße, auch hier zum Tragen kommen können. Insbesondere sind weitere geeignete Wirkstoffe, die hier auch als "pharmakologisch ähnlich oder vergleichbar " bezeichnet sind, solche, die den Opiaten oder Opioiden zuzurechnen sind, da viele von ihnen nicht nur pharmakodynamisch, sondern auch pharmakokinetische Ähnlichkeiten mit Buprenorphin aufweisen, also eine relativ niedrige Dosis, eine gute Membrangängigkeit und einen hohen First-Pass-Effekt. Insbesondere bevorzugt sind Morphin- oder Dihydromorphinderivate sowie Substanzen aus der Methadon und aus der Fentanylgruppe.

[0017] Um einer mißbräuchlichen oder nicht bestimmungsgemäßen Anwendung keinen Vorschub zu leisten, wird die erfindungsgemäße Arzneizubereitung in der Regel dosisweise vorzerteilt und voneinander separiert in einer geeigneten Verpackung vorliegen, so daß zur Entnahme einer Dosiseinheit jeweils nur diese entnehmbar gemacht wird, wie etwa im Falle einer Blisterpackung, in welcher jede Dosiseinheit in einem Tiefziehnapf einzeln eingesiegelt ist. Im Rahmen von Programmen zur Behandlung der Opiatoder Cocainabhängigkeit kann es jedoch auch sinnvoll sein, z. B. den betreuenden Ärzten die Zubereitung in Form von Verpakkungseinheiton anzubieten, in denen sie als unzerteiltes blatt- oder bandförmiges Material vorliegt, von welchem sich die Dosiseinheiten zum Zwecke der Applikation abteilen lassen. Dies erleichtert eine Massenapplikation und gibt den verabreichenden Ärzten die Möglichkeit, unterschiedliche Dosiseinheiten je nach Dosisbedarf aus ein und demselben Material abzuteilen.

[0018] Da von der erfindungsgemäßen Arzneizubereitung ein gegenüber bekannten Zubereitungen erhöhtes Ausmaß der Bioverfügbarkeit zu erwarten ist, muß die Dosierung gegebenenfalls angepaßt werden. Im Falle des Buprenorphins wird die analgetische Einzeldosis bei 0,1 bis 1 mg liegen, in der Suchttherapie bzw. Substitutionstherapie jedoch möglicherweise deutlich höher.

Die Herstellung der Arzneizubereitung erfolgt erfindungsgemäß in mehreren Schritten. Zur Herstellung des bahnförmigen Ausgangsmaterials, aus dem zuletzt entweder die Einzeldosen oder aber ganze Verpakkungseinheiten durch Schneiden oder Stanzen abgeteilt werden, sind zwei grundlegende Verfahrensvarianten geeignet. Die erste Gruppe von Verfahren umfaßt jene, bei denen mit wässrigen bzw. lösemittelhaltigen Flüssigkeiten teilweise höherer Viskoität ein Band oder eine Prozessfolie gleichmäßig beschichtet und anschließend einem Trocknungsprozeß unterworfen wird. Hierzu wird zunächst die Beschichtungsmasse hergestellt, wozu mindestens ein wasserlösliches, zur Filmbildung befähigtes Polymer, der oder die Wirkstoffe und eine geeignete, verdampfbare Flüssigkeit innig gemischt werden müssen. Bedarfweise können weitere Hilfsstoffe wie zerfallmodifizierende Polymere, Weichmacher, Füllstoffe, texturvermittelnde Substanzen, Pigmente, Farbstoffe, Geschmackkorrigenzien, Löslichkeitsvermittler, Substanzen zur Einstellung des pH-Wertes, Glättungsmittel, Mattierungsmittel, Zerfallbeschleuniger etc. eingearbeitet werden. Alternativ läßt sich das bahnförmige Ausgangsmaterial durch thermoplastische Formung, d. h. ohne Zuhilfenahme von Flüssigkeiten herstellen. Hierzu gehören alle Hot-Melt-Beschichtungs- und alle Extrusionsverfahren. Eine Voraussetzung ist in diesem Fall, daß das zur Filmbildung befähigte Polymer oder Polymergemisch thermoplastisch formbar ist. Die erforderlichen Zutaten werden gemischt und unter Einwirkung von Druck und/oder Wärme durch Extrudieren, Blasen oder durch Beschichten von Bändern oder Folien geformt und nach dem Erstarren der weiteren Verarbeitung zugeführt. Für die Herstellung von erfindungsgemäßen Zubereitungen mit mehrschichtigem Aufbau eignen sich entsprechend modifizierte Verfahren, wobei es unerheblich ist, ob mehrere bahnförmige Materialien gleichzeitig oder nacheinander hergestellt und zusammengefügt werden.

Patentansprüche

1. Buccale Arzneizubereitung zur Bekämpfung starker Schmerzzustände oder Suchttherapie mit Buprenorphin, Morphin-, Dihydromorphin-Derivaten, Substanzen aus der Methadon- oder Fentanylgruppe oder als therapeutisch geeignetes Salz als Wirkstoff, **gekennzeichnet durch** eine im wäßrigen Medium der Mundhöhle zerfallfähige oblatenförmige Darreichungsform mit einer mucoadhäsiven, wirkstoffhaltigen Schicht auf der Basis von wasserlöslichen, filmbildenden Polymeren für die rasche Wirkstoffübertragung **durch** kurze Diffusionswege bei einer der wirksamen Dosis angemessenen großen Fläche, wobei die Darreichungsform eine der mucoadhäsiven Fläche entgegengesetzte nicht-mucoadhäsive Außenschicht mit geringerer Permeabilität für den Wirkstoff aufweist.

2. Arzneizubereitung nach Anspruch 1, **gekennzeichnet durch** einen zwei oder mehrschichtigen

Aufbau mit einer mucoadhäsiven wirkstoffhlatigen Schicht auf der Basis von wasserlöslichen, filmbildenden Polymeren für die rasche Wirkstoffaufnahme **durch** kurze Diffusionswege.

3. Arzneizubereitung nach Anspruch 1 oder 2, **gekennzeichnet durch** einen Einzeldosen-Buprenorphingehalt von 0,1-1 mg.

4. Arzneizubereitung nach einem der vorangehenden Ansprüche, **dadurch gekennzeichnet, daß** sie durch den Zusatz eines haftungsvermittelnden Hilfsstoffes oder Hilfsstoffgemisches mit bio- bzw. mucoadhäsiven Eigenschaften ausgerüstet ist.

5. Arzneizubereitung nach Anspruch 4, **dadurch gekennzeichnet, daß** als weiterer Wirkstoff ein Opiatantagonist oder partieller Opiatantagonist vorhanden ist.

Claims

1. Buccal pharmaceutical preparation for treating acute conditions of pain or for addiction therapy, comprising as active substance buprenorphine, morphine, dihydromorphine derivatives, substances from the methadone or fentanyl groups as such or as a therapeutically suitable salt, **characterized by** a wafer-shaped administration form, disintegratable in the aqueous medium of the oral cavity, which has a mucoadhesive, active substance-containing layer based on water-soluble, film-forming polymers, for rapid active substance transfer through short diffusion paths, while having a large surface appropriate to the effective dose, the said administration form having a non-muco-adhesive outer layer, opposed to the mucoadhesive surface, which outer layer has a lower permeability to the active substance.

2. Pharmaceutical preparation according to claim 1, **characterized by** a two- or multi-layered structure having a mucoadhesive active substance-containing layer based on water-soluble, film-forming polymers for rapid active substance uptake through short diffusion paths.

3. Pharmaceutical preparation according to claim 1 or 2, **characterized by** a single-dose buprenorphine content of 0.1-1 mg.

4. Pharmaceutical preparation according to any one of the preceding claims, **characterized in that** it is equipped with bioadhesive or mucoadhesive properties by the addition of an adhesion-promoting auxiliary substance or auxiliary substance mixture.

5. Pharmaceutical preparation according to claim 4, **characterized in that** as a further active substance an opiate or a partial opiate antagonist is present.

Revendications

1. Préparation médicamenteuse destinée à être libérée dans la cavité buccale et à soulager des douleurs intenses ou à traiter une toxicomanie, qui comprend, en tant que principe actif, de la buprénorphine, des dérivés de la morphine et de la dihydromorphine, des substances du groupe de la méthadone ou du fentanyle, ou leurs sels thérapeutiquement appropriés, **caractérisée par** une forme galénique de type cachet apte à se désintégrer dans le milieu aqueux de la cavité buccale, qui porte une couche mucoadhésive contenant le principe actif, à base de polymères filmogènes hydrosolubles, permettant un transfert rapide du principe actif par un court trajet de diffusion, avec une surface dont les dimensions sont ajustées en fonction de la dose efficace, la forme galénique présentant une couche extérieure non-mucoadhésive, opposée à la surface mucoadhésive et moins perméable au principe actif.

2. Préparation médicamenteuse selon la revendication 1, **caractérisée par** une structure bicouche ou multicouche qui comprend une couche mucoadhésive contenant le principe actif, à base de polymères filmogènes hydrosolubles, permettant un transfert rapide du principe actif par un court trajet de diffusion.

3. Préparation médicamenteuse selon la revendication 1 ou 2, **caractérisée par** une teneur en buprénorphine correspondant à une dose individuelle de 0,1-1 mg.

4. Préparation médicamenteuse selon l'une quelconque des revendications précédentes, **caractérisée en ce que**, par suite de l'addition d'un adjuvant ou d'un mélange d'adjuvants favorisant l'adhérence, elle présente des propriétés bio- et/ou mucoadhésives.

5. Préparation médicamenteuse selon la revendication 4, **caractérisée en ce que** comme principe actif supplémentaire, elle contient un antagoniste des opiacés ou un antagoniste partiel des opiacés.

EDIBLE FILM CONTAINING GLUCOMANNAN

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Applicant(s): UNIE COLLOID KK +
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Abstract of **JP 62126950 (A)**

PURPOSE:To obtain the titled film having excellent strength, water- and heat- resistance and suitable for packaging a food in divided portions, by uniformly kneading glucomannan, etc., in a system consisting of one or more kinds of compounds selected from polyhydric alcohols, sugar alcohols, etc., dissolving the product in water, forming a film from the solution and drying the obtained film.; CONSTITUTION:1pt.wt. of glucomannan and optionally other natural polysaccharides are uniformly kneaded in an aqueous solution having a concentration of 60-90% and containing 0.2-20pts.wt. of at least one kind of compound selected from polyhydric alcohols (e.g. glycerol), sugar alcohols (e.g. sorbitol), monosaccharides (e.g. glucose), disaccharides (e.g. sucrose) and oligosaccharides (e.g. a product obtained by decomposing starch of sweet potato, etc., with an enzyme or acid, etc.) optionally in the presence of an alkali (e.g. NaOH). The kneaded product is dissolved in water to obtain a coagulated material having desired hardness and viscoelasticity. The coagulated material is formed to a film of 1-1,000mu thick e.g. by wet-casting method and the film is dried to obtain the objective edible film.

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⑤④発明の名称　グルコマンナンを含む可食性フィルム

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明　細　書

1．発明の名称

グルコマンナンを含む可食性フィルム

2．特許請求の範囲

(1) 多価アルコール、糖アルコール、単糖類、二糖類及びオリゴ糖から選ばれた少なくとも1種からなる系の中で、グルコマンナン或いはグルコマンナンと他の天然多糖類を均一に混練して得られた生成物を水に溶解しフィルム状に成形乾燥してなるグルコマンナンを含む可食性フィルム。

(2) 多価アルコール、糖アルコール、単糖類、二糖類及びオリゴ糖から選ばれた少なくとも1種からなる系の中で、グルコマンナン或いはグルコマンナンと他の天然多糖類をアルカリの存在下に均一に混練して得られた生成物を水に溶解しフィルム状に成形乾燥してなるグルコマンナンを含む可食性フィルム。

3．発明の詳細な説明

〔産業上の利用分野〕

本発明は、水に浸漬しても或いは水中で加熱しても溶解せず、しかも通気性、通水性を有するグルコマンナンを含む可食性フィルムに関する。このフィルムは透明で充分な強度を有し、薄く製膜することが可能であるため各種食品を包装し、食感に影響することなくそのまま食することができ、食品の付加価値を高め、流通性を向上させるなど広い用途を有する。

〔従来の技術〕

従来、グルコマンナンは水の系、すなわち水溶液中でアルカリと反応させた後、加熱処理によって凝固体、すなわちコンニャクを製造する用途に用いられていた。しかしながら、水の系でグルコマンナンを反応させる従来の方法によれば、凝固体の組織が不均一なためその用途がもっぱらコンニャクに限定されていた。

また、可食性フィルムとしては、澱粉系、ゼラチン系等があるがいずれも強度が不充分であり、サイクロデキストリン、酵母から核酸や細胞膜等を除去した特殊蛋白質を使用するものは高価にはなるが、耐水性や強度はこれに対応して向上して

いなかった。

〔発明が解決しようとする問題点〕

本発明は、グルコマンナンを用い、強度、耐水性、耐熱性を同時に向上させ、透明な薄い被膜にして食品を小分けし、包装しそのまま違和感なく食することができる可食性フィルムを提供することを目的とする。

〔問題解決の手段〕

本発明は、多価アルコール、糖アルコール、単糖類、二糖類及びオリゴ糖から選ばれた少なくとも1種からなる系の中で、アルカリの存在下又は不存在下にグルコマンナン或いはグルコマンナンと他の天然多糖類を均一に混練して得られた生成物を水に溶解しフィルム状に成形乾燥することを特徴とする。

本発明に係るグルコマンナンは、サトイモ科に属する草木の地下球茎でコンニャク芋（Amorphophallus Konjac K.Koch）に含まれる多糖類であり、異形細胞とよばれる長径 0.5～1.05mm、短径0.37～0.5mm の粒子である。化学構造はグルコースとマンノースが1：2の割合で鎖状に結合し、更にアセチル基とリン酸基が側鎖としてエステル結合している高分子多糖類である。

本発明に係る、多価アルコールとして、プロピレングリコール、グリセリン等が挙げられる。糖アルコールとしては、ソルビトール、マンニトール、マルチトール、キシリトール、還元澱粉糖化物等が挙げられる。単糖類としてはグルコース、フラクトース、ガラクトース、キシロース等が使用される。二糖類としてはサッカロース、マルトース、ラクトース等が使用される。オリゴ糖としてはさつま芋、じゃが芋、とうもろこし等の澱粉の酵素、酸などによる分解産物が使用され、二糖類、三糖類、四糖類、五糖類、六糖類等が含まれている。

本発明は、これら多価アルコール、糖アルコール、単糖類、二糖類及びオリゴ糖から選ばれた少なくとも1種からなる系の中で行われることに特徴がある。これらの系の中でとは、それ自体液状のものはそのまま、あるいはわずかに希釈して使用し、粉体のものは60～90％水溶液、好ましくは70～80％水溶液として、この中にグルコマンナン或いはグルコマンナンと他の多糖類を混練していく。

本発明に使用するアルカリは通常の無機、有機のアルカリ性物質であればよく、例えば、水酸化ナトリウム、水酸化カリウム、水酸化カルシウム、水酸化マグネシウム、水酸化バリウム、炭酸ナトリウム、炭酸カリウム、炭酸カルシウム、炭酸アンモニウム、炭酸マグネシウム、炭酸水素ナトリウム、炭酸水素アンモニウム、塩基性アミノ酸、アミンなどが挙げられる。アルカリを添加すると一般に可食性フィルムの強度、耐熱性が向上する。

本発明はグルコマンナンに他の天然多糖類を混合して使用してもよい。使用される他の天然多糖類としては、サイクロデキストリン、カラギナン、ローカストビーンガム、グアーガム、セルロース、アルギン酸、アルギン酸ソーダ、アルギン酸プロピレングリコールエステル、プルラン、寒天、タマリンド、ペクチン、キサンタンガム、澱粉などが挙げられる。

グルコマンナンと多価アルコール、糖アルコール、単糖類、二糖類及びオリゴ糖から選ばれた少なくとも1種の化合物との配合比は、グルコマンナン1重量部に対し、これら化合物 0.2～20重量部、好ましくは 0.5～15重量部である。

上記原料を混練して得られた化合物は、一般に多少湿り気のある粉体である。これを水に溶解したものは粘稠な溶液であり、常温放置、凍結、冷蔵または加熱により不可逆的に凝固する性質を有する。しかも得られた凝固体は水の添加量により任意の物性、特に硬度、粘弾性を調整することができる。得られた凝固体は耐水性、耐熱性であり、この性質を利用して、湿式キャスト法、凍結乾燥法、押出し成形法等公知の方法で1～1000μの任意の厚さの可食性フィルムが得られる。更に、これらフィルムに食品成分を混合、付着させることにより種々の味覚を有するフィルム状食品が得られる。

〔作用〕

グルコマンナンは上述の通りアセチル基やリン酸基を有する複雑な構造であるため、多数の水酸基が高濃度に存在する系の中で反応し、複雑なマトリックスを形成するものと考えられる。ここに水を加えることにより三次元構造がより発達し、不可逆的凝固体を形成するに至り、容易にフィルム状にすることができる。

〔実施例１〕

グルコマンナン１０重量部、グリセリン１０重量部を常温で混練して得られた生成物５重量部に水９５重量部を加え、粘稠な溶液を得た。この溶液を湿式キャスト法により厚さ１０μの被膜を製造した。

おにぎりの表面に大量のふりかけをまぶし、これを前記の可食性フィルムで包み、重なり部分は僅かな水をつけて押さえた。１２時間後、フィルムは水分を吸収しているが、溶けることなく強度を保持していた。フィルム毎食べたとき、フィルムの存在を全く感じさせず、おにぎりの鮮度をよく保持していた。

〔実施例２〕

グルコマンナン１０重量部、グリセリン１０重量部及び水酸化カルシウム0.1 重量部を混練し、実施例１と同様にしてフィルムを製造した。このフィルムに、人参、しいたけ、長ねぎ、キャベツ等の野菜をみじんぎりした混合物をだんご状に包み、これを牛肉の３cm角程度の塊と共にだし汁の中で煮込んだ。野菜はよく味がしみ、しかも煮崩れることなくそのまま箸でつまんで食べることができた。食感に関してはフィルムの存在を全く感じさせなかった。

〔実施例３〕

グルコマンナン１０重量部に代えて、グルコマンナン６重量部とカラギナン４重量部を用いた以外は実施例１と同様にしておにぎりを包装した。実施例１とほぼ同様の結果が得られた。

〔実施例４〕

グルコマンナン１０重量部に代えて、グルコマンナン６重量部とカラギナン４重量部を用いた以外は実施例２と同様にして野菜の煮物を行った。実施例２とほぼ同様の結果が得られた。

〔実施例５〕

グルコマンナン６重量部、カラギナン４重量部、７０％ソルビット水溶液１０重量部を混練し、実施例１と同様にしてフィルムを製造した。クラッカーの上をレーズン、プラム、生クリームで飾り、上から上記フィルムで覆い、端部をクラッカーの裏側に押しつけた。この食品は１２時間後も飾りが崩れず、食感に変化なくフィルム毎食べることができた。

〔実施例６〕

グルコマンナン６重量部、寒天４重量部、８０％サッカロース水溶液１０重量部及び水酸化カルシウム0.1 重量部を混練し、フィルム製造にあたっては凍結乾燥法を利用し、－２０℃で減圧下に乾燥した以外は実施例１と同様にしてフィルムを製造した。被膜が破れ、中の魚卵がばらばらになった扇たらこをこのフィルムでたらこ大の大きさに包んだ。この食品は型崩れしない通常のたらこは同様に取扱うことができ、生でも焼いてもフィルム毎食べることができた。

〔実施例７〕

グルコマンナン６重量部、寒天２重量部、カラギナン２重量部、グリセリン４重量部、７０％ソルビット水溶液２重量部、８０％サッカロース水溶液２重量部を混練し、フィルム厚さを２０μにした以外は実施例１と同様にして可食性フィルムを製造した。このフィルムをサラミソーセージの外皮に使用した。フィルムは充分な強度を有し、製造上の支障もなく、得られたサラミソーセージは皮をむかずにそのまま食べることができた。

〔実施例８〕

グルコマンナン６重量部、アルギン酸４重量部、グリセリン１０重量部を常温で混練して得られた生成物５重量部に水９５重量部を加え、粘稠な溶液を得た。この溶液を 100重量部に、うに20重量部を混合し、押出し成形法により厚さ 200μのシート状うにを得た。このシート状うにはそのまま食べることができ、また、他の食品の上に載せてうにの料理法を拡大することができた。

〔実施例９〕

グルコマンナン６重量部、セルロース４重量部、グルコース１０重量部を常温で混練して得られた生成物５重量部に水９５重量部を加え、粘稠な溶液を得た。この溶液を 100重量部に、かつをフレークをすりつぶして得たかつをペースト２０重量部を混練し、凍結乾燥法により厚さ約３０μの味つけフィルムを得た。このフィルムはそのまま食べることもできるが、海苔巻の手法で御飯を包み、円筒状のかつを味つけ御飯にすることもできた。

〔実施例１０〕

グルコマンナン６重量部、プルラン２重量部、キサンタンガム２重量部、マルトース１０重量部を常温で混練して得られた生成物８重量部に水９２重量部を加え、粘稠な溶液を得た。厚さ５μとした以外は実施例１と同様にして可食性フィルムを製造した。このフィルムの表面に梅ペーストを塗布し、５０℃、３０分再乾燥した。梅の味のするフィルム状食品が得られた。

〔効果〕

本発明に係るグルコマンナンを含む可食性フィルムは半透明で各種食品の包装、小分けが可能であり、食品の保存性を高めるばかりでなく、味付けフィルムも製造することができ、食品の形態を無限に拡大することができる。

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PRODUCTION OF TRANSPARENT EDIBLE FILM

Publication number: JP2265444 (A)
Publication date: 1990-10-30
Inventor(s): SAITO TOSHIAKI; SUNADA FUMIYUKI +
Applicant(s): FUJI OIL CO LTD +
Classification:
- international: ***A23J3/00; A23J3/16; A23L1/00; A23L1/48;*** (IPC1-7): A23J3/00; A23J3/16; A23L1/00; A23L1/48
- European:
Application number: JP19890085898 19890404
Priority number(s): JP19890085898 19890404

Also published as:
JP2708869 (B2)

Abstract of **JP 2265444 (A)**

PURPOSE:To improve surface smoothness and transparency by finely dividing and dispersing residual bubbles in a soybean protein paste or solution defoamed under reduced pressure, applying the resultant paste or solution onto a smooth surface and drying the formed film. CONSTITUTION:A soybean protein paste or solution prepared by emulsifying >=60% (expressed in terms of crude protein) soybean protein, as necessary, fats and oils, saccharides, a wetting agent or plasticizer, emulsifying agent, coloring matter, seasoning, etc., and water using a Stephan device, silent cutter, etc., is defoamed under reduced pressure until the air content attains <=8vol.%. The resultant paste or solution is vigorously stirred under conditions of cut off outside air, finely divided and dispersed so as to afford most of the residual bubbles having <=50mum particle diameter thereof.; The obtained paste or solution is then applied onto a smooth surface and the resultant film is dried.

⑲日本国特許庁（JP）　⑪特許出願公開

⑫公開特許公報（A）　平2−265444

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⑭発明の名称　透明な可食性フイルムの製造方法

⑳特　願　平1−85898

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⑫発明者　西東　俊明　大阪府泉南郡熊取町久保976

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明細書

1. 発明の名称

透明な可食性フィルムの製造方法

2. 特許請求の範囲

(1) 大豆たん白ペースト乃至溶液の製膜原料を減圧下で脱泡し、脱泡後の該溶液等を外部の空気を遮断した条件下で攪拌して残存気泡を微細化分散させて後、平滑面上に塗膜、乾燥することを特徴とする透明な可食性フィルムの製造方法。

(2) 減圧下で大豆たん白ペースト乃至溶液を調合することによって脱泡を行う特許請求の範囲第1項記載の方法。

3. 発明の詳細な説明

〔産業上の利用分野〕

この発明は、透明な可食性フィルムの製造に関し、特に食品を包装した場合、包装材料を透して内容物が明瞭に識別できる食品を提供するのに用いる透明な可食性フィルムの製造方法に関するものである。

〔従来の技術〕

近年、食生活の多様化、或は食品の加工技術の向上等に伴って、種々の可食性フィルムが開発されている。特に、着香、着味及び着色等の技術の改良がなされ、可食性フィルムを利用した食生活のバラエティー化がより一層進められている。それに伴い、可食性フィルムの用途範囲も拡がり、更に、多種多様な風味、食感及び外観を有する可食性フィルム材料の開発が期待されている。

伝統的には、湯葉、ワンタン、春巻き、ギョウザ、油揚に具材を包んだ巾着類及び湯葉で具材を巻いた湯葉巻類等の可食性被膜乃至可食性被膜を利用した様々な食品がある。これらは、被膜の特性を上手に利用し、被膜の食感を味わう為に膜自体を食したり、調理中に分散し易い具材或は調理液中に溶出する様な具材を捕捉する手段として被膜が利用されている。

一方、伝統的な被膜食品に対して、工業的に大量に生産される大豆たん白の可食性フィルムの製造法（例えば、特開昭60−156354）も提

案される。

しかし、これらの被膜の殆どは、不透明であるため、これらの被膜を用いた食品、特に具材を被膜で捕捉した包装食品を食する時に、具材を視覚で確認し、その色或は形状を楽しみ・味わいながら食する様なことはできなかった。一般に、食品の味は、舌で味わう味覚だけで決まるものではなく、嗅覚で感じる臭い、食感としての舌触り・歯応え、及び視覚で感じる色・形状等が総合されて決定されるものであると言われている。ところが、適当な透明度の高い可食性フィルムがないため、具材を被膜で包んだ食品の殆どは、中に何が入っているのか分からず、視覚による具材の確認がなされないまま食されているのが現状であった。

従来、透明度の高い可食性フィルムとしては、オブラート等の多糖類系のフィルムが市販されているが、それらは調理加工中に水に溶け、調理加工に用いる可食性フィルムとしては適当ではなかった。また、水不溶性であっても、調理加工に適する強度が必要であり、調理中に破れてはならないことと、更には、食品材料として比較的安価に入手ができねばならないため、前記の様な可食性被膜で包まれる食品の被膜材として用いることのできる透明な可食性フィルムの入手は極めて困難であった。

特に、前述の水不溶性であることが必須要件であるので、オブラート等の様に透明度が高くても水に溶けてしまうものは用いることはできない。従って、熱変成等により水不溶性となる大豆たん白の被膜が注目される。しかし、従来の大豆たん白被膜は透明度が低く、包まれている具材を明瞭の識別することができない欠点があった。その為、大豆たん白被膜の実質的な透明度の向上を図り、膜厚を薄くすることを試みたが、膜厚を薄くすると強度が極端に低下し、特に湿潤時の強度の低下が著しいため、調理加工のときに破裂して具材が飛び出したり、被膜自体を汁物に用いた場合には、被膜自体を箸ですくいあげることも困難な状態となり使用に耐え得るものではなかった。

〔発明が解決しようとする問題点〕

前述の様に、可食性フィルムの多くは調理加工に用いられるため、湿潤時、特に湿潤加熱時に充分な被膜強度が要求される。そのため、湿潤によって溶解するような素材は、可食性フィルムの原料として適当でなく、加熱変成等によって不溶化する大豆たん白が原料として用いるのに最も適している。

しかし、従来の大豆たん白の可食性フィルムは透明度が低く、油揚、湯葉等の伝統的食品だけでなく、工業規模で生産される大豆たん白の可食性フィルムであっても透明度で充分満足できるものは得られていなかった。

特に、調理加工中或は食する時に可食性フィルムに対して外力が働き、その外力に抗しうる膜厚が必要とされた。従って、外力に充分に耐え得る強度が維持できる膜厚が必要で、その膜厚に於いて可食性フィルムは内包する具材を識別できる程度の透明度が必要である。例えば、透明な大豆たん白の可食性フィルムを巾着類に用いる場合には、強度的に少なくとも約５０μｍの膜厚が要求される。ところが、工業的に生産される従来の大豆たん白の可食性フィルムであっても気泡が大量に含有されているため、この程度の膜厚にすると充分な透明度は得られていなかった。

この発明は、前述の様に原料素材、膜厚に制限が加えられる中で、可食性フィルムを包材として用いた場合に内包物が判別できる程度の透明度を有し、滑らかな表面を有する可食性フィルムを製造する方法を提供するものである。

〔問題点を解決するための手段〕

この発明は、大豆たん白ペースト乃至溶液の製膜原料を減圧下で脱泡し、脱泡後の該溶液等を外部の空気を遮断した条件下で撹拌して残存気泡を微細化分散させて後、平滑面上に塗膜、乾燥することを特徴とする透明な可食性フィルムの製造方法に関するものである。

従来、大豆たん白の可食性フィルムを製造する際に、可食性フィルムに柔軟性を付与させること或は工程の簡略化のために、殆どの場合製膜原料の溶液は気泡が含有した状態で被膜形成に供給さ

れていた。本発明の目的である透明な可食性フィルムを得ようとするとき、気泡の存在が大きな障害となり、透明度の向上を阻んでいた。本発明者らは、気泡の除去による透明度の向上に着目し研究を重ねたが、完全に脱泡するには装置面、運転費面で経費が嵩み、採算的に好ましくない結果であった。また、仮に完全脱泡を行っても、本願発明の大豆たん白の溶液等の場合は、平滑面に塗布するまでの間に大豆たん白の溶液等がゲル化してしまう。これを防ぐために、該溶液が塗布工程に至る間は撹拌を継続する。この間に、該溶液は外部の空気を噛み込み、気泡の数は従前の可食性フィルムに比較し極端に少ないものの、気泡が点在し、可食性フィルムの外観を悪くし、その商品価値を著しく低下させていた。

また、脱泡後、たん白のゲル化を防止するための撹拌を外部空気の遮断下で行っても、残存気泡を微細化するに至らない撹拌である場合、得られた可食性フィルムには大粒の気泡が残存して、商品かちを極端に低下させてしまう。これは、例え

可食性フィルムの透明度及び強伸度等が満足されても商品としての価値がなく、通常、肉眼で観察される気泡が可食性フィルム1cm当たり1～2個存在すると商品としてのかちは半減する。

本発明は、この様な大豆たん白の溶液等の脱泡を簡単な設備で安価な経費にて行い、溶液等には気泡が残存する不完全脱泡であっても、得られる可食性フィルムは肉眼では殆ど気泡の残存が観察されない透明度が高く、表面が滑らかなものを得る方法を提供するものである。

即ち、本発明は、不完全な脱泡の大豆たん白の溶液等を、外部の空気を遮断した条件下で強撹拌し、残存する気泡の殆どを粒径50μm以下になるように微細化し、しかる後平滑面に被膜状に塗布し、乾燥することによって、含気状態で乾燥しても気泡の存在を感じさせない透明度の高い可食性フィルムを得る方法である。一般には、各種素材の可食性フィルムを製造する場合、含気状態で乾燥すると、その気泡が肉眼観察が容易でない程度に微細化されていても、乾燥中に微細気泡が破

裂合体、或は膨張し大きな気泡に成長して肉眼観察でき、フィルムの透明度を低下させる様になる場合が多い。

ところが、意外にも本発明の大豆たん白の場合、含気率を調整することにより残存気泡の膨張、破裂合体等はみられず透明度の高い可食性フィルムを得ることができた。これは、大豆たん白はゲル化能が大きく、溶液等を平滑面に塗布後直ちにゲル化が始まり、微細気泡を含有した状態でたん白質の分子構造の骨格が確立する。この時、乾燥工程での加熱によって微細気泡が膨張しようとする力と、分子構造の確立に伴いこの膨張を抑制しようとする膜自体の力のバランスが含気率の調整でコントロールされる。即ち、特定の含気率以下に調整することによって、乾燥工程で気泡を膨化させずに透明度の高い可食性フィルムを得ることができるのである。

この様に脱泡後撹拌し、平滑面に塗布された被膜状大豆たん白ペースト乃至溶液は、直ちに乾燥工程に導いて乾燥してもよいが、該溶液のたん白濃度の低いこと等によりゲル化速度が遅い場合、分子構造の骨格の確立には時間がかかるので、適宜ゲル化を進行させ、所謂スワリ現象が生じるのを待って乾燥を開始するのが望ましい。

本発明の大豆たん白ペースト乃至溶液とは、大豆たん白及び水の他、任意成分として、油脂、糖類、湿潤剤乃至可塑剤、乳化剤、色素、調味料、他種たん白等の公知の原料を含むことができる。

大豆たん白は、大豆または脱脂大豆の水抽出物、等電点分離物（所謂分離たん白）、11S分離大豆たん白のようなたん白の分画物、またはそれらの乾燥物の形態で用いることができる。一般に、粗たん白質（以下CPという）の含量が高いもの程、製品の風味、強度及び透明度に優れる。大豆たん白固形物中のCPは60%以上のものを用いるのがよく、大豆たん白ペースト乃至は溶液中に含まれるCPの量が6～35%となるような量が使用される。

油脂の添加は、製品の風味の向上に役立つが、透明度の低下に繋がるため、CPに対して40%

以下が望ましい。グルコース、蔗糖、デキストリン、澱粉等の糖類は、被膜の食感の調整に有用であるが、得られる可食性フィルムの透明度及び強度の低下に繋がる傾向にあり、その添加は極力抑えるのが好ましい。グリセリン、ソルビット等の湿潤剤乃至可塑剤は、乾燥製品に可塑性、つや等を与えるのに役立ち、ＣＰに対して１～５０％の範囲で添加するのが好ましい。

この様にして配合された製膜原料は、ステファン或はサイレントカッターで大豆たん白ペースト乃至溶液に調合されるが、真空ステファン等の減圧下撹拌装置を用いて、調合と同時に脱泡するか、或は一旦調合した溶液等を真空脱泡機で脱泡する何れの方法を用いても良い。

かくして、大豆たん白ペースト乃至溶液は脱泡されるが、脱泡は溶液等の含気率が８容量％以下、更に好ましくは１容量％以下になるまで行う。含気率が８容量％を越えると、次の残気泡を微細化分散する工程で気泡は微細化されても、微細気泡の数が余りにも多いため、乾燥工程での気泡が膨張、破裂合体される等により肥大化した気泡が残存し、乾燥後の可食性フィルムは細孔が生じ、それに伴い白濁して透明度が低下してしまい好ましくない。含気率を８％以下にすると、微細気泡は幾分膨化するが破裂合体するに至らず、白濁は殆ど観察されない可食性フィルムが得られる。更に、含気率を１％以下にすると、ゲル化した被膜の分子構造に伴い被膜の膨化抑制力が勝ためと考えられる力のバランスによって、気泡は微細なまま保持され、白濁は認められない非常に透明な可食性フィルムが得られる。

含気率を８容量％以下（好ましくは１％以下）まで脱泡し、しかる後、溶液等を外部の空気を遮断する条件下にて撹拌し、残存気泡を微細化させる。この様にして得られる溶液等から製造する可食性フィルムは、透明度が高く、視覚的な品質低下に繋がる膨化合体気泡による可食性フィルムの表面及び組織の乱れは全く観察されない透明度の高い可食性フィルムを製造することができるのである。

塗布被膜は、被膜中の大豆たん白のゲル化状態に応じて乾燥工程で加熱されるが、その加熱の方法は特に限定されない。一般に、大豆たん白被膜の乾燥に用いられている加熱方法には、熱風による雰囲気加熱方法、塗布面である平滑面を加熱する方法及び遠赤外線又は電磁波を用いてフィルムの内部からの加熱方法、或はこれらを併用する方法等があるが、それらの何れもが適用できる。

大豆たん白ペースト乃至溶液を塗布する平滑面は、該溶液等が均一に塗布でき、乾燥後の塗布膜の剥離性が良いものであれば何れも採用される。通常は、ポリテトラフルオロエチレン（商品名：テフロン）等のフッ素化合物が用いられる。

かくして得られた可食性フィルムは、高い透明度を有し、水に戻しても強度及び歯応えがあり、それ自体、透明な湯葉様食品として汁物の具材として用いることができる他、他の具材を包むことのできる包材としても用いるられる。例えば、この可食性フィルムを包材として用い、ギョウザ、春巻、ロールキャベツ、湯葉巻様の食品等を得ることができ、内包物の形状、色合を明瞭に識別できる食品を得ることができる。

〔実施例〕

以下この発明を実施例で説明する。

実施例１

粉末状分離大豆たん白（「フジプロ－Ｒ」不二製油㈱製造；粉末中のＣＰは85％）100 部、湿潤剤40部、乳化剤２部、及び水 560部をサイレントカッター中で乳化し、次いで60mmHgの真空下で脱泡（含気率 0.3容量％）した後、インラインミキサー（㈱エバラ製作所製）で回転数10000rpmの撹拌を行い、残存気泡を完全に微細化し、常圧下では残存気泡が殆ど観察されない大豆たん白溶液を得た。得られた溶液を直ちにテフロン（商品名）コーティングした無端ベルト上に、厚さ0.5 mmになるように展延し、しかる後、２分間常温部を通過後加熱部に入るようにしてベルトを進め、加熱部は、遠赤外線照射部（通過時間30秒）及び熱風（ 105℃）乾燥部（通過時間３分）からなり、加熱部通過後の被膜は水分約10％に乾燥し、次いで

連続的に剥離、巻き取りを行って大豆たん白の可食性フィルムを得た。

比較例として、インラインミキサーの回転数を500rpmに落とす以外は実施例1と全く同様にして大豆たん白の可食性フィルムを得た。

各々の可食性フィルムの物理特性は第1表に示す通りである。

第　1　図

特性値	実施例1	比較例
可食性フィルムの膜厚（μm）	64	66
粒径50μm以上の気泡の数（個／cm²）	0	5
引張強度（kg／cm²）	132.6	116.7
引張伸度（%）	95.8	98.4
透明度（%）	87	86

比較例で得られた可食性フィルムには、視覚で観察される気泡が多数あり、商品価値を著しく低下させていた。これに対し、本実施例のものは、気泡の存在は全く確認されない商品価値として優れたものであった。

但し、透明度とは、空気の光透過量に対する可食性フィルムの光透過量の割合を意味する。

実施例2

粉末状分離大豆たん白（「フジプロ－R」不二製油㈱製造；粉末中のＣＰは85%）100部、湿潤剤40部、乳化剤2部、及び水580部を真空ステファンで60mmHgの真空下で調合、脱泡（含気率0.2容量%）した後、インラインミキサー（㈱エバラ製作所製）で回転数10000rpmの撹拌を行い、残存気泡を完全に微細化し、常圧下では残存気泡が殆ど観察されない大豆たん白溶液を得た。得られた溶液を直ちにテフロン（商品名）コーティングした無端ベルト上に、厚さ0.5 mmになるように展延し、しかる後、2分間常温部を通過後加熱部に入るようにしてベルトを進め、加熱部は、遠赤外線照射部（通過時間30秒）及び熱風（105℃）乾燥部（通過時間3分）からなり、加熱部通過後被膜は水分約10%に乾燥し、次いで連続的に剥離、巻き取りを行って大豆たん白の可食性フィルムを得た。

比較例として、真空ステファンを220mmHgの真空度とする以外は、実施例2と同様にして調合、脱泡し、含気率14容量%の溶液を得た。この溶液から実施例2と同様にして大豆たん白の可食性フィルムを得た。

各々の可食性フィルムの物理特性は第2表に示す通りである。

第　2　図

特性値	実施例1	比較例
可食性フィルムの膜厚（μm）	63	86
粒径50μm以上の気泡の数（個／cm²）	0	無数の微細気泡
引張強度（kg／cm²）	134.6	65.3
引張伸度（%）	97.4	60.6
透明度（%）	87	65

比較例からは、無数の気泡を含有した濁りの有る可食性フィルムが得られ、それは透明度低く、引張強伸度の低いものであった。これに対して、本実施例の可食性フィルムは、優れた透明度、並びに引張強伸度を有し、この可食性フィルムを用いて挽き肉、きのこ及び野菜類を細かく刻んでなる具材を詰め、袋状にヒートシールした巾着様食品は、内包物が明瞭に確認できる興味ある食品であった。

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PACKAGING FILM

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Publication date: 1993-06-15
Inventor(s): NINOMIYA HIROFUMI; ISHII KAZUHIRO; NAGAKURA YOSHIHIKO +
Applicant(s): MITSUBISHI RAYON CO +
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- European:
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Abstract of **JP 5147140 (A)**

PURPOSE:To obtain a packaging film excellent in strength, usable as a packaging material such as a medium bag or a large bag and also excellent from the aspect of environment by providing a polysaccharide layer based on water- soluble polysaccharide to at least the single surface of a porous base material. CONSTITUTION:It is pref. to form a polysaccharide layer from a composition containing water-soluble polysaccharide and polyhydric alcohol in order to impart flexibility to a film. As a porous base material, paper, a nonwoven fabric, a fabric or a foamable plastic sheet are designated but paper or a nonwoven fabric is pref. from the aspect of the adhesion to the polysaccharide layer and film physical properties. A packaging film is obtained by providing the polysaccharide layer based on water-soluble polysaccharide to at least the single surface of the porous base material. This packaging film has sufficient strength, especially, excellent tear strength.

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(54)【発明の名称】　包装用フイルム

(57)【要約】
【目的】　引裂伸度や引張強伸度等のフィルム強度に優れ、中袋や大袋等の包装材料等としても使用することが可能となり、環境面でも優れた包装用フィルムを得る。
【構成】　紙や不織布等の多孔質基材の少なくとも片面に、カラギーナン等の水溶性多糖類を主成分とする多糖類層を形成した包装用フィルム。

【特許請求の範囲】
【請求項１】　多孔質基材の少なくとも片面に水溶性多糖類を主成分とする多糖類層を有することを特徴とする包装用フィルム。
【請求項２】　多孔質基材が、紙あるいは不織布であることを特徴とする請求項１記載の包装用フィルム。
【発明の詳細な説明】
【０００１】
【産業上の利用分野】本発明は、優れたフィルム物性を有する包装用フィルムに関し、さらに詳しくは、高いフィルム強度を有するとともに良好な外観を呈し、水溶性多糖類を使用することによって環境面においても優れた包装用フィルムに関するものである。
【０００２】
【従来の技術】従来、水溶性の多糖類を用いた多糖フィルムとしては、オブラートやプルランフィルム等が知られている。また、特開平２－３０８７６０号公報や特開平２－３０８７６１号公報に記載されているように、カラギーナンを主成分とする多糖類と多価アルコールを主成分とする多糖フィルムが、包装用フィルムとして使用可能であることが知られている。
【０００３】
【発明が解決しようとする課題】しかし、オブラートやプルランフィルムでは、そのフィルム物性に限界があり、包装用フィルムとしては殆ど使用されていない。また、カラギーナン等の多糖類からなる多糖フィルムは、可食性、温水溶解性や酸素遮断性等の特徴を有しており、包装材料としての有効利用が期待されているが、フィルム強度が十分ではなく小袋包材としての使用に限定され、中袋あるいは大袋等の包装材料としての使用はできなかった。
【０００４】そこで、本発明の目的は、包装用フィルムとして十分なフィルム強度を有し、中袋あるいは大袋等の包装材料としては使用可能な多糖フィルムを提供することにある。
【０００５】
【課題を解決するための手段】本発明者等は、このような状況に鑑み、包装用フィルムのフィルム強度について鋭意検討した結果、本発明に到達したものである。すなわち、本発明の包装用フィルムは、多孔質基材の少なくとも片面に水溶性多糖類を主成分とする多糖類層を有することを特徴とするものである。
【０００６】本発明のフィルムを構成する多糖類層として使用することのできる水溶性多糖類としては、アルギン酸及びそのナトリウム塩等の塩類、ファーセレラン、カラギーナン、寒天、ペクチン、タマリンドガム、キサンタンガム、グアガム、タラガム、ローカストビーンガム、アラビノガラクタン、アラビアガム、ジェランガム、カードランガム、プルラン、キトサン、、スターチ、デキストリン、カルボキシルメチルセルロース等の水溶性セルロース誘導体等が挙げられる。特に好ましい水溶性多糖類としては、フィルムの成形性やフィルムの物性等の点から、アルギン酸及びそのナトリウム塩等の塩類、ファーセレラン、カラギーナン、寒天から選ばれる１種以上を主成分とするものが挙げられる。中でも、フィルムの強度特性、温水溶解性等の点からカラギーナンが最も好ましく、カラギーナンを水溶性多糖類中２０重量％以上、好ましくは５０重量％以上含有させることにより、より十分な温水溶解性を発揮させることができる。
【０００７】また、上記水溶性多糖類を２種以上組み合わせることにより、強度特性等の性能を改良させることも可能である。例えば、ポリアニオン多糖類であるカラギーナンには、ポリカチオン多糖類であるキトサン等を共存させると両者間に架橋反応が起こり強固なネットワークを形成するため、高強度のフィルムが必要な場合には適宜に選定して用いることができる。
【０００８】本発明の多糖類層には、フィルムに柔軟性を付与するために水溶性多糖類と多価アルコールを含む組成物から多糖類層を形成することが好ましい。本発明で用いられる多価アルコールとしては、湿気保持特性等の性質を有するもので、エチレングリコール、プロピレングリコール等の二価アルコール、グリセリン等の三価アルコール、ソルビトール、マンニトール、マルチトール、キシリトール、還元澱粉糖化物等の糖アルコール、グルコース、フラクトース、ガラクトース、キシロース等の単糖類、サッカロース、マルトース、ラクトース等の二糖、澱粉の分解物等のオリゴ糖等が挙げられる。本発明の多糖類層中の多価アルコールの含有量は、水溶性多糖類１重量部に対して０．２～１重量部であることがフィルムの物性の点で好ましい。
【０００９】このように多価アルコールを含有した多糖類層を形成することにより、フィルムに付与される柔軟性は－５０～－４０℃の低温においても保持され、低温でのハンドリングにおいてフィルムにヒビ割れ等が発生せず、環境安定性を高めることができる。環境安定性をさらに向上させるには、室温で液状あるいは半液状の多価アルコールと室温で固形である多価アルコールとの重量比率は３／１～１／３であることが好ましい。室温で液状あるいは半液状の多価アルコールとしては、プロピレングリコール、グリセリンあるいは両者の混合物等が挙げられ、室温で固形である多価アルコールとしてはソルビトール、マンニトール、マルチトール、キシリトール、還元澱粉糖化物等の糖アルコール、グルコース、ガラクトース、キシロース等の単糖類、サッカロース、マルトース、ラクトース等の二糖類、澱粉の分解物等のオリゴ糖等あるいはこれらの２種以上を組み合わせたもの等が挙げられる。
【００１０】本発明の多糖類層においては、フィルムの物性を大きく損なわない範囲で、無機物あるいは有機物

の粉末、着色料、香料等の添加物を加えることもできる。また、多糖類層の厚さは特に限定されるものではないが、包装を目的とする場合にはヒートシール性および強度を勘案して１０～１００μｍ範囲とするのが好ましい。

【００１１】本発明に使用される多孔質基材としては、紙類、不織布、織布、発泡性プラスチックシート等が挙げられるが、多糖類層との密着性およびフィルム物性の点で紙類あるいは不織布が好ましい。さらに、セルロース等の天然物で構成された基材を使用することにより、包装用フィルム全体が天然物で構成されることになり、環境面で非常に優れた包装用フィルムとなり、より好ましいものである。

【００１２】本発明において、多孔質基材の厚さおよび目付は特に限定されるものではないが、フィルムの柔軟性の維持および多糖類層との接着性の向上のためには、厚さおよび目付の小さい基材が好ましく、厚さ２００μｍ以下、目付４０ｇ／ｍ^2 以下が好ましい。さらに好ましくは、厚さ１００μｍ以下、目付２０ｇ／ｍ^2 以下のものである。

【００１３】本発明の包装用フィルムは、例えば以下のような方法によって製造することができる。

多孔質基材に水溶性多糖類を主成分とする水溶液を塗布するか、多孔質基材を水溶性多糖類を主成分とする水溶液中に浸漬した後に乾燥させる。

水溶性多糖類を主成分とする水溶液をドラムやベルト等の支持体上に流延し、乾燥させながら多孔質基材を積層した後、さらに乾燥させる。

あらかじめ水溶性多糖類を主成分とする水溶液をドラムやベルト等の支持体上に流延し、乾燥させることによって得られた多糖フィルムを、多孔質基材に加熱圧着等の方法によって積層する。

【００１４】上記の製造法において、多糖フィルムは多価アルコール類と水との重量比が２０／８０～０．２／９９．８の媒体に水溶性多糖類を溶解した水溶液を流延しフィルム状に賦形した後、乾燥することにより製造できる。また、水に水溶性多糖類を溶解した水溶液に多価アルコール類／水の重量比が２０／８０乃至０．２／９９．８となるように多価アルコール類を混合した溶液を流延しフィルム状に賦形した後、乾燥することによっても製造できる。水溶液中の水溶性多糖類の濃度は２０重量％以下とすることが好ましく、より好ましくは１０重量％以下である。これは、水溶性多糖類の濃度が２０重量％を超えると水溶性多糖類の水への完全な溶解が困難となり、フィルムへの賦形性が低下するためである。また、水溶性多糖類水溶液の調整は、７０℃以上に加熱した条件下で溶解性を促進させて行うことが好ましい。さらに、必要により水溶性多糖類は、予め水中で膨潤させ溶解性を高めるようにしてもよい。水溶性多糖類を溶解させる媒体のｐＨは６～９程度でよいが、アルカリ領域で溶解が促進されるアルギン酸等の多糖類では、媒体のｐＨ領域を適宜アルカリ側にして溶解させてもよい。得られた水溶性多糖類水溶液は脱泡した後、ドラム、スチールベルト、ポリテトラフルオロエチレン含浸ガラス繊物、各種プラスッチクフィルムやシート等の支持体上に所定の厚みになるように流延し、支持体側からの伝熱、熱風あるいは赤外線輻射等により多糖類層中の水分率が２５重量％以下、好ましくは２０重量％以下となるように乾燥することによって、多糖類層フィルムを製造することができる。

【００１５】本発明の包装用フィルムでは、水溶性多糖類としてカラギーナン等を使用した場合、多糖類層に自己ヒートシール性が発現するので、多糖類層面を接着面とすることにより、袋等の製造は容易になる。また、高度のシール強度を必要とする場合には、天然物接着剤、感圧接着剤、ホットメルト接着剤等を使用することが好ましい。

【００１６】

【実施例】以下、実施例を用いて本発明をさらに説明する。なお、実施例におけるフィルムの引張強伸度および直角型引裂強度は、それぞれＪＩＳ Ｚ １７０７およびＪＩＳＫ６７３２に準拠して、フィルムの長手方向にたいして平行にサンプリングした試験片をもちいて測定した。

【００１７】実施例１

κ－カラギーナン７重量部とグリセリン３．５重量部を水１００重量部の混合液中に分散させ、８５℃に昇温して６０分間撹拌しカラギーナンを溶解させた。得られた溶液を温度８５℃に保持したまま減圧脱泡した後、８５℃の熱板上に固定した薄葉紙（目付１４ｇ／ｍ^2 ）に塗布した。次いで、水分率が１５重量％となるまで乾燥し、目付７２ｇ／ｍ^2 、厚さ６５μｍのフィルムを得た。得られたフィルムの引張強伸度と直角型引裂強度を測定し、その結果を表１に示した。

【００１８】実施例２

κ－カラギーナン５重量部、ローカストビーンガム１重量部、グリセリン３．５重量部を水１００重量部の混合液中に分散させ、８５℃に昇温して６０分間撹拌しカラギーナンおよびローカストビーンガムを溶解させ、得られた溶液を温度８５℃に保持したまま減圧脱泡した。脱泡溶液を回転させた加熱ドラム上に連続して流延し、流延させた溶液が乾燥固化する前（一部の水が除去された状態の粘性溶液）に、たばこプラグ用工程紙（目付２０ｇ／ｍ^2 ）を加圧積層した後、乾燥し連続的にフィルムをドラムから剥離し、紙管に捲き取った。得られたフィルムは、水分率１３重量％、目付７９ｇ／ｍ^2 、厚さ７１μｍであった。フィルムの引張強伸度と直角型引裂強度を測定し、その結果を表１に示した。

【００１９】比較例１

κ－カラギーナン５重量部、ローカストビーンガム１重

量部、グリセリン３．５重量部を水１００重量部の混合液中に分散させ、８５℃に昇温して６０分間撹拌しカラギーナンおよびローカストビーンガムを溶解させ、得られた溶液を温度８５℃に保持したまま減圧脱泡した。脱泡溶液を回転させた加熱ドラム上に連続して流延し乾燥した後、連続的にフィルムをドラムから剥離し、紙管に捲き取った。得られた多糖フィルムは、水分率１５重量％であった。フィルムの引張強伸度と直角型引裂強度を測定し、その結果を表１に示した。

【００２０】

【表１】

【００２１】

【発明の効果】本発明の包装用フィルムは、多孔質基材に水溶性多糖類を主成分とする多糖類層を形成した構成とすることにより、フィルム強度に優れ、特に引裂強度に優れているため、中袋や大袋等の包装材料等としても使用することが可能となり、環境面でも優れている。

フロントページの続き

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EDIBLE CASING FILM AND PREPARATION OF PROCESSED FOOD USING THE FILM

Publication number: JP7322812 (A)
Publication date: 1995-12-12
Inventor(s): NOUMI TOMOYOSHI; TANAKA YOSHINAO +
Applicant(s): OSAKA KAGAKU GOKIN KK +
Classification:
- international: ***A22C13/00; A23L1/00; A23L1/325; C08J7/04;*** (IPC1-7): A22C13/00; A23L1/00; A23L1/325; C08J7/04; C08L1/00
- European:
Application number: JP19940141244 19940530
Priority number(s): JP19940141244 19940530

Abstract of **JP 7322812 (A)**

PURPOSE:To produce an edible easing film having excellent water-resistance, adhesiveness to meat and heat-resistance and useful for the easing of processed meat such as ham, sausage or boiled fish paste like crab leg meat by forming a surface-treating layer of a chitosan salt on the surface of a polysaccharide film containing gelan gum. CONSTITUTION:This film is produced by forming a surface-treating layer composed of a chitosan salt (preferably acetate, lactate, citrate or malate of chitosan) on at least one surface of a film of a polysaccharide [preferably xanthan gum, alginic acid(salt), KAPPA-carrageenan, furcellaran, low-methoxy pectin, gelatin or casein) containing preferably >=20wt.% of gelan gum. A meat raw material is packaged with the film contacting the chitosan salt-treated layer with the meat and cooked to produce a processed food.

(19)日本国特許庁（ＪＰ）　(12) **公開特許公報（A）**　(11)特許出願公開番号

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(54)【発明の名称】　可食性ケーシングフィルムおよびこれを用いた加工食品の製造法

(57)【要約】
【構成】　本発明の可食性ケーシングフィルムは、ジェランガムを含有する多糖類フィルムの少なくとも片面にキトサン塩の表面処理層が設けられている。
【効果】　本発明の可食性フィルムは耐水性に優れ、ハムやカマボコなどの加工食肉との密着性がよく、しかも良好な食感を有するので加工食品製造用ケーシングに好適である。

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【特許請求の範囲】

【請求項1】　ジェランガムを含有する多糖類フィルムの少なくとも片面にキトサン塩の表面処理層を設けてなる可食性ケーシングフィルム。

【請求項2】　10重量%以上のジェランガムを含有する請求項1の可食性ケーシングフィルム。

【請求項3】　キトサン塩がキトサンの酢酸塩、乳酸塩、クエン酸塩およびリンゴ酸塩から選ばれた少なくとも1種のキトサン塩である請求項1の可食性ケーシングフィルム。

【請求項4】　請求項1の可食性ケーシングフィルムのキトサン塩処理層を食肉原料に接するように成形し、これをクッキングすることを特徴とする加工食品の製造法。

【発明の詳細な説明】

【0001】

【産業上の利用分野】本発明は、畜肉及び魚肉製品、特にハム、ソーセージやカニ足様カマボコ等の製造において可食性ケーシングフィルムとして使用される肉密着性、耐熱性、耐水性に優れた多糖類フィルムに関する。

【0002】

【従来の技術および課題】ハム、ソーセージやカニ足様カマボコなどの加工食品を製造するには、加工時にその形状を整えるため、原料となる調味した畜肉、魚肉などを適当な可食性のケーシングで成形しクッキングを行う。このような可食性ケーシングフィルムとしては、従来コラーゲンやカラギーナン、寒天、プルラン、アルギン酸などのフィルムが用いられている。

【0003】しかしながら、コラーゲンフィルムは製造工程が煩雑でありフィルムが脆弱で加工性も低く、またフィルムが硬いため喫食時の食感も良くない。一方、カラギーナン、寒天、プルラン、アルギン酸などのフィルムは、成形した食肉への密着性がなく、加工時の熱と肉の水分とによってフィルムが溶解し外観や食感が悪くなる。

【0004】本発明の目的は、ハムやカマボコなどのタンパク質の加工食品の本体と密着性を有し、しかも良好な食感を有する加工食品製造用ケーシングに用いられる可食性フィルムを提供することにある。

【0005】

【課題を解決するための手段】本発明者等はこのような状況に鑑み、畜肉及び魚肉製品の成形に適した可食性ケーシングフィルムについて鋭意検討した結果、本発明に到達したものである。本発明はジェランガムを含有する多糖類フィルムの少なくとも片面をキトサン塩にて処理した可食性フィルムおよびこれを用いた加工食品の製造法を提供するものである。

【0006】本発明の可食性フィルムに用いられる多糖類としては、キサンタンガム、ローカストビーンガム、グアガム、タラガム、κ－カラギーナン、ι－カラギーナン、λ－カラギーナン、寒天、ファーセレラン、タンマリンドガム、カードラン、低メトキシペクチン、高メトキシペクチン、プルラン、アラビアガム、アルギン酸及びその塩類、カルボキシメチルセルロース、可溶性セルロース誘導体、可溶性デンプン、その塩類及びこれらの混合物が挙げられる。また、ゼラチン、カゼインなどフィルム成形性に優れたタンパク質を併用してもよい。これらフィルム原料のうち、フィルム成形性、キトサン塩との反応性を考慮すると特にキサンタンガム、アルギン酸及びその塩類、κ－カラギーナン、ファーセレラン、低メトキシペクチン、ゼラチン、カゼイン及びその塩類から選択するのが好ましい。

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【0007】本発明可食性フィルムの多糖類フィルムには、必須成分としてポリアニオン多糖類であるジェランガムが配合される。フィルムに対するジェランガムの配合量は10重量%以上、好ましくは20重量%以上である。ジェランガムの配合量が10重量%より少ないとポリカチオン多糖類であるキトサン塩との架橋反応が低下し可食性フィルムの耐熱水性、肉密着性が悪くなる。

【0008】さらに可食性フィルムに柔軟性を付与するため多価アルコール類を配合するのが好ましい。このような多価アルコール類としては、グリセリン、エチレングリコール、プロピレングリコールなどの2～3価のアルコール及びソルビット、マンニトール、マルチトール、キシリトール、還元澱粉糖化物等の糖アルコール、オリゴ糖及びこれらの混合物などが挙げられる。

【0009】これら多価アルコールの配合量はフィルムに適度な柔軟性と強度を与えるよう可食性フィルム全体に対して15～40重量%であるのが好ましい。多価アルコールの配合量が40重量%を越えるとフィルムがブロッキングを生じ、一方、配合量が15%より少ないとフィルム自体が脆くなり製造が困難である。

【0010】本発明の可食性フィルムの厚さは10～50μmであるのが好ましい。フィルムの厚みが10μm未満であるとフィルム強度が不十分であり加工時にフィルムが破損しやすい。また、フィルムの厚みが50μmを越えると食感が悪くなり好ましくない。

【0011】本発明の可食性フィルムには、さらに公知の着色料、香辛料、香料、甘味料、調味料等を添加したり表面に付着させてもよい。

【0012】本発明可食性フィルムの表面処理層に用いられるキトサン塩としては、酢酸塩、乳酸塩、クエン酸塩、リンゴ酸塩および塩酸塩などから選ばれる1種以上の塩が好ましい。これらキトサン塩は、キトサンを酢酸、乳酸、クエン酸、リンゴ酸、塩酸等のpH4以下の酸性溶液に加えることにより得られる。酸の使用量はキトサン1重量部に対して1～3重量部であるのが好ましい。また、pH調整のため酢酸ナトリウム、クエン酸三ナトリウム、乳酸ナトリウム等を添加してもよい。キトサンと酸とを水溶液中にて反応させるキトサン溶液にコ

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ーティングに適した粘度を付与するため、プルラン、可溶性澱粉、酸化澱粉、デキストリン等の澱粉系物質、あるいはこれらの混合物を配合してもよい。

【0013】可食性フィルムの製造

本発明の可食性フィルムを製造するには、ジェランガム、その他の水溶性多糖類、多価アルコールを水に分散させて加熱、溶解し均一な水溶液を調製する。水溶液の調整にあたっては、使用原水中の金属イオンが多糖類の溶解性を阻害しないよう金属封鎖剤、例えばクエン酸三ナトリウム、リン酸二ナトリウム、プロリン酸四ナトリウム、ヘキサメタリン酸ナトリウム酸を添加するのが好ましい。このようにして得られたフィルムは耐熱性に優れ、キトサンとの反応性が高い。ついで、この水溶液を脱泡し、適宜のプラスチックフィルム、ドラム、スチールベルトなどの支持体上に所定の厚みになるように流延し、これを熱風、赤外線輻射熱あるいは支持体からの伝熱等によりフィルムの含水率が20重量%以下となるよう乾燥する。

【0014】一方、キトサンをpH4以下の酸性溶液に溶解して、キトサン塩とし、前記のジェランガムを含有する水溶性多糖類のフィルム表面にコートし乾燥する。かかる塗工は、前記水溶性多糖類フィルムの乾燥前後どちらでもよいが、フイルム乾燥前にコートすることが好ましく、このようにして製膜されたフイルムは、連続してロール状に巻き取ることができる。

【0015】本発明の可食性フイルムはフラットフィルムまたはチューブ状とし、キトサン塩をコートした面を食肉に接するようにして用いる。食肉が充填されたケーシングは従来と同様のクッキングを行うことにより可食性フイルムが食肉に密着する。

【0016】なお、チューブ状にして使用する場合には、可食性の接着剤を用いて成形することができる。このような接着剤としてはプルラン、アラビアガム、α－化澱粉、可溶性澱粉、ゼラチン、カゼイン及びその塩類、キトサン、アルギン酸及びその塩類が挙げられる。接着層の厚みは特に限定されるものではないが0.5～10μmであるのが好ましい。

【0017】

【作用】キトサンは酢酸、塩酸など酸が存在すると塩をつくって溶解しカチオン性高分子コロイドとなる。このカチオン性高分子コロイドはジェランガム、キサンタンガム、アルギン酸ナトリウム等のアニオン性高分子コロイドと架橋反応しゲル生成を起こし、また、タンパク質を凝集させる。このためアニオン性高分子コロイドを含有するフィルムと食肉の密着層となるものと考えられる。

【0018】

【実施例】つぎに本発明を実施例によりさらに具体的に説明する。

【0019】［実施例1］ジェランガム2重量部、キサンタンガム1重量部、ローカストビーンガム1重量部およびグリセリン2重量部をイオン交換水100重量部に分散させ、95℃に加熱し60分間攪拌して溶解し、スモーク色素としてキビ色素1重量部を加えた。この液を80℃で減圧脱泡した後、厚み25μmのポリエチレンテレフタレート（PET）フィルム上に連続して流延した。その上にキトサン2重量部を2%酢酸水溶液100重量部に溶解した液をスプレーでコートした。ついでこのフィルムを熱風乾燥機中で110℃の熱風にて乾燥し、PETフィルムと一緒に巻き取った。PETフィルムより剥離して得られた可食性フィルムは、厚み20μm、含水率17%であった。このフィルムを、接着層にプルランを用いてキトサン塩コート面が内面となるように直径50mm×長さ150mmのチューブに成形した。このチューブにピックル液を125%加水した豚肉300gを充填し同時に弾性ネットを被着した。この肉を70℃－湿度5%にて30分間乾燥した後、温度80℃－湿度99%で90分間蒸煮し、続いて、温度5℃－湿度30%で15時間冷却してボイルハムを得た。

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【0020】多糖類フィルムは溶解することなく肉に密着しておりハム表面に燻煙加工を行ったと同様のスモーク色を付けることができた。また、弾性ネットも容易に剥離しネットの肉およびフィルムへの食い込みはなく、従来のフィルムに比べ歩留りも向上するとともに、カット加工や調理においてもフィルムの剥離は見られず、見栄えの良いハムが製造できた。

【0021】［実施例2］ジェランガム2重量部、κ－カラギーナン1重量部、ローカストビンーガム1重量部、プルラン1重量部およびグリセリン2重量部をイオン交換水100重量部に分散させ、95℃に加熱して60分間撹拌し溶解した。この液を厚み25μmのPETフィルムの上に流延した。その上にキトサン1重量部、プルラン9重量部を3%クエン酸溶液100重量部に溶解した液を、転写ローラーを用いてフィルム表面にコートした。これを実施例1と同様の方法で乾燥し厚み30μm、水分15%のフィルムを得た。このフィルムをアルギン酸糊により接着して直径100mm×長さ250mmのチューブに成形した。このチューブにピックル液を100%加水した豚肉500gを充填すると同時に弾性ネットを被着した。この肉を温度70℃－湿度35%にて10分間、続いて温度75℃－湿度15%にて20分間乾燥し、スモークを温度75℃で20分間した後、スチームで温度80℃－湿度99%で90分間蒸煮し、温度5℃－湿度30%で15時間冷却してロースハムを得た。

【0022】得られたハムの可食性フィルムは溶解することなく肉に密着していた。また、スモークの透過性もよく弾性ネットも容易に剥離しネットの肉への食い込みはなかった。さらに、従来のフィルムに比べ歩留りも向上し、カット加工や調理においてもフィルムの剥離は見

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られず、食感も良く見栄えに優れたハムができた。

【0023】［比較例1］多糖類フィルムにキトサン塩のコートをしなかったこと以外は実施例1と同様にして可食性フィルムを製造した。得られたフィルムを用いて、実施例1と同様に肉を包装しハムに加工したが、フィルムの一部が加熱時に溶解した。また、フィルムの肉に対する密着性も低く見た目も悪かった。

【0024】［比較例2］多糖類フィルムにキトサン塩のコートをしなかったこと以外は実施例2と同様にして可食性フィルムを製造した。得られたフィルムを用いて、実施例2と同様に肉を包装しハムに加工したが、フィルムの一部が加熱時に溶解した。また、フィルムの肉に対する密着性も低く見た目も悪かった。

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【0025】

【発明の効果】本発明の多糖類を主成分とする可食性フィルムは耐熱性、耐水性に優れ、ハムやカマボコなどのタンパク質からなる加工食品との密着性がよく、しかも良好な食感を有するので加工食品製造用ケーシングに好適である。また、クッキング時に用いる弾性ネットの剥離が良く、歩留りの良い畜肉及び魚肉製品を得ることができる。

フロントページの続き

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GELATIN SOLID SUBSTANCE

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Publication date: 2001-10-10
Inventor(s): HARATANI MASAHIRO +
Applicant(s): KOBAYASHI PHARMA +
Classification:
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Abstract of **JP 2001279100 (A)**

PROBLEM TO BE SOLVED: To obtain a gelatin solid substance capable of avoiding stirring/ degassing treatment at a high temperature for a long period of time since foams are hardly mixed in a production process or can be removed by a short-time degassing treatment even if mixed.
SOLUTION: This gelatin solid substance is characterized in that the gelatin solid substance is a gelatin solid substance contains gelatin and a terpene-based compound and the ratio of the terpene-based compound formulated is 0.005-10 pts.wt. based on 100 pts.wt. of the gelatin solid substance.

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(54)【発明の名称】　ゼラチン固形物

(57)【要約】
【課題】製造過程で気泡が混入しにくいか、混入しても短時間の脱気処理で除去できるため、高温下での長期間の撹拌／脱気処理を回避できる、ゼラチン固形物を提供する。
【解決手段】ゼラチン及びテルペン系化合物を含有するゼラチン固形物であって、テルペン系化合物の配合割合がゼラチン固形物１００重量部あたり０．００５～１０重量部であることを特徴とするゼラチン固形物。

【特許請求の範囲】
【請求項１】ゼラチン及びテルペン系化合物を含有するゼラチン固形物であって、テルペン系化合物の配合割合がゼラチン固形物１００重量部あたり０．００５～１０重量部であることを特徴とするゼラチン固形物。
【請求項２】ゼラチン溶解液に発生する気泡に対する消泡剤としてテルペン系化合物を配合してなることを特徴とする、ゼラチン及びテルペン系化合物を含有するゼラチン固形物。
【請求項３】ゼラチン固形物１００重量部中のゼラチンの配合割合が２０～８０重量部である請求項１記載のゼラチン固形物。
【請求項４】テルペン系化合物として、テルペン系ケトンまたはテルペン系アルコールの少なくとも１種を含有することを特徴とする請求項１乃至３のいずれかに記載のゼラチン固形物。
【請求項５】テルペン系化合物として、メントールまたはその誘導体の少なくとも１種を含有することを特徴とする請求項１乃至３のいずれかに記載のゼラチン固形物。
【請求項６】さらに可塑剤を含有する請求項１乃至５のいずれかに記載のゼラチン固形物。
【請求項７】請求項１乃至６のいずれかに記載のゼラチン固形物からなるゼラチン皮膜を外皮として有するカプセル。
【発明の詳細な説明】
【０００１】
【発明の属する技術分野】本発明は食品、医薬品、医薬部外品又は化粧品等に広く利用されているカプセル剤の皮膜として有利に利用できるゼラチン固形物に関する。より詳細には、本発明は、その製造工程で気泡が混入しにくいか若しくは混入しても短時間の脱気処理で除去でき、効率的に製造できるゼラチン固形物に関する。さらに本発明は、製造の効率化に伴って高温下で曝される時間が短縮できるため、品質の劣化が少なく所望のゲル強度を安定して備えるゼラチン固形物に関する。
【０００２】
【従来の技術】ゼラチンは、ソフトカプセル基材として食品、医薬品や化粧品の分野で、また写真感光材料などの工業分野で広く利用されている。
【０００３】従来より採用されているゼラチンの溶解方法には、①冷水に十分浸漬し膨潤させた後に加熱溶解させる方法と、②温水中に強力な撹拌でもって分散させ、溶解させる方法がある。しかしながら、前者①の方法は工業的に時間がかかるという問題があり、後者②の方法は溶解時間は短縮できるが、ママコが発生したり、泡の巻き込みが発生するという問題がある。
【０００４】ママコは、ゼラチンが溶媒に添加される際にゼラチン粉粒体が集合体となった状態で外側だけが溶解することにより生じ、その結果、外側に形成されたゲル状の被膜が内側のゼラチンを粉粒体のままで包囲して、ゼラチンの溶解を妨げる。このため、ゼラチン粉粒体が集合体となって外側が溶解する前に、強力に撹拌することによって、十分分散させることが必要となる。
【０００５】しかしながら、かかる方法によってママコの発生は抑制できても、強力な撹拌によって気泡が発生しゼラチン内に混入するという問題が生じる。このため、かかる気泡の発生及び混入を回避するために、消泡剤を配合する方法、緩和な撹拌力で時間をかけながら撹拌する方法、溶解後加温状態で脱泡処理を行う方法等を適宜組み合わせて使用されているのが実情である。
【０００６】
【本発明が解決しようとする課題】本発明者らは、研究の過程で、かかる従来のゼラチンの調製方法によると、撹拌処理や脱泡処理においてゼラチン含有溶液（ゼラチン溶解溶液）が長時間にわたって加温状態に曝されるため、粘度低下が生じて最終的に調製されるゼラチン固形物のゲル強度が不安定となり経時的に低下する現象が生じること、その結果、カプセルの製造においては、ゼラチンシート基材間で接合率（ゲル強度）が異なる種々のシートが形成されるためカプセル成型が困難になること、シート状に調製する際に厚さの調節が困難になること、また濁りが生じてクリア感に優れたゼラチン基材が調製できないこと、等といった種々の問題が発生することを見出した。
【０００７】そこで本発明は、上記問題を解決する手段を提供することを目的とするものである。具体的には、本発明はゼラチン固形物の調製に際してゼラチン溶解液に気泡が混入しないか又は混入しても簡便に除去できるゼラチン固形物を提供することを目的とする。また本発明は、容易に脱泡できるため高温下での長期間の撹拌／脱気処理を回避して調製できるゼラチン固形物を提供することを目的とする。すなわち別の観点から、本発明は製造の効率化、特に脱気時間の短縮化を実現できるゼラチン固形物を提供することを目的とする。また、本発明は脱気時間の短縮化に伴って劣化が少なく、カプセル基材として良好な品質を備えたゼラチン固形物を提供することを目的とする。
【０００８】
【課題を解決するための手段】本発明者らは、上記課題を解決すべく鋭意研究を重ねた結果、ゼラチンを含有する組成物に特定の割合でテルペン系化合物、特にメントール又はその誘導体等のテルペン系アルコールを配合することによって、当該化合物が消泡剤若しくは脱泡剤として機能して、ゼラチンを含有する粉体組成物を温水に溶解撹拌する際に気泡が混入しにくく、また混入した気泡はその後の脱気処理で短時間に除去できることを見出した。さらにその他の配合成分として使用される香料などの揮発性成分は、脱気工程において損失の大きい成分であるが、本発明においてはそれを殆ど損失させないか

若しくは損失度を低減させることができ、成分定量性が高く、安定した品質のゼラチン固形物が調製できることを見出した。そして、かかる製造工程で調製されたゼラチン固形物は、製造工程において長期間高温に曝されることから回避できるため、粘度低下が少なく安定したゲル強度を備えており、このためカプセルとしての成型が容易でカプセル基材として有用であることが確認された。本発明は、かかる知見に基づいて開発されたものである。

【0009】すなわち本発明は下記（1）～（6）に掲げるゼラチン固形物である：

（1）ゼラチン及びテルペン系化合物を含有するゼラチン固形物であって、テルペン系化合物の配合割合がゼラチン固形物100重量部あたり0.005～10重量部であることを特徴とするゼラチン固形物。

（2）ゼラチン溶解液に発生する気泡に対する消泡剤としてテルペン系化合物を配合してなることを特徴とする、ゼラチン及びテルペン系化合物を含有するゼラチン固形物。

（3）ゼラチン固形物100重量部中のゼラチンの配合割合が20～80重量部である（1）記載のゼラチン固形物。

（4）テルペン系化合物として、テルペン系ケトンまたはテルペン系アルコールの少なくとも1種を含有することを特徴とする（1）乃至（3）のいずれかに記載のゼラチン固形物。

（5）テルペン系化合物として、メントールまたはその誘導体の少なくとも1種を含有することを特徴とする（1）乃至（3）のいずれかに記載のゼラチン固形物。

（6）さらに可塑剤を含有する（1）乃至（5）のいずれかに記載のゼラチン固形物。

【0010】また本発明は上記（1）乃至（6）のいずれかに記載のゼラチン固形物からなるゼラチン皮膜を外皮として有するカプセルである。

【0011】なお、本発明においてゼラチン固形物とは、固体状（立方形、球状、楕円形、円柱形、円錐形、多形など）やシート状の一定形状を有する弾性ゼラチン体を意味するものである。また固体状ゼラチンの適用例としては、ゲル状芳香剤やゲル状防虫剤などがあり、またシート状ゼラチンの適用例としては口腔投与用のカプセル用被膜剤（カプセル外皮）などがある。

【0012】

【発明の実施の形態】本発明のゼラチン固形物は、基本的な成分としてゼラチンとテルペン系化合物を含有するものである。

【0013】本発明で用いられるゼラチンは、可食性であればよく、ゼラチン、酸性ゼラチン、アルカリ性ゼラチン、ペプタイドゼラチン、低分子ゼラチン、ゼラチン誘導体等がいずれも包含される。これらは単独で使用されても、2種以上を任意に組み合わせて使用されてもよい。好ましくはカプセル基剤として用いられる可食性のゼラチンである。

【0014】本発明のゼラチン固形物に含まれるゼラチンの配合割合は、特に制限されないが、通常20～80重量部、好ましくは50～70重量部の範囲から適宜選択される。

【0015】本発明において用いられるテルペン系化合物は、可食性のものであればよく、例えばメントン／イソメントン、(－)-メントン、(＋)-メントン、(－)-イソメントン、(＋)-イソメントン、l－カルボン、d－カルボン、ジヒドロカルボン、プレゴン、ピペリトン及びショウノウ等のテルペン系ケトン；イソプレゴール、l－イソプレゴール、d－ネオイソプレゴール、d－イソプレゴール、d－ネオイソプレゴール、l－メントール、dl-メントール、d－ネオメントール、d－イソメントール、d－ネオイソメントール、d－テルピネオール及びベリラアルコール等のテルペン系アルコール等が包含される。これらは1種単独で用いてもよく、また2種以上を任意に組み合わせて用いることもできる。

【0016】好ましくはメントールまたはメントールの誘導体である。メントール誘導体には、上記に掲げるもののほか、乳酸l－メンチル等を挙げることができる。これらもまた1種単独で用いても、2種以上を任意に組み合わせて用いてもよい。より好ましくはl－メントール、dl-メントールである。

【0017】本発明のゼラチン固形物に配合されるテルペン系化合物の配合割合は、特に制限されないが、ゼラチン固形物100重量部あたり0.005～10重量部、好ましくは0.01～5重量部、より好ましくは0.05～3.5重量部の範囲を挙げることができる。

【0018】また、これらのテルペン系化合物は、本発明のゼラチン固形物に含まれるゼラチン100重量部に対して、通常0.025～15重量部、好ましくは0.025～10重量部、より好ましくは0.1～5重量部の割合となるように用いられることが望ましい。

【0019】本発明のゼラチン固形物には、上記成分に加えて、さらに可塑剤を配合することができる。

【0020】本発明で用いられる可塑剤としては、グリセリン；D－ソルビトール、ショ糖、マンニトール、果糖、ショ糖アルコール及び異性化糖等の糖類；プロピレングリコール及びポリエチレングリコール等のグリコール類を好適に挙げることができる。これらは1種単独で用いられても、また2種以上を任意に組み合わせて使用することもできる。本発明においては可塑剤の一つとして少なくともグリセリンを用いるのが好ましく、成形性の観点からはグリセリンと上記糖類又はグリコール類の少なくとも1種を併用することが好ましい。

【0021】ゼラチン固形物に配合される上記可塑剤の配合割合としては、最終ゼラチン固形物100重量部あたり、通常1～50重量部、好ましくは5～40重量

部、より好ましくは１０～３０重量部となるような割合を挙げることができる。

【００２２】なお、可塑剤を用いる場合、上記テルペン系化合物は当該可塑剤１００重量部に対して０．２～２０重量部、好ましくは０．５～１２．５重量部、より好ましくは０．５～１１．５重量部となるような割合で用いることができる。

【００２３】さらに本発明のゼラチン固形物には、本発明の効果を損なわないことを限度として、上記成分に加えて色素や顔料等の着色料、香料（芳香剤）、甘味料、防腐剤、崩壊剤、界面活性剤、矯味剤、矯臭剤、消泡剤、クエン酸やリンゴ酸等の有機酸等を配合することができる。

【００２４】ここで香料は、合成品並びに天然物の別を問うことなく、用途等に応じて適宜選択することができる。特に限定されるものではないが、通常は食品添加物に指定されている可食性の香料を使用することが好ましい。具体的には、レモンオイル、オレンジオイル、グレープフルーツオイル、ライムオイル、ペパーミント、スペアミント、ハッカ、ラベンダー等の精油を挙げることができる。これらの香料は、１種単独で使用しても任意の2種以上を混合して使用することもできる。

【００２５】また甘味料としては、前述するゼラチン固形物の成分と相溶性があって本発明の効果を損なわないものであれば特に制限されず、例えばショ糖、マンニトール、ソルビトール；キシロースやキシリトールなどの低甘味度甘味料；またはサッカリンナトリウム、ステビオサイド、酵素処理ステビオサイト、アスパルテーム、カンゾウ抽出物、ソーマチン等の高甘味度甘味料等を挙げることができる。これらの甘味料のゼラチン固形物に対する配合割合は特に制限されず適宜選択調製することができるが、該ゼラチンから調製されるカプセルの呈味及び風味のよさから、ゼラチン固形物１００重量部あたり０．１～１０重量部、好ましくは０．５～５重量部（甘味料を糖度の点からショ糖に換算した割合）の範囲で含まれることが望ましい。

【００２６】着色料としては、可食性色素であればいずれも使用でき、法定色素、合成系食用色素及び天然系食用色素等を広く挙げることができる。具体的には、合成系食用色素として、食用赤色２号、食用赤色３号、食用赤色色素１０２号、食用赤色１０４号、食用赤色１０５号、食用赤色１０６号、食用黄色４号、食用黄色５号、食用青色１号、食用青色２号、製剤金茶色ＮＨ、製剤梅漬紅色、製剤メロン色、製剤緑色Ｙ、製剤チョコレート色Ｎｏ．４、製剤チョコレート色Ｎｏ．５など；天然系食用色素として、ウコン色素製剤、クチナシ黄色素及び製剤、合成β－カロチン製剤、パーム油カロテン製剤、ベニバナ黄色素及び製剤、アトナー色素製剤、トウガラシ色素製剤、紅麹色素及び製剤、シソ色素製剤、赤大根色素製剤、赤キャベツ色素製剤、ムラサキイモ色素、ラック色素及び製剤、コチニール色素製剤、クチナシ青色素及び製剤、クロロフィル製剤、クチナシ色素製剤、カカオ色素及び製剤などがあげられるが、これらに限定されない。これらの着色料のゼラチン固形物に対する配合割合は特に制限されず適宜選択調製することができる。

【００２７】消泡剤としては、可食性の消泡剤であれば良く、ポリジメチルシロキサンなどのシリコーン系消泡剤；多価アルコールエステル、脂肪酸ショ糖エステルなどの界面活性剤系消泡剤；またエタノール、プロパノールなどのアルコール類などが例示されるが、これに限定されない。

【００２８】本発明のゼラチン固形物は、常法に従って、各成分を水とともに混合し、次いで乾燥固化することによって弾性を備えたゼラチン固形物として調製することができる。また上記混合工程は、必要に応じて、加熱、撹拌及び脱気工程を組み合わせて行うことができる。該混合物の加熱温度としては、ゼラチンの溶解温度以上であればよく、例えば６０℃以上、好ましくは７０～８０℃の範囲から選択される。

【００２９】本発明のゼラチン固形物は、具体的には次のように調製することによって気泡を含まないゼラチン固形物として得ることができる。すなわち、まず４０～８０℃の温水にテルペン系化合物や必要に応じて可塑剤を添加混合して撹拌する。次いで、６０～８０℃の条件下でゼラチンを配合して撹拌し、得られたゼラチン混合溶液を均一に混合し、ゼラチン溶解液とした後に脱気処理する。

【００３０】ここでゼラチン混合溶液の撹拌は、７０～８０℃の条件下で行われることが好ましい。また、脱気処理は５０～８０℃、好ましくは６０～７５℃の条件下で、０．５～１００分間、好ましくは１～５０分間、より好ましくは３～３０分間にわたって行うことが望ましい。なお、脱気処理は、ジャケット式脱泡釜や真空脱泡撹拌機等のように、加熱と脱気が同時に行える脱気装置を用いることによって簡便に行うことができる。

【００３１】次いで得られるゼラチン溶解液を所望の形状に成形して乾燥固化することによってゼラチン固形物を調製することができる。当該乾燥工程は、特別な手段を要するものではなく、例えば気流式回転乾燥機などを用いて常法に従って行うことができる。かくして得られるゼラチン固形物は、通常３～１５重量％程度、好ましくは４～８重量％程度の水分含有率を有する弾性体として調製される。

【００３２】本発明のゼラチン固形物は、後述する実施例で示すように、製造工程においてゼラチン溶解液に混入した気泡を短時間の脱気処理で簡便に除去できるものであることを特徴とするものである。このため、本発明のゼラチン固形物は、加温状態下（高温条件下）に曝される時間が有意に短縮でき、その結果、乾燥固化して調製されるゼラチン固形物は粘度低下が有意に抑制され

る。ゆえに、得られるゼラチン固形物は、乾燥時期にかかわらず製造ラインの初期から後期にかけて安定したゲル強度を発現し、このため製造工程において一定のゲル強度を有するゼラチン固形物が安定的に調製できる。

【００３３】さらに、本発明のゼラチン固形物は、加温状態下（高温条件下）に曝される時間が有意に短縮できるため、乾燥固化後、濁りの発生が抑制でき、これによってクリア感（透明感）に優れたゼラチン固形物となる。

【００３４】本発明のゼラチン固形物は、好適にはカプセル基材（皮膜、外皮）として用いることができる。本発明のゼラチン固形物を外皮として有するカプセルは、従来公知のカプセルの製造法、例えば平板法またはロータリーダイ法等に準じて調製することができる。

【００３５】具体的には、まず、上記の方法に従ってゼラチン及びテルペン系化合物、必要に応じて可塑剤を含む各種の成分を混合し、撹拌、脱気処理して得られたゼラチン溶解液（カプセル皮膜用液）を型枠に流してシート状に成形する。該シート基材の厚みとしては、通常０．２～１．５㎜、好ましくは０．４～１㎜を挙げることができる。次いで、カプセルは２枚のシート基材を対向方向に回転する一対の円筒型カプセル形成用金型間に供給し、同時にそのシート間に充填内容物を封入しながら両シートを接着させて金型形状のカプセル部分を打ち抜く方法によって製造することができる。このようにして得られるカプセルは乾燥後、タンブラー等で磨きをかけて仕上げられる。

【００３６】カプセルの形状は、特に制限されずオーバール（フットボール）型、オブロング（長楕円）型、及びラウンド（球状）型等の一般的な形状のほか、涙型、三角形などの変形（異形）型を採用することもできる。カプセルの大きさも特に制限されないが、服用するには直径３０㎜以下であることが望ましく、食感も好ましい。具体的には直径１～１０㎜の範囲のものを挙げることができる。

【００３７】上記カプセルに充填する内容物は特に制限されない。好ましくは可食性物であり、例えば可食性油脂や該油脂を含む食品、ビタミン、ミネラル、鉱油等を含む栄養補強剤、医薬品などの組成物を挙げることができる。より具体的には、ビタミンA類及び誘導体、ビタミンD類、ビタミンE類及び誘導体、ビタミンK類、γ－オリザノール、リノレン酸、カロチン類などの脂溶性成分；中鎖脂肪酸トリグリセリド、大豆油、小麦胚芽油、トウモロコシ油、綿実油、オリーブ油、ゴマ油、サンフラワー油、落花生油、ナタネ油、ヒマワリ油、パセリ油等の可食性油脂などを例示することができる。なお、これらの成分中には、食品フレーバー、香料、甘味料などの呈味料、色素や顔料等の着色料、安定剤、保存剤等の各種添加剤を配合することができる。なお、香料として、例えばレモンオイル、オレンジオイル、グレープフルーツオイル、ライムオイル、ペパーミント、スペアミント、ハッカ等の精油を挙げることができる。

【００３８】このようにして得られるカプセルは、医薬品、医薬部外品、化粧品、及び食品などに好適に用いることができる。

【００３９】

【実施例】以下、実施例を挙げて本発明の特徴とするところをより明確にする。ただし、本発明はこれらの実施例等に何ら限定されるものではない。

実施例１～３

（１）表１に示す原料を用いて下記の方法に従ってシート状ゼラチン固形物（実施例１～３、比較例１、２）を作製した。なお、表１の各成分の割合は、特に言及しないかぎり、重量部を意味するものである。

【００４０】

【表１】

	実施例１	実施例２	実施例３	比較例１	比較例２
ゼラチン	100	100	100	100	100
グリセリン	30	30	30	30	30
ソルビトール	15	15	15	15	15
メントール	0.84	0.13	0.84	－	－
水	95	95	87	95	95
バッチ量	17.0 kg	17.0 kg	327.0 kg	17.0 kg	17.0 kg
消泡剤	全量に対して 4 g	全量に対して 4 g	－	全量に対して 4 g	－
脱気時間	5 分	１０分	4分	３５分	１３０分

【００４１】＜調製方法＞５０Ｌ容量の溶解タンクに入った約８５℃の逆浸透膜沪過膜水７．４Ｌ中に、グリセリン及びソルビトールをいれて混合し７０～８０℃条件下で、真空撹拌機を用いて撹拌した。なお、実施例１～３については、ソルビトールの添加に引き続いてメントールを配合し、上記温度条件下で各成分を混合し撹拌した。次いで、この中にゼラチンを加えて撹拌し、約８０℃に維持しながら溶解してゼラチン混合溶液を調製した。実施例１及び２並びに比較例１については、さらに消泡剤（商品名：トルハーNo.1、田辺製薬製）を配合して撹拌してゼラチン溶解液とした。

【００４２】これを、ジャケット式釜を有する真空脱気

装置を用いて約７５℃条件下で脱気処理した。具体的には水封式真空ポンプを利用して内圧が400mgHgから700mgHgになるように脱気処理を施した。ここで各ゼラチン溶解液について、脱気開始から脱気完了までの時間を測定し、脱気に要した時間（脱気時間）を求めた。なお脱気は、ジャケット式脱泡釜内の温度が７０℃になった時点でゼラチン溶解液を目視観察し気泡が確認されないことをもって、脱気完了と判断した。このとき気泡が確認された場合には、再度同じ操作を繰り返す。結果を表１に併せて示す。

【００４３】脱気終了後、ゼラチン溶解液を約６３℃に冷却し、次いで６０℃で一定時間放置した後、型枠に流し込み、２０～２８℃、湿度３０％の条件下で乾燥し、厚み０．７mm、水分含有率７～１５重量％のシート状ゼラチン固形物（実施例１～３、比較例１、２）を作製した。

【００４４】（２）上記で得られた各シート状ゼラチン固形物について、突き抜け強度を測定し、ゲル強度を評価した。

【００４５】具体的には、各シート状ゼラチン固形物を10cm×10cmに切断した後、レオメーター（SUN RHEO METER CR-300）の直径３mm針タイプのフランジが、該試料を12mm／分速度で突き抜けるのに必要な負荷力（kg）を測定した。突き抜け強度試験は、各ゼラチン溶解液について、脱気後６０℃で３０分間放置した後に乾燥成型したシート状ゼラチン試料（30分放置）と、脱気後６０℃で６００分間放置した後に乾燥成型したシート状ゼラチン試料（600分放置）のそれぞれについて行った。結果を表２に示す。なお、結果は各試料について１０回ずつ測定した平均値として表す。

【００４６】

【表２】

	実施例１	実施例２	実施例３	比較例１	比較例２
30分放置後成形	14.3 kg	13.6 kg	13.8 kg	12.2 kg	11.8 kg
600分放置後成形	14.1 kg	13.2 kg	13.6 kg	10.5 kg	10.1kg

【００４７】以上の結果から明らかなように、本発明のゼラチン固形物によれば、メントールを含有することによって顕著に脱気時間が短縮できた。またこのメントールの効果は消泡剤の存在下でも用量依存的に発揮されることがわかった。

【００４８】また、比較例１及び２のシート状ゼラチン固形物は、ゲル強度の経時的低下が観察されたが、本発明のシート状ゼラチン固形物は経時的に安定したゲル強度を有していた。これは、比較例のシート状ゼラチン固形物はその製造工程、特に脱気工程において長時間加温状態（７０℃）に曝されることに原因があると考えられた。すなわち、比較例のシート状ゼラチン固形物は、高温下での脱気処理に長期間要するためゼラチン溶解液が高温に長時間曝されて、その結果粘度が低下してゲル強度が不安定となり経時的に低下すると考えられた。

【００４９】ゲル強度はゼラチンの接合率（接合度）と関係する。このため、比較例のシート状ゼラチン固形物によれば、ゲル強度の経時的変動によって、製造時期（乾燥させるまでの時間や乾燥時間など）の相違に伴ってカプセルを成形する際のゼラチンシート基材間に接合率の差が生じ、カプセルの成形（基材の貼り合わせ）の調製が困難となった。さらに、粘度劣化によってカプセル製造時の皮膜厚が調節しにくかった。

【００５０】一方、本発明のシート状ゼラチン固形物は、短時間で脱気が完了するため加温状態（７０℃）での暴露の影響が少なく、このため上記のような問題が生じなかったものと考えられた。本発明のゼラチン固形物は、脱気工程が短縮できて製造の効率化が図られるだけでなく、得られるゼラチンの性能からもカプセルの製造に有利に用いられることが判明した。

【００５１】実施例４

食用ゼラチン１００重量％、食用グリセリンを３５重量％、ソルビトール１０重量％、水１００重量％及び色素０．０１５重量％からなるゼラチン混合溶液を用いて、上記実施例１に記載する方法に従ってシート状ゼラチン固形物を調製した。なお、色素はグリセリンの配合前に温水に配合して用いた。次いで、ロータリーダイ式ソフトカプセル製造機により、２枚のシート状ゼラチン固形物間に透明清澄な食用油からなるカプセル内容物を圧入し、両基材シートを接着させて前記内容物を該皮膜内に封入し、ソフトカプセル（直径６×８mm、オーバール型）を製造した。本発明のゼラチン固形物は、製造工程で加温の影響を殆ど受けないため濁りが抑制でき透明感に優れている。このため、得られたカプセルは極めてクリア感のあるものであった。

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(54) Title: THIN FILM WITH NON-SELF-AGGREGATING UNIFORM HETEROGENEITY, PROCESS FOR THEIR PRODUCTION AND DRUG DELIVERY SYSTEMS MADE THEREFORM

(57) Abstract: The invention relates to the film products and methods of their preparation that demonstrate a non-self-aggregating uniform heterogeneity. Desirably, the films disintegrate in water and may be formed by controlled drying process, or other process that maintains the required uniformity of the film. Desirably, the films contain a pharmaceutical and/or cosmetic active agent with no more than a 10% variance of the active agent pharmaceutical and/or cosmetic active agent per unit area of the film.

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THIN FILM WITH NON-SELF-AGGREGATING UNIFORM HETEROGENEITY, PROCESS FOR THEIR PRODUCTION AND DRUG DELIVERY SYSTEMS MADE THEREFROM

FIELD OF THE INVENTION

The invention relates to rapidly dissolving films and methods of their preparation. The films may also contain an active ingredient that is evenly distributed throughout the film. The even or uniform distribution is achieved by controlling one or more parameters, and particularly the elimination of air pockets prior to and during film formation and the use of a drying process that reduces aggregation or conglomeration of the components in the film as it forms into a solid structure.

BACKGROUND OF THE RELATED TECHNOLOGY

Active ingredients, such as drugs or pharmaceuticals, may be prepared in a tablet form to allow for accurate and consistent dosing. However, this form of preparing and dispensing medications has many disadvantages including that a large proportion of adjuvants that must be added to obtain a size able to be handled, that a larger medication form requires additional storage space, and that dispensing includes counting the tablets which has a tendency for inaccuracy. In addition, many persons, estimated to be as much as 28% of the population, have difficulty swallowing tablets. While tablets may be broken into smaller pieces or even crushed as a means of overcoming swallowing difficulties, this is not a suitable solution for many tablet or pill forms. For example, crushing or destroying the tablet or pill form to facilitate ingestion, alone or in admixture with food, may also destroy the controlled release properties.

As an alternative to tablets and pills, films may be used to carry active ingredients such as drugs, pharmaceuticals, and the like. However, historically films and the process of making drug delivery systems therefrom have suffered from a number of unfavorable characteristics that have not allowed them to be used in practice.

Films that incorporate a pharmaceutically active ingredient are disclosed in expired U.S. 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 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.

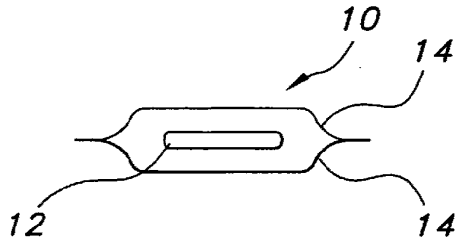

FIG. 1

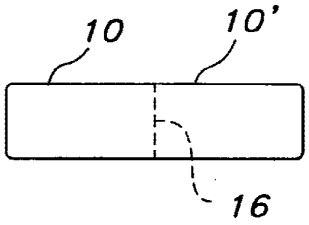

FIG. 2

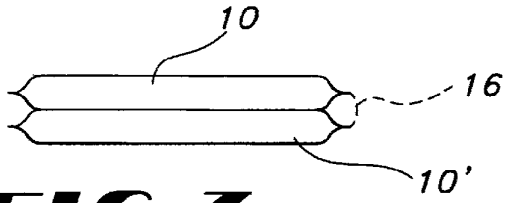

FIG. 3

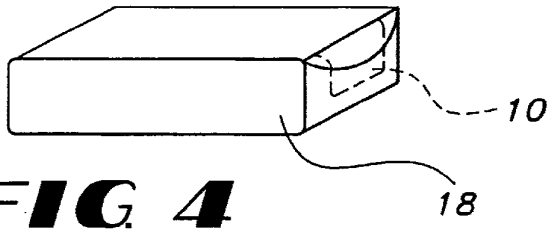

FIG. 4

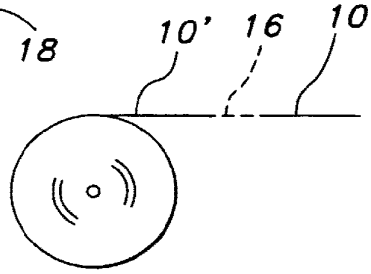

FIG. 5

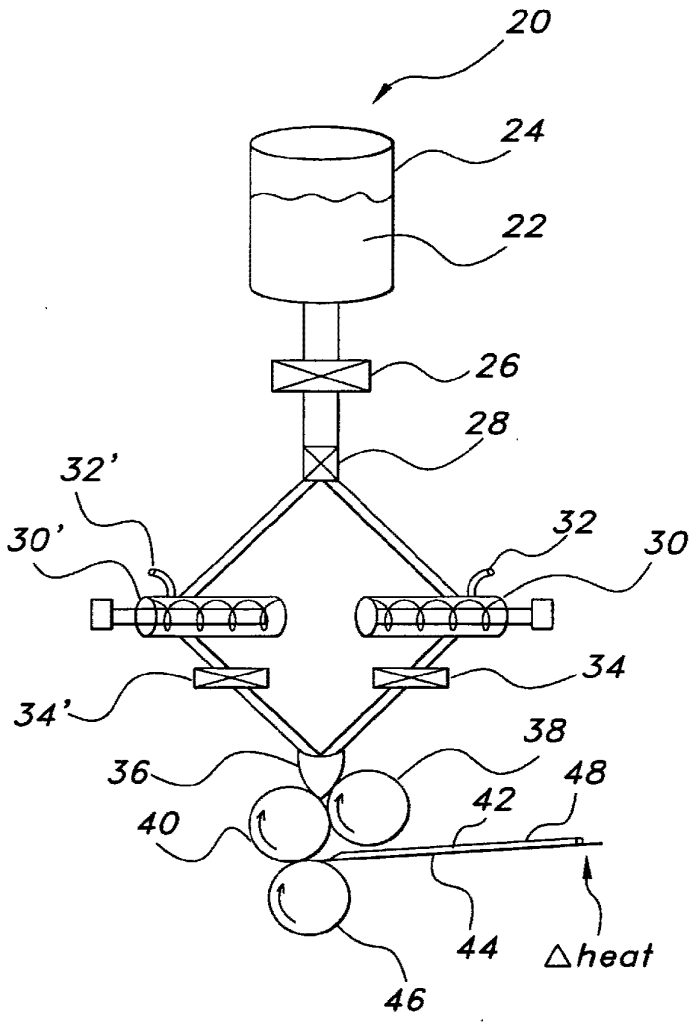

FIG. 6

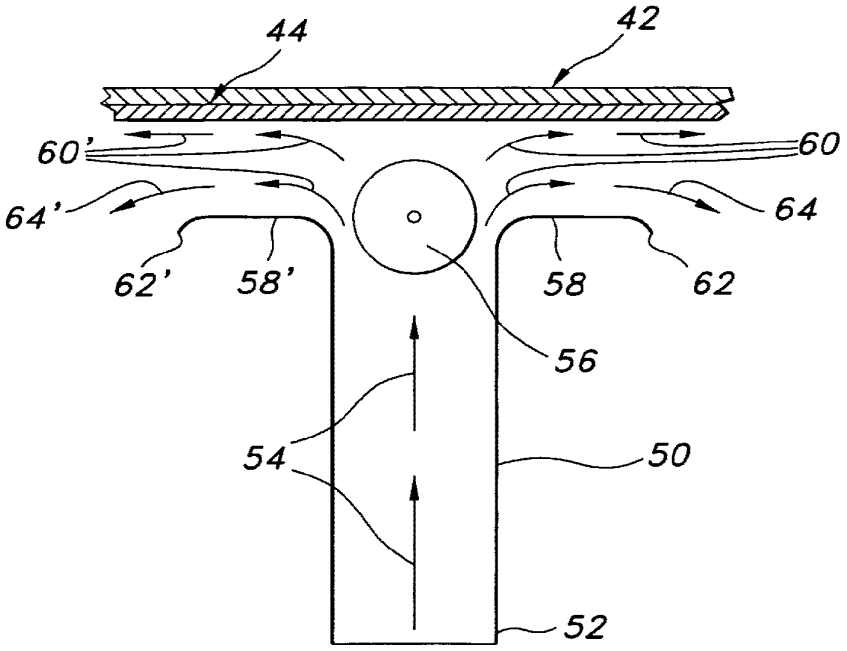

FIG 7

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
X	US 5 393 528 A (STAAB ROBERT J) 28 February 1995 (1995-02-28) column 11, line 1-6,41-47	1-76
X	EP 1 110 546 A (JOHNSON & JOHNSON CONSUMER) 27 June 2001 (2001-06-27) page 4, line 32-37	1-76

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 January 2003	06/02/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Skjöldebrand, C

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

INTERNATIONAL SEARCH REPORT

Interna Application No
PCT/US 02/32575

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 849 246 A (SCHMIDT WOLFGANG) 18 July 1989 (1989-07-18) cited in the application the whole document	1-76
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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
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 02/32575

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 32, 44 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1-75 (in part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-75 (in part)

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

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

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

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

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

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat pplication No
PCT/US 02/32575

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Information on patent family members

Internati__ Application No
PCT/US 02/32575

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European Patent Office
Office européen des brevets

(11) EP 0 598 606 B1

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention of the grant of the patent:
30.06.1999 Bulletin 1999/26

(51) Int. Cl.[6]: **A61L 25/00**

(21) Application number: **93309172.0**

(22) Date of filing: **17.11.1993**

(54) Extrudable compositions for topical or transdermal drug delivery

Extrudierbare Zusammensetzungen zur topischen oder transdermalen Wirkstoffabgabe

Compositions extrudables pour l'administration topique ou transdermique de médicaments

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB IE IT LI LU MC NL PT SE

(30) Priority: **18.11.1992 US 979509**

(43) Date of publication of application:
25.05.1994 Bulletin 1994/21

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EP 0 598 606 B1

Description

[0001] 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.

[0002] 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.

[0003] 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.

[0004] 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.

[0005] In EPO application 0297828, Charkoudian *et al* describe a bandage which is coated or impregnated with a soft, waxy, low melting point composition containing a medicament. In example 1 a solution of polyethylene glycol and benzocaine is coated onto a non-woven 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 pyrrolidine (PVP), polyethylene glycol and benzocaine, and letting the methanol evaporate. The resulting composition is extremely tacky and dissolves extremely slowly on contact with wound exudate. Moreover, since the compositions have melting points below 40°C, they cannot be subjected to conventional ethylene oxide sterilisation techniques.

[0006] In US 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 plasticiser.

[0007] International patent application WO91/05574 describes water-resistant hydrogel-forming wound dressings or skin coating compositions suitable for household and veterinary use. These compositions comprise a first hydrophilic polymer, and a second polymer that interacts with the first polymer to produce a water-resistant hydrogel that is film-forming and suitable for use in wound dressings.

[0008] 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 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 liquid 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.

[0009] Accordingly, it is an object of the present invention to provide an extrudable composition for the topical or transdermal delivery of a medicament, which, upon contact with body fluid, releases a controlled amount of medicament to the area to be treated.

[0010] 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.

[0011] 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.

[0012] 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

[0013] 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.

[0014] 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.

[0015] 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). After contact with body fluids, the composition dissolves into a matrix and releases the medicament, but it still possess good structural integrity.

[0016] 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.

[0017] 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 plasticiser selected from the group consisting of glycerin and polyethylene glycol; and
(d) about 0.01-10% by weight of medicament.

[0018] 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 94.4°C (170 °F), or E-beam or cobalt sterilization techniques. In addition, they are also sufficiently flexible so that they are comfortable to wear.

[0019] 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

[0020]

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

[0021] 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.

[0022] 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.

[0023] 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..

[0024] 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.

[0025] 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.

[0026] 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.

[0027] 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.

[0028] 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.

[0029] 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.

[0030] 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%.

[0031] 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.

[0032] 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.

[0033] 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.

[0034] 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, polymeth-

acrylic 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.

[0035] 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%.

[0036] 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.

[0037] 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.

[0038] 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.

[0039] 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.

[0040] 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.

[0041] 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.

[0042] 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."

[0043] 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%.

[0044] 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 CAR-

BOWAX 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.

[0045] 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.

[0046] 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).

[0047] 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.

[0048] 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.

[0049] 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.

[0050] 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.

[0051] 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 0.1 cm (1.0 mil) to "thick" films of about 2 cm (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 7.15 kg/cm (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.

[0052] 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.

[0053] 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.

[0054] 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.

[0055] This invention will now be illustrated in greater detail by reference to the following examples. In these examples, all the parts, percents and ratios are by weight unless otherwise indicated.

EXAMPLE 1

[0056] An ointment film was formed by adding 100 g of polyethylene oxide (POLYOX N-10) to 200 g 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 g 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

[0057] 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/g
	Neomycin Sulfate[2]	3.5 mg/mg
	Polymyxin B Sulfate[3]	10,000 units/g
B	Neomycin Sulfate[2]	3.5 mg/mg
	Polymyxin B Sulfate[3]	10,000 units/g
C	Benzalkonium Chloride	0.13 (% w/w)

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

[0058] Samples A, B and C were not sterilized.

[0059] Additional samples were prepared as follows:

Sample D = Sample A ethylene oxide sterilized at 91.7°C (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.

[0060] 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.

[0061] 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

(continued)

Clear Zone in Millimeters			
Sample	M. luteus	S. epidermidis	B. bronchiseptica
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

[0062] The above results demonstrate that the compositions of the present invention (Samples A-D) exhibit good antimicrobial activity.

EXAMPLE 3

[0063] 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

[0064] Approximately 100 g 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 allyl 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 - Allyl 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%

[0065] 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

[0066] 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 0.635 cm (1/4") or less.

Extruding the Ointment

[0067] A Killian extruder was used for extrusion. Initial settings were as follows:

ZONE 1	ZONE 2	ZONE 3	ZONE 4	DIE	SCREW SPEED	LINE SPEED
83.3°C (150 °F)	88.9°C (160 °F)	97.2°C (175 °F)	100°C (180 °F)	111.1°C (200 °F)	50 RPM	6.4 m (21 FT)/MIN

[0068] 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

[0069] 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.

[0070] 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 %)

[0071]

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

[0072]

Polyvinylpyrrolidone - 40 g
Polyethylene Glycol 400 - 60 g
Methanol - 125 ml

[0073] 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

[0074] 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 - Allyl 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

[0075] 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 33.9 to 101.7 grammes/m^2 (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

[0076] 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

[0077] 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

[0078] 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

[0079] 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

[0080] 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

[0081] 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.

[0082] 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.

[0083] Various modifications can be made to the above-described embodiment without departing from the 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;
   c) a plasticizer; and
   d) a medicament, characterised in that these compounds are present in the following amounts: 5-70% of (a), about 1-10% of (b), about 10-80% of (c) and about 0.01-10% of (d) by weight.

2. The composition of claim 1 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.

3. The composition of claim 1 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.

4. The composition of claim 1 wherein (a) comprises at least one polymer selected from the group consisting of hydroxypropyl cellulose and polyethylene oxide.

5. The composition of claim 4 wherein said polyethylene oxide has a number average molecular weight of greater than about 600,000.

6. The composition of claim 4 wherein said polyethylene oxide has a number average molecular weight of less than about 600,000.

7. The composition of claim 4 wherein said polyethylene oxide has a number average molecular weight of between about 100,000 and 400,000.

8. The composition of claim 4 wherein said hydroxypropyl cellulose has a number average molecular weight greater than about 60,000.

Patentansprüche

1. Zusammensetzung, welche umfaßt:

   a) thermoplastisches wasserlösliches Polymer;

   b) ein wasserlösliches Polymer, das von einer Carbonsäure abgeleitet ist, oder ein pharmazeutisch annehmbares Salz desselben;

   c) einen Weichmacher; und

   d) ein Arzneimittel, dadurch gekennzeichnet, daß diese Verbindungen in den folgenden Mengen vorliegen: 5-70 Gew.-% von (a), etwa 1-10 Gew.% von (b), etwa 10-80 Gew.% von (c) und etwa 0,01-10 Gew.-% von (d).

2. Zusammensetzung nach Anspruch 1, dadurch gekennzeichnet, daß sie etwa 10-40 Gew.-% von (a), etwa 1-10 Gew.-% von (b), etwa 30-80 Gew.-% von (c) und etwa 0,01-10 Gew.-% von (d) umfaßt.

3. Zusammensetzung nach Anspruch 1, dadurch gekennzeichnet, daß sie etwa 23-30 Gew.-% von (a), etwa 5-7 Gew.-% von (b), etwa 60-70 Gew.-% von (c) und etwa 0,01-10 Gew.-% von (d) umfaßt.

4. Zusammensetzung nach Anspruch 1, dadurch gekennzeichnet, daß (a) wenigstens ein Polymer umfaßt, das ausgewählt ist aus der Gruppe, die aus Hydroxypropylcellulose und Polyethylenoxid besteht.

5. Zusammensetzung nach Anspruch 4, dadurch gekennzeichnet, daß besagtes Polyethylenoxid ein Molekulargewicht im Zahlenmittel von mehr als etwa 600.000 aufweist.

6. Zusammensetzung nach Anspruch 4, dadurch gekennzeichnet, daß besagtes Polyethylenoxid ein Molekulargewicht im Zahlermittel von weniger als etwa 600.000 aufweist.

7. Zusammensetzung nach Anspruch 4, dadurch gekennzeichnet, daß besagtes Polyethylenoxid ein Molekulargewicht im Zahlermittel von zwischen etwa 100.000 und 400.000 aufweist.

8. Zusammensetzung nach Anspruch 4, dadurch gekennzeichnet, daß besagte Hydroxypropylcellulose ein Molekulargewicht im Zahlenmittel von mehr als etwa 60.000 aufweist.

Revendications

1. Composition comprenant:

   a) un polymère hydrosoluble thermoplastique;

b) un polymère hydrosoluble dérivé d'un acide carboxylique ou d'un de ses sels pharmaceutiquement acceptables;

c) un plastifiant; et

d) un médicament,

caractérisée en ce que ces composés sont présents dans les proportions suivantes: 5-70% de (a), environ 1-10% de (b), environ 10-80% de (c) et environ 0,01-10% de (d), en poids.

2. Composition selon la revendication 1, comprenant environ 10-40% de (a), environ 1-10% de (b), environ 30-80% de (c) et environ 0,01-10% de (d), en poids.

3. Composition selon la revendication 1, comprenant environ 23-30% de (a), environ 5-7% de (b), environ 60-70% de (c) et environ 0,01-10% de (d), en poids.

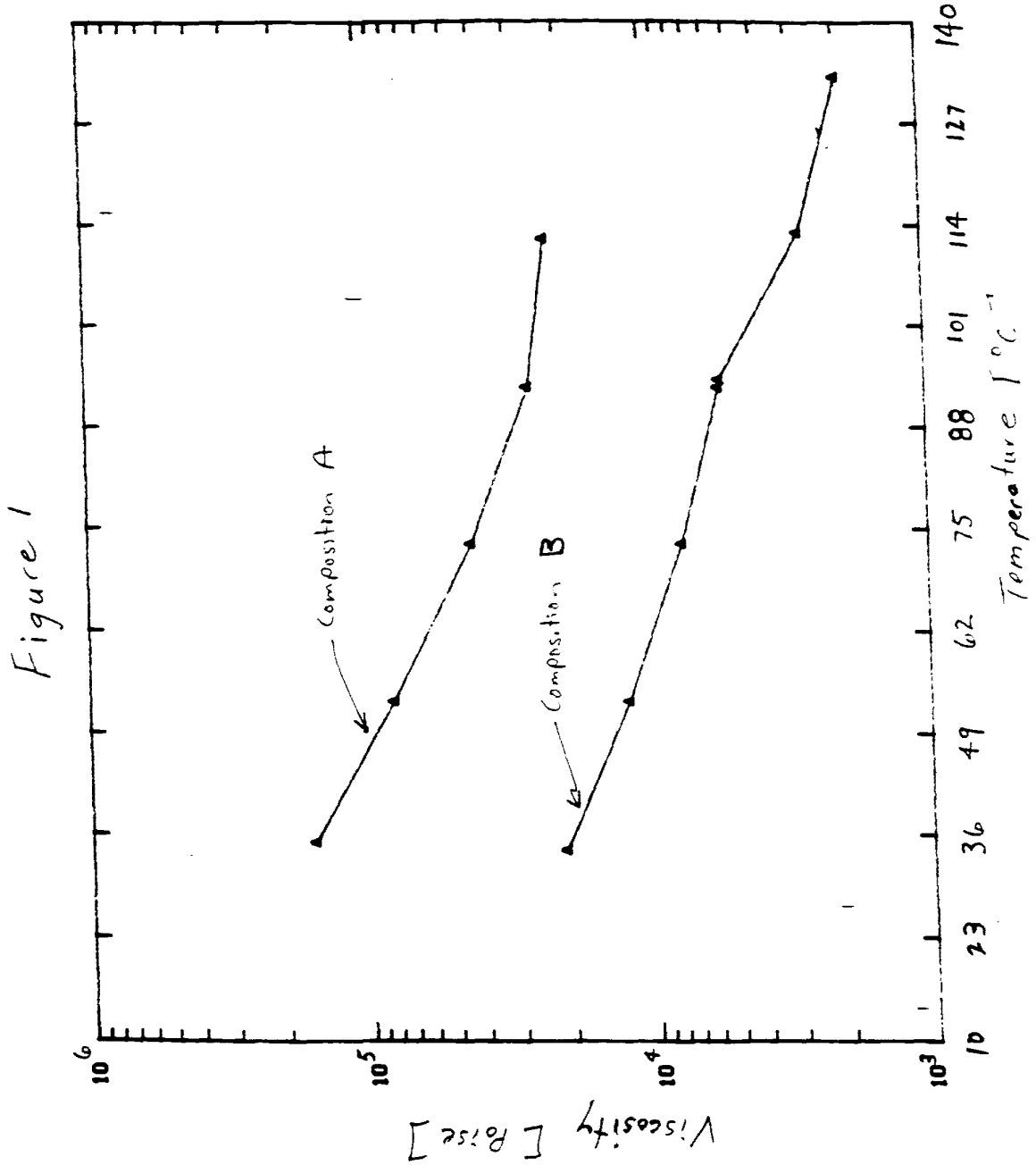
4. Composition selon la revendication 1, dans laquelle (a) comprend au moins un polymère choisi dans le groupe constitué par l'hydroxypropylcellulose et le poly(oxyde d'éthylène).

5. Composition selon la revendication 4, dans laquelle ledit poly(oxyde d'éthylène) possède une masse moléculaire moyenne en nombre supérieure à environ 600 000.

6. Composition selon la revendication 4, dans laquelle ledit poly(oxyde d'éthylène) possède une masse moléculaire moyenne en nombre inférieure à environ 600 000.

7. Composition selon la revendication 4, dans laquelle ledit poly(oxyde d'éthylène) possède une masse moléculaire moyenne en nombre comprise entre environ 100 000 et 400 000.

8. Composition selon la revendication 4, dans laquelle ladite hydroxypropylcellulose possède une masse moléculaire moyenne en nombre supérieure à environ 60 000.



Electronic Acknowledgement Receipt

EFS ID:	9662803
Application Number:	12537571
International Application Number:	
Confirmation Number:	5630
Title of Invention:	SUBLINGUAL AND BUCCAL FILM COMPOSITIONS
First Named Inventor/Applicant Name:	Garry L. Myers
Customer Number:	23869
Filer:	Jon Anthony Chiodo/Shannon Farischon
Filer Authorized By:	Jon Anthony Chiodo
Attorney Docket Number:	1199-82
Receipt Date:	15-MAR-2011
Filing Date:	07-AUG-2009
Time Stamp:	15:21:50
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 (SB/08)	1199-82_IDS_statement_03_15_11.pdf	6018805 5464a30277e19d9b31bb10616a5c3c92d716bfbd	no	6

Warnings:	
Information:	

2	Foreign Reference	EP00949925B11with_Abstract.pdf	469190 f74a7c46b63deadd6e9642bc7a8f4837512ae472	no	6
Warnings:					
Information:					
3	Foreign Reference	JP_Ref_with_Eng_Abstract_62126950.pdf	203877 12be05ad71c3ca1b5cfbdf9f0288b5feb94f8ae3	no	5
Warnings:					
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4	Foreign Reference	JP_Ref_with_Eng_Abstract_2265444.pdf	329568 b15d47f3fe9d9ec1d6d997dfedd3ee38518f643f	no	6
Warnings:					
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5	Foreign Reference	JP_Ref_with_Eng_Abstract_5147140.pdf	292584 9456ba86499359374c630eac6ded80db59b16366	no	5
Warnings:					
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6	Foreign Reference	JP_Ref_with_Eng_Abstract_7322812.pdf	272080 32d4cc8ce5d5d07dae1ce14c8937c9911546d808	no	5
Warnings:					
Information:					
7	Foreign Reference	JP_Ref_with_Eng_Abstract_2001279100.pdf	568298 ca05d153fccc24e0aad2fc76f23b6c5bf5334a39	no	8
Warnings:					
Information:					
8	Foreign Reference	WO03030882A1.pdf	3475928 6765b86ed501f644117c54ab5c50a5067894038d	no	77
Warnings:					
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9	NPL Documents	Lazaridou.pdf	847618 9e5337902da51d9c474dd1818817af78b2f7a237	no	12
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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
12/537,571	08/07/2009	Garry L. Myers	1199-82

CONFIRMATION NO. 5630

23869
HOFFMANN & BARON, LLP
6900 JERICHO TURNPIKE
SYOSSET, NY 11791

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Title:SUBLINGUAL AND BUCCAL FILM COMPOSITIONS

Publication No.US-2011-0033541-A1
Publication Date:02/10/2011

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(Not for submission under 37 CFR 1.99)

Application Number	12537571
Filing Date	2009-08-07
First Named Inventor	Myers et al
Art Unit	1614
Examiner Name	
Attorney Docket Number	1199-82

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	2	5800832		1998-09-01	Tapolsky et al	
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	2	20050147658	A1	2005-07-07	Tapolsky et al	

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	Application Number	12537571
	Filing Date	2009-08-07
	First Named Inventor	Myers et al
	Art Unit	1614
	Examiner Name	
	Attorney Docket Number	1199-82

	3	20050048102	A1	2005-03-03	Tapolsky et al	
	4	20060281775	A1	2006-12-14	Kelly, II et al	
	5	20070148097	A1	2007-06-28	Finn et al	
	6	20080254105	A1	2008-10-16	Tapolsky et al	

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	1	9817251	WO		1998-04-30	Virotex Corporation		☐
	2	9955312	WO		1999-11-04	Virotex Corporation		☐
	3	2007070632	WO	A2	2007-06-21	Biodelivery Sciences Int., Inc.		☐
	4	2008011194	WO	A2	2008-01-24	Biodelivery Sciences Int., Inc.		☐

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	12537571
	Filing Date	2009-08-07
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	Art Unit	1614
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	Attorney Docket Number	1199-82

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	Abeer M. Al-Ghananeem et al., "Effect of pH on Sublingual Absorption of Oxycodone Hydrochloride." AAPS PharmSciTech 2006; 7(1) Article 23 (http://www.aapspharmscitech.org)	☐
	2	Mahmood et al., "A limited sampling method for the estimation of AUC and Cmax of carbamazepine and carbamazepine epoxide following a single and multiple dose of a sustained-release product." BrJ Clin Pharmacol 1998; 45: pp 241-246	☐

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	Application Number	12537571
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	Art Unit	1614
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☐ See attached certification statement.

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

☒ None

SIGNATURE

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Signature	/Jon A. Chiodo Reg. No. 52,739/	Date (YYYY-MM-DD)	2009-09-03
Name/Print	Jon A. Chiodo	Registration Number	52,739

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(71) Applicant *(for all designated States except US)*: VIROTEX CORPORATION [US/US]; Suite 350, 4200 Research Forest Drive, The Woodlands, TX 77381 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: TAPOLSKY, Gilles, H. [FR/US]; 62 South Piney Plains, The Woodlands, TX 77382 (US). OSBORNE, David, W. [US/US]; 19 Quiet Oak Circle, The Woodlands, TX 77381 (US).

(74) Agent: PORTER, Gregory, L.; Arnold, White & Durkee, P.O. Box 4433, Houston, TX 77210 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: PHARMACEUTICAL CARRIER DEVICE SUITABLE FOR DELIVERY OF PHARMACEUTICAL COMPOUNDS TO MUCOSAL SURFACES

(57) Abstract

The present invention relates to a pharmaceutical delivery device for application of a pharmaceutical to mucosal surfaces. The device comprises an adhesive layer and a non–adhesive backing layer, and the pharmaceutical may be provided in either or both layers. Upon application, the device adheres to the mucosal surface, providing localized drug delivery and protection to the treatment site. The kinetics of erodability are easily adjusted by varying the number of layers and/or the components.

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PHARMACEUTICAL CARRIER DEVICE SUITABLE FOR DELIVERY OF PHARMACEUTICAL COMPOUNDS TO MUCOSAL SURFACES

FIELD OF THE INVENTION

The present invention relates generally to a water-erodable pharmaceutical carrier which adheres to mucosal surfaces for the localized delivery of pharmaceutical compounds and protection of the treatment site.

BACKGROUND OF THE INVENTION

The localized treatment of body tissues, diseases, and wounds requires that the particular pharmaceutical component be maintained at the site of treatment for an effective period of time. Given the tendency of natural bodily fluids to rapidly wash away topically applied pharmaceutical components, the topical treatment of wet mucosal tissues has been problematic. In the mouth, saliva, natural replacement of the mucosal tissue, as well as, eating, drinking, and speaking movements are some of the problems that have limited the effectiveness and residence time of pharmaceutical carriers.

Bioadhesive carriers are known in the art and include gels, pastes, tablets, and films. These products, however, may lack one or several of the preferred characteristics for an efficient and commercially acceptable pharmaceutical delivery device. Some characteristics which are preferred by users of bioadhesive carriers include water-erodability; ease of handling and application to the treatment site; ease of comfort; minimal foreign body sensation; and unidirectional, specific release into the mucosal tissue. Other preferred characteristics for an effective and user-friendly product for the treatment of mucosal surfaces include the use of pharmaceutically approved components or materials; instantaneous adhesion to mucosal surface upon application; increased residence time for the protection of the affected tissue or the delivery of the pharmaceutical component; and ease of removal of the delivery device from the affected tissue or natural erosion of the delivery device at the delivery site.

Bioadhesive gels which are used for application to mucosal tissues and especially the oral cavity are known in the art. For example, U.S. Patent No. 5,192,802 describes a bioadhesive teething gel made from a blend of sodium carboxymethyl cellulose and xanthan gum. The gel may also have potential use in the treatment of canker sores, fever blisters, and hemorrhoids. However, this type of pharmaceutical carrier has a very limited residence time, given that body fluids such as saliva quickly wash it away from the treatment site. Bioadhesive gels are also described in U.S. Patent Nos. 5,314,915; 5,298,258; and 5,642,749. The gels described in those patents use an aqueous or oily medium and different types of bioadhesive and gelling agents.

Denture adhesive pastes are another type of bioadhesive product known in the art. However, these preparations are used primarily for their adhesive properties, to adhere dentures to the gums, rather than for the protection of tissue or for the topical delivery of pharmaceuticals, although drugs such as local anesthetics may be used in the paste for the relief of sore gums. U.S. Patent Nos. 4,894,232 and 4,518,721 describe denture adhesive pastes. The '721 Patent describes a combination of sodium carboxymethyl cellulose and polyethylene oxide in polyethylene glycol.

Pastes have also been used as film protectants and as drug delivery systems. One such example having film forming and adhesive properties is the product commercialized under the name Orabase®-B, which is a thick gel or paste for the relief of mouth sores. Ingredients include guar gum, sodium carboxymethyl cellulose, tragacanth gum, and pectin. Even though it does provide numbing to the area of application, the film forming behavior and bioadhesion do not last. Thus, this product has a limited residence time.

Bioadhesive tablets are described in U.S. Patent No. 4,915,948. The water-soluble bioadhesive material used in this device is a xanthan gum or a pectin combined with an adhesion enhancing material such as a polyol. Although residence time is improved with the use of bioadhesive tablets, they are not user friendly, especially when used in the oral cavity, given the unpleasant feelings associated with their solidity, bulkiness, and slow erosion time.

Bioadhesive tablets are also described in U.S. Patent Nos. 4,226,848; 4,292,299; and 4,250,163, and are single layer or bilayer devices having an average thickness of 0.2 to 2.5 mm. The bioadhesive tablets described in these patents utilize a non-adhesive component such as cellulose ether, a bioadhesive component such as polyacrylic acid, sodium carboxymethyl cellulose, or polyvinylpyrrolidone, and a binder for tableting purposes. The cellulose derivatives may or may not be water-erodable.

The use of bandages or bioadhesive laminated films, which are thinner and flexible and therefore have a decreased foreign body sensation, is described in U.S. Patent Nos. 3,996,934 and 4,286,592. These products are used to deliver drugs through the skin or mucous. The laminated films usually include an adhesive layer, a reservoir layer, and a backing layer. Bioadhesive devices designed to release drug through the skin at a given rate and over a period of time are usually not water soluble, and thus are not dissolved or washed away by bodily fluids.

In addition to film systems for the delivery of drug through the skin, film delivery systems for use on mucosal surfaces are also known. These types of systems, which are water-insoluble and usually in the form of laminated, extruded or composite films, are described in U.S. Patent Nos. 4,517,173; 4,572,832; 4,713,243; 4,900,554; and 5,137,729. The '173 Patent describes and claims a membrane-adhering film consisting of at least three layers, including a pharmaceutical layer, a poor water soluble layer, and an intermediate layer. The pharmaceutical layer includes the drug and a cellulose derivative selected from hydroxypropyl cellulose, methyl cellulose, and hydroxypropyl methyl cellulose. The poor water soluble layer is made by the combination of one or more cellulose derivatives with a poor water soluble fatty acid, and the intermediate layer is made of cellulose derivatives. The '832 Patent relates to a soft film for buccal delivery, made by the combined use of a water soluble protein, a polyol, and a polyhydric alcohol such as cellulose and polysaccharides, and also teaches the use of coloring or flavoring agents. The '243 Patent describes a single or multi-layered bioadhesive thin film made from 40-95% water soluble hydroxypropyl cellulose, 5-60% water-insoluble ethylene oxide, 0-10% water-insoluble ethyl cellulose,

propyl cellulose, polyethylene, or polypropylene, and a medicament. The films are three-layered laminates and include a bioadhesive layer, a reservoir layer, and a non water-soluble outer protective layer. The '729 Patent teaches a soft adhesive film applicable to the oral mucosa containing a systemic drug and comprising a mixture of a vinyl acetate non water-soluble homopolymer, an acrylic acid polymer, and a cellulose derivative. Finally, the '554 Patent describes a device for use in the oral cavity having an adhesive layer including a mixture of an acrylic acid polymer, a water-insoluble cellulose derivative, and a pharmaceutical preparation, and a water-insoluble or sparingly soluble backing layer. The adhesive layer contains the pharmaceutical, and upon application to the mucosal surface, delivers the drug. The '554 Patent also states that "it is impossible to achieve an adhesive device for application to body tissue without all three components, that is, acrylic acid polymer, water insoluble cellulose derivative and a water insoluble or sparingly soluble backing layer."

JP 56-100714 describes a preparation which comprises a coating layer and an active ingredient layer. The coating layer adheres to the mucosal membrane and is comprised of a cellulose ether or an acrylic acid polymer or salt. The active ingredient layer comprises an ointment base comprised of water-insoluble substances such as fats and oils, waxes, hydrocarbons, higher fatty acids, higher alcohols, polyhydric alcohols or glycerol esters. A surfactant and active ingredient are also present in the active ingredient layer. Thus, the active ingredient is mixed with an essentially non-water erodable substance. The previous examples of thin films to be applied in the oral cavity by adhesion onto the mucosal tissues all utilize polymers which are water-insoluble by nature or which are made water-insoluble by crosslinking, and claim a long residence time. Therefore, unfortunately, the above examples of thin films do not provide a water erodable device with good adhesive properties. Therefore, upon release of the desired amount of drug, the thin films of water insoluble polymers must be peeled off the site of application. Such peeling often removes tissue from the mucosal tissue and is painful to the patient. What is needed in the art is a water-erodable

pharmaceutical delivery device which provides good adhesion and localized delivery of a pharmaceutical with minimal discomfort to the patient.

SUMMARY OF THE INVENTION

The present invention relates to a novel water-erodable pharmaceutical carrier device for application to mucosal surfaces to provide protection of and localized delivery of pharmaceutical to the site of application, surrounding tissues, and other bodily fluids such as blood or lymph, having an effective residence time, with minimal discomfort and ease of use. In one embodiment, the pharmaceutical delivery device includes a layered film disk which is water-erodable. The device comprises a layered film disk having an adhesive layer and a backing layer, both water-erodable, having the pharmaceutical in one or more of the layers.

In another embodiment, the pharmaceutical delivery device further comprises a third layer between the first adhesive layer and the second backing layer. The third layer is a water-erodable adhesive layer which has a surface area sufficient to encompass said first adhesive layer and contact the mucosal surface. In this manner, localized delivery of a pharmaceutical may be accomplished in a unidirectional manner toward the mucosal layer.

The adhesive layer(s) comprise(s) a film-forming polymer such as hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, hydroxyethyl methyl cellulose, polyvinyl alcohol, polyethylene glycol, polyethylene oxide, ethylene oxide-propylene oxide co-polymers, collagen and derivatives, gelatin, albumin, polyaminoacids and derivatives, polyphosphazenes, polysaccharides and derivatives, chitin, or chitosan, alone or in combination and a bioadhesive polymer such as polyacrylic acid, polyvinyl pyrrolidone, or sodium carboxymethyl cellulose, alone or in combination.

The non-adhesive backing layer(s) comprise(s) hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxyethylmethyl cellulose, hydroxypropylmethyl cellulose, polyvinyl alcohol, polyethylene glycol, polyethylene oxide, or ethylene oxide-propylene oxide co-polymers, alone or in combination.

In another embodiment of the invention, one or more of the layers of the device further comprise a component which acts to adjust the kinetics of the erodability and provide a convenient manner of altering the release of the pharmaceutical and the lifespan of the device. A component which acts to adjust the kinetics of the erodability is a water-based emulsion of a polylactide, polyglycolide, lactide-glycolide copolymers, poly-ε-caprolactone and derivatives, polyorthoesters and derivatives, polyanhydrides and derivatives, ethyl cellulose, vinyl acetate, cellulose acetate, and polyisobutylene, alone or in combination. Another component which acts to adjust the kinetics of the erodability is alkyl-glycol, propylene glycol, polyethyleneglycol, oleate, sebacate, stearate or esters of glycerol, or phthalate, alone or in combination.

In another embodiment of the invention, the number of layers of the device further may be varied to adjust the kinetics of the erodability and provide a convenient manner of altering the release of the pharmaceutical and the lifespan of the device.

In a preferred embodiment, the backing layer comprises two or more layers with different erodibility kinetics.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a three layered film disk wherein layers 2 and 3 are bioadhesive layers and layer 1 is a backing layer.

Figure 2 is a three layered film disk wherein two of the layers are bioadhesive layers and the other layer is a backing layer. The bioadhesive layer, layer 3, which will adhere to the mucosal tissue is of smaller surface area and encompassed by the second bioadhesive layer, layer 2, to provide unidirectional delivery. Layer 1 is a backing layer.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, the term "water-erodable" means that the component, device, layer, etc. erodes in water-based media such as saliva, over time. Such erosion in water may be due to factors such as dissolution, dispersion, friction, gravity, etc.

As used herein, the term "kinetics of erodability" or "erosion kinetics" refers to the timing of the release of pharmaceutical from the carrier device (release profile), as well as, the timing of the erosion of the device itself over time (lifespan or residence time of the device). As described herein, kinetics of erodability are based on factors such as type and amount of components in the device, thickness and number of layers in the device, and additives or excipients in the device. In a case in which all the components of the device are very water soluble, the kinetics of erodability will closely parallel the solubility kinetics.

In the present invention, a novel water-erodable pharmaceutical device which adheres to mucosal surfaces is provided. The present invention finds particular use in the localized treatment of body tissues, diseases, or wounds which may have moist surfaces and which are susceptible to bodily fluids, such as the mouth, the vagina, or other types of mucosal surfaces. The device carries a pharmaceutical, and upon application and adherence to the mucosal surface, offers a layer of protection and delivers the pharmaceutical to the treatment site, the surrounding tissues, and other bodily fluids. The device provides an appropriate residence time for effective drug delivery at the treatment site, given the control of erosion in aqueous solution or bodily fluids such as saliva, and the slow, natural erosion of the film concomitant or subsequent to the delivery. In one embodiment, the pharmaceutical delivery device comprises a layered film disk having an adhesive layer and a backing layer, both water-erodable, having the pharmaceutical in either or both layers.

Unlike bioadhesive gels and pastes known in the art, which have a very limited residence time, given the tendency of bodily fluids such as saliva to wash away the gel from the treatment site, the present invention offers an increased residence time because of its filmy consistency and components. A typical residence time for an aqueous gel or paste, such as Orajel®, Orabase®, or Kanka® is a few minutes. This short residence time is a consequence of a limited or poor adhesion. In a typical aqueous gel, the mucoadhesive components are either in solution, suspension, or swollen. Once applied to the mucosal surface, however, the water based gel does not instantaneously penetrate the lipophilic mucosal surface. The composition and water affinity of these gels results in a tendency to

quickly mix with the saliva, rapidly pulling away the different components of the gel, and limiting the residence time. The same tendency is expected with pastes, the increase in viscosity only slightly delaying the timing. The present invention, by its solid form and its instantaneous adhesion to the mucosal surface, allows a lasting contact, a consequence of the entanglement of polymer chains and glycoproteins of the mucosal tissue which assures adhesion. Erosion kinetics in the saliva and other aqueous media are influenced by the physical state of the device. While a gel or solution will readily mix with saliva and/or other bodily fluids, a solid form of the same or similar composition, such as the film of the present invention, dissolves / erodes more slowly.

Also, unlike the bioadhesive tablets which are known in the art, the pharmaceutical device of the present invention minimizes the discomfort associated with application of a foreign substance for a period of time sufficient to provide effective drug delivery to the treatment site. Often, users of the bioadhesive tablets of the prior art experience unpleasant sensations due to their solidity, bulkiness, and slow dissolution time if erodable, especially when used in the oral cavity. Moreover, the typical thickness of bioadhesive tablets, which may or may not be water soluble, is a couple of millimeters, and because of their thickness, the preferred site of application is on the upper gingival area. This site is usually unsatisfactory for local delivery as the type of compounds to be delivered, their bioavailability, and pharmokinetics is limited. In contrast to tablets, the device of the present invention offers the advantages of an effective residence time with minimal discomfort and ease of use, and is an appropriate vehicle for the local, as well as systemic, delivery of pharmaceutical, given its thinner, flexible form.

Finally, unlike the film systems known in the art which are used to deliver pharmaceutical through the skin or mucous, the device of the present invention is made of water-erodable components and thus is bioerodable. The use of water-erodable components allows the device to erode over a period of time, with natural bodily fluids slowly dissolving or eroding away the carrier, while the pharmaceutical remains at the application site. Unlike bandages and other non-water-erodable film systems, the user of the present invention does

not have to remove the device following treatment. Nor does the user experience the sensation of the presence of a foreign object at the mucosal surface or within the body cavity, given that upon application, water absorption softens the device, and over time, the device slowly dissolves or erodes away.

The residence time of the device of the present invention depends on the erosion rate of the water-erodable polymers used in the formulation and their respective concentrations. The erosion rate may be adjusted, for example, by mixing together components with different solubility characteristics or chemically different polymers, such as hydroxyethyl cellulose and hydroxypropyl cellulose; by using different molecular weight grades of the same polymer, such as mixing low and medium molecular weight hydroxyethyl cellulose; by using excipients or plasticizers of various lipophilic values or water solubility characteristics (including essentially insoluble components); by using crosslinking agents such as glyoxal with polymers such as hydroxyethyl cellulose for partial crosslinking; or by post-treatment irradiation or curing, which may alter the physical state of the film, including its crystallinity or phase transition, once obtained. These strategies might be employed alone or in combination in order to modify the erosion kinetics of the device.

Upon application, the pharmaceutical delivery device adheres to the mucosal surface and is held in place. Water absorption softens the device, thereby diminishing the foreign body sensation. As the device rests on the mucosal surface, delivery of the drug occurs. Residence times may be adjusted over a wide range depending upon the desired timing of the delivery of the chosen pharmaceutical and the desired lifespan of the carrier. Generally, however, the residence time is modulated between about a few seconds to about a few days. Preferably, the residence time for most pharmaceuticals is adjusted from about 30 minutes to about 24 hours. More preferably, the residence time is adjusted from about 1 hour to about 8 hours. In addition to providing drug delivery, once the device adheres to the mucosal surface, it also provides protection to the treatment site, acting as an erodable bandage.

In one embodiment, the present invention comprises a film disk having an adhesive layer and a non-adhesive backing layer which can be comprised of components having a

similar or different hydrophilicity. The pharmaceutical component may be included in either layer, although preferably, it is included in the adhesive layer, which is closest to the treatment site and which will have a slower erosion time, given that the backing layer protects the interior, adhesive layer and will typically erode first.

The adhesive layer may comprise at least one film-forming water-erodable polymer (the "film-forming polymer") and at least one pharmacologically acceptable polymer known for its bioadhesive capabilities (the "bioadhesive polymer"). The film forming polymer may comprise hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, hydroxyethyl methyl cellulose, polyvinyl alcohol, polyethylene glycol, polyethylene oxide, ethylene oxide-propylene oxide co-polymers, collagen and derivatives, gelatin, albumin, polyaminoacids and derivatives, polyphosphazenes, polysaccharides and derivatives, chitin and chitosan, alone or in combination. Preferably, the film-forming polymer comprises hydroxyethyl cellulose. Preferably, in the case of hydroxyethyl cellulose, the average molecular weight (Mw estimated from intrinsic viscosity measurements) is in the range 10^2 to 10^6 and more preferably in the range 10^3 to 10^5, while in the case of hydroxypropyl cellulose, the average molecular weight (Mw obtained from size exclusion chromatography measurements) is in the range 50×10^3 to 1.5×10^6, and more preferably between 80×10^3 to 5×10^5.

The bioadhesive polymer of the adhesive layer may comprise polyacrylic acid (PAA), which may or may not be partially crosslinked, sodium carboxymethyl cellulose (NaCMC), and polyvinylpyrrolidone (PVP), or combinations thereof. These bioadhesive polymers are preferred because they have good and instantaneous mucoadhesive properties in a dry, film state. In the case of sodium carboxymethyl cellulose, typical average molecular weights comprise 50,000 to 700,000, and preferably 60,000 to 500,000, with a degree of substitution of 0.7. The substitution range varies between 0.5 and 1.5, and preferably between 0.6 and 0.9. The polyvinyl pyrrolidone can be characterized according to its average molecular weight and comprises between 5,000 and 150,000, preferably between 10,000 and 100,000.

The simultaneous use of PAA with some grades of PVP may result in the precipitation of one or both components. This precipitation may not be ideal to obtain a homogenous layer and may slightly alter the overall adhesive properties of the device.

While not wishing to bound to a particular theory, it is believed that the adhesion properties of the present invention are the result of the entanglement of polymer chains and interactions with glycoproteins of the mucosal surface. The chemical nature of the bioadhesive polymers, including chain and side groups and crosslinking agents, generates interactions between the mucosal constituents and the polymer or polymers, such as physical entanglement, Van der Waals interactions, and hydrogen bonding. Given that the composition of mucosal tissues differs from one individual to another and changes naturally over time, the use of a combination of bioadhesive polymers or the use of a combination of different grades of the same polymer is preferred. The use of a combination of at least two bioadhesive polymers maximizes the adhesion capabilities of the device, although use of a single bioadhesive polymer is effective as well.

The ratio of the bioadhesive polymer to the film-forming polymer in the adhesive layer may vary, depending on the type of pharmaceutical and the amount of pharmaceutical to be used. However, the content of combined components in the adhesive layer is usually between 5 and 95% by weight, preferably between 10 and 80% by weight. In terms of weight percent of the different bioadhesive polymers PAA, NaCMC, and PVP, some examples are provided below and using the examples one skilled in the art will be able to readily adjust the percentages to obtain a pharmaceutical device having desired characteristics for a given application. Preferred combinations include PAA and NaCMC, NaCMC and PVP, or PAA and PVP, and also include the use of different grades of the same polymer.

The non adhesive backing layer may comprise a water-erodable, film-forming pharmaceutically acceptable polymer such as hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, hydroxyethylmethyl cellulose, polyvinylalcohol, polyethylene glycol, polyethylene oxide, ethylene oxide-propylene oxide co-polymers, collagen and derivatives, gelatin, albumin, polyaminoacids and derivatives,

polyphosphazenes, polysaccharides and derivatives, chitin and chitosan, alone or in combination. The backing layer component may or may not be crosslinked depending on the desired erosion kinetics. In one embodiment, the preferred backing layer component comprises hydroxyethyl cellulose or hydroxypropyl cellulose, and more preferably comprises hydroxyethyl cellulose. Preferably, in the case of hydroxyethyl cellulose, the average molecular weight (Mw estimated from intrinsic viscosity measurements) is in the range 10^2 to 10^6, and more preferably in the range 10^3 to 10^5, while in the case of hydroxypropyl cellulose, the average molecular weight (Mw obtained from size exclusion chromatography measurements) is in the range of 50×10^3 to 1.5×10^6 and more preferably from 80×10^3 to 5×10^5.

As described above, the erosion kinetics of one or more of the layers (adhesive layer, backing layer, or both) may be altered in many different ways in order to modify the residence time and the release profile of a drug. One way is by crosslinking or plasticizing the film-forming polymer. Crosslinking agents known in the art are appropriate for use in the invention and may include glyoxal, propylene glycol, glycerol, dihydroxy-polyethylene glycol of different sizes, butylene glycol, and combinations thereof. The amount of crosslinking agent used may vary, depending on the particular polymers and crosslinking agent but usually should not exceed 5% molar equivalent of the polymeric material, and preferably comprises 0 to 3% molar equivalent of the polymeric material.

Another way of altering the residence time and release profile is by employing a component in one or more of the layers which acts to adjust the kinetics of the erodability of the layer. While these components will vary widely depending upon the particular pharmaceutical delivery device employed, preferred components include water-based emulsions of polylactide, polyglycolide, lactide-glycolide copolymers, poly-ε-caprolactone and derivatives, polyorthoesters and derivatives, polyanhydrides and derivatives, ethyl cellulose, vinyl acetate, cellulose acetate, silicone, polyisobutylene and derivatives, alone or in combination.

Emulsifiers typically used in the water-based emulsions described above are, preferably, either obtained *in situ* if selected from the linoleic, palmitic, myristoleic, lauric, stearic, cetoleic or oleic acids and sodium or potassium hydroxide, or selected from the laurate, palmitate, stearate, or oleate esters of sorbitol and sorbitol anhydrides, polyoxyethylene derivatives including monooleate, monostearate, monopalmitate, monolaurate, fatty alcohols, alkyl phenols, alyl ethers, alkyl aryl ethers, sorbitan monostearate, sorbitan monooleate and sorbitan monopalmitate.

Furthermore, in the case of the water-insoluble polymeric materials such as the polyesteraliphatic family (co-polymers of lactide-glycolide, caprolactone, etc.) the average molecular weight (Mw) is in the range 10^2 to 10^5 and, more preferably, 10^3 to 10^4, while in the case of the cellulosic family (ethyl cellulose, cellulose acetate, etc.), the average molecular weight (Mw estimated from intrinsic viscosity measurements) is in the range 10^2 to 10^6 and more preferably in the range 10^3 to 10^5.

Yet another manner of modifying the erosion kinetics of any layer, is by employing excipients which plasticize the film concomitantly. Suitable excipients or plasticizers modifying the erosion behavior of the layer(s) may include alkyl-glycol such as propylene glycol, polyethyleneglycols, oleate, sebacate, stearate or esters of glycerol, phthalate and others.

It is also possible to modify the erosion kinetics of the device of the instant invention by adjusting the thickness and number of layers. Typically, the thicker the layers, the slower the release of pharmaceutical and the longer the release profile. Correspondingly, the more layers there are, the slower the release of pharmaceutical and the longer the release profile. In a preferred embodiment, the backing layer comprises two or more layers with different erosion kinetics.

Moreover, combinations of different polymers or similar polymers with definite molecular weight characteristics may be used in order to achieve preferred film forming capabilities, mechanical properties, and kinetics of dissolution in any layer. Some

combinations for use in the invention are provided in the examples below and may include ¾ of hydroxyethyl cellulose and ¼ of hydroxypropyl cellulose; 4/5 of low molecular weight hydroxyethyl cellulose and 1/5 of medium molecular weight hydroxyethyl cellulose; and 8/9 of low molecular weight hydroxyethyl cellulose and 1/9 of high molecular weight hydroxyethyl cellulose. As mentioned previously, combinations of water-erodable polymers may be employed in order to modify the erosion kinetics of the device. A particularly preferred combination includes ½ hydroxyethyl cellulose, 1/6 hydroxypropylcellulose, and 2/6 of a pseudolatex, i.e. emulsion of polymer, of lactide-glycolide copolymer.

The pharmaceutical component of the present invention may comprise a single pharmaceutical or a combination of pharmaceuticals, which may be incorporated in the adhesive layer, the backing layer, or both. Pharmaceuticals which may be used, either alone or in combination, include anti-inflammatory analgesic agents, steroidal anti-inflammatory agents, antihistamines, local anesthetics, bactericides and disinfectants, vasoconstrictors, hemostatics, chemotherapeutic drugs, antibiotics, keratolytics, cauterizing agents, antiviral drugs, antirheumatics, antihypertensives, bronchodilators, anticholinergics, antimenimic compounds, hormones and macromolecules, peptides, proteins and vaccines.

Examples of anti-inflammatory analgesic agents include acetaminophen, methyl salicylate, monoglycol salicylate, aspirin, mefenamic acid, flufenamic acid, indomethacin, diclofenac, alclofenac, diclofenac sodium, ibuprofen, ketoprofen, naproxen, pranoprofen, fenoprofen, sulindac, fenclofenac, clidanac, flurbiprofen, fentiazac, bufexamac, piroxicam, phenylbutazone, oxyphenbutazone, clofezone, pentazocine, mepirizole, tiaramide hydrochloride, etc. Examples of steroidal anti-inflammatory agents include hydrocortisone, predonisolone, dexamethasone, triamcinolone acetonide, fluocinolone acetonide, hydrocortisone acetate, predonisolone acetate, methylpredonisolone, dexamethasone acetate, betamethasone, betamethasone valerate, flumetasone, fluorometholone, beclomethasone diproprionate, fluocinonide, etc.

Examples of antihistamines include diphenhydramine hydrochloride, diphenhydramine salicylate, diphenhydramine, chlorpheniramine hydrochloride,

chlorpheniramine maleate isothipendyl hydrochloride, tripelennamine hydrochloride, promethazine hydrochloride, methdilazine hydrochloride, etc. Examples of local anesthetics include dibucaine hydrochloride, dibucaine, lidocaine hydrochloride, lidocaine, benzocaine, p-buthylaminobenzoic acid 2-(die-ethylamino) ethyl ester hydrochloride, procaine hydrochloride, tetracaine, tetracaine hydrochloride, chloroprocaine hydrochloride, oxyprocaine hydrochloride, mepivacaine, cocaine hydrochloride, piperocaine hydrochloride, dyclonine, dyclonine hydrochloride, etc.

Examples of bactericides and disinfectants include thimerosal, phenol, thymol, benzalkonium chloride, benzethonium chloride, chlorhexidine, povidone iode, cetylpyridinium chloride, eugenol, trimethylammonium bromide, etc. Examples of vasoconstrictors include naphazoline nitrate, tetrahydrozoline hydrochloride, oxymetazoline hydrochloride, phenylephrine hydrochloride, tramazoline hydrochloride, etc. Examples of hemostatics include thrombin, phytonadione, protamine sulfate, aminocaproic acid, tranexamic acid, carbazochrome, carbaxochrome sodium sulfanate, rutin, hesperidin, etc.

Examples of chemotherapeutic drugs include sulfamine, sulfathiazole, sulfadiazine, homosulfamine, sulfisoxazole, sulfisomidine, sulfamethizole, nitrofurazone, etc. Examples of antibiotics include penicillin, meticillin, oxacillin, cefalotin, cefalordin, erythromcycin, lincomycin, tetracycline, chlortetracycline, oxytetracycline, metacycline, chloramphenicol, kanamycin, streptomycin, gentamicin, bacitracin, cycloserine, etc.

Examples of keratolytics include salicylic acid, podophyllum resin, podolifox, and cantharidin. Examples of cauterizing agents include the chloroacetic acids and silver nitrate. Examples of antiviral drugs include protease inhibitors, thymadine kinase inhibitors, sugar or glycoprotein synthesis inhibitors, structural protein synthesis inhibitors, attachment and adsorption inhibitors, and nucleoside analogues such as acyclovir, penciclovir, valacyclovir, and ganciclovir.

Examples of proteins, peptides, vaccines, genes and the like include heparin, insulin, LHRH, TRH, interferons, oligonuclides, calcitonin, and octreotide.

The amount of active pharmaceutical (s) to be used depends on the desired treatment strength and the composition of the layers, although preferably, the pharmaceutical component comprises from about 0.001 to about 99, more preferably from about 0.003 to about 30, and most preferably from about 0.005 to about 20% by weight of the device.

Plasticizers, flavoring and coloring agents, and preservatives may also be included in the pharmaceutical delivery device of the present invention in the adhesive layer, the backing layer, or both. The amount may vary depending on the drug or other components but typically these components comprise no more than 50, preferably no more than 30, most preferably no more than 15% by total weight of the device.

A permeation enhancer may be added to the device to improve absorption of the drug. Typically, such a permeation enhancer is added to the layer in which the pharmaceutical is to be contained. Suitable permeation enhancers include natural or synthetic bile salts such as sodium fusidate; glycocholate or deoxycholate; fatty acids and derivatives such as sodium laurate, oleic acid, oleyl alcohol, monoolein, and palmitoylcarnitine; chelators such as disodium EDTA, sodium citrate and sodium laurylsulfate, azone, sodium cholate, sodium 5-methoxysalicylate, sorbitan laurate, glyceryl monolaurate, octoxynonyl-9, laureth-9, polysorbates, etc.

The thickness of the device may vary, depending on the thickness of each of the layers and the number of layers. As stated above, both the thickness and amount of layers may be adjusted in order to vary the erosion kinetics. Preferably, if the device has only two layers, the thickness ranges from 0.05 mm to 1 mm, and more preferably from 0.1 to 0.5 mm. The thickness of each layer may vary from 10 to 90% of the overall thickness of the layered device, and preferably varies from 30 to 60%. Thus, the preferred thickness of each layer may vary from 0.01 mm to 0.9 mm, and more preferably from 0.03 to 0.6 mm.

While the device of the invention only requires two layers, i.e., an adhesive layer and a backing layer, it is often preferable to have additional layers. One instance in which this might be advantageous is when specific unidirectional flow of a pharmaceutical is required toward a mucosal layer. The layered device described above provides some directional

release, i.e., release will mainly be toward the mucosa and not, for instance, into the oral or vaginal cavity. However, due to the swelling characteristics of the thin film, a small amount of pharmaceutical may also be released through the sides of the device and the backing layer if all the layers are of the approximately the same surface area and are essentially on top of one another. While a preferential, but not specific, release is acceptable, and even desirable, for many pharmaceuticals, other pharmaceuticals may require unidirectional, specific release into the mucosal tissue.

An example of when unidirectional release may be desirable is when the pharmaceutical to be delivered has a specific therapeutic window or has undesirable side effects if absorbed in the gastrointestinal tract. Furthermore, some pharmaceuticals are enzymatically degraded. Therefore, a bioerodible mucoadhesive system allowing a transmucosal unidirectional delivery and protecting the drug being delivered from enzymes present, for instance, in the oral or vaginal cavities would have advantages.

In such instances when unidirectional release is desired, an additional layer may be placed between the first adhesive layer and the second backing layer. The third layer is a water-erodable adhesive layer which has a surface area sufficient to encompass said first adhesive layer and contact the mucosal surface. The third layer may be comprised of any of the components described above for the first adhesive layer and thus may be the same or different than the first adhesive layer. Figure 2 illustrates a disk having a third layer which encompasses the first adhesive layer.

If a bioadhesive layer is to be of a smaller surface area than the other layers then it is usually between about 5 and about 50, preferably between about 10 and about 30% smaller than the other layers.

In the aforementioned manner, localized delivery of a pharmaceutical may be accomplished in a unidirectional manner. For instance, if pharmaceutical is present in the first adhesive layer then it is prevented from being released through the sides and back of the device. If pharmaceutical is present in the backing layer, then it is prevented from entering

the mucosal layer to which the device is adhered. Likewise, if a pharmaceutical is present in the first adhesive layer and the backing layer, they are prevented from mixing.

The pharmaceutical delivery device of the present invention may be prepared by numerous methods known in the art. In one embodiment, the components are dissolved in an aqueous medium or a combination of water and lower alkanols to prepare a solution, a gel, or a suspension that can be used for coating. Solvents for use in the present invention may comprise water, methanol, ethanol, or low alkyl alcohols such as isopropyl alcohol, or acetone. The final solvent content or residual solvent content in the film may be the result of either or both layers. The solvent may also be used as a plasticizer or an erosion rate-modifying agent.

Each solution is then coated onto a substrate. Eventually, one of the components might be in suspension. Each solution is casted and processed into a thin film by techniques known in the art, such as by film dipping, film coating, film casting, spin coating, or spray drying using the appropriate substrate. The thin film is then allowed to dry. If desired, the drying step can be accomplished in any type of oven in order to facilitate the process. However, as one skilled in the art will appreciate, the solvent residual, which may effect the erosion kinetics, depends on the drying procedure. The film layers may be filmed independently and then laminated together or may be filmed one on the top of the other.

The film obtained after the two layers have been laminated together or coated on top of each other may be cut, if desired, into any type of shape which is suitable for application to the mucosal tissue. Suitable shapes may include disks, ellipses, squares, rectangles, parallepipedes, as well as, shredded, meshed, or porous films depending upon the purpose and location where the device is to be employed. Likewise, the surface area of the device of the present invention will necessarily vary depending on many factors with the major factor being where the device is to be employed. Typically, the surface area may be from about 0.1 to about 30, preferably from 0.5 to about 20 square centimeters.

Methods for treating mucosal surfaces, surrounding tissues, and bodily fluids for localized and systemic drug delivery are also provided. In one embodiment, the method

comprises applying an adherent film of the invention to the treatment site in order to provide protection to the treatment site and drug delivery. The adherent film may comprise any of the layered devices provided herein. In a preferred embodiment, the method comprises application of a layered pharmaceutical carrier device having a first adhesive layer and a second non-adhesive backing layer as described above, each layer having a thickness of from 0.01 mm to 0.9 mm. The pharmaceutical or combination of pharmaceuticals may be present in the adhesive layer, the non-adhesive backing layer, or both layers.

While the pharmaceutical carrier described in this application readily adheres to mucosal tissues, which are wet tissues by nature, it can also be used on other surfaces such as skin or wounds. The water-soluble film of the present invention will adhere to the skin if prior to application the skin is wet with an aqueous-based fluid such as water, saliva, or perspiration. The film will typically adhere to the skin until it erodes due contact with water by, for example, showering, bathing or washing. The film may also be readily removed by peeling without significant damage to tissue.

While it is in contact with the skin, the film may act as a washable, erodable bandage to protect the area where it has been applied. It is also possible to employ the film as a transdermal drug delivery system to facilitate the healing process and keep the wound or burn free of germs and debris. A significant advantage of the instant invention over conventional alternatives is that not only is the film washable, but also, perspiration helps the adhesion of the device instead of preventing or reducing it as with conventional transdermal patches.

The pharmaceutical carrier of the present invention can also be used as a wound dressing. By offering a physical, compatible, oxygen and moisture permeable, flexible barrier which can be washed away, the film can not only protect a wound but also deliver a pharmaceutical in order to promote healing, asepty, scarification, to ease the pain or to improve globally the condition of the sufferer. Some of the examples given below are well suited for an application to the skin or a wound. As one skilled in the art will appreciate, the formulation might require incorporating a specific hydrophilic / hygroscopic excipient which would help in maintaining good adhesion on dry skin over an extended period of time.

Another advantage of the present invention when utilized in this manner is that if one does not wish that the film be noticeable on the skin, then no dyes or colored substances need be used. If, on the other hand, one desires that the film be noticeable, a dye or colored substance may be employed.

EXAMPLE 1

A 100 ml solution for the non-adhesive backing layer was made using 87.98% by weight water USP, 0.02% by weight FD&C red 40 dye, and 12% by weight hydroxyethyl cellulose (Mw 9 x 10^4). Using a Werner Mathis Labcoater, the substrate (Mylar 1000D or other polyester films such as 3M ScotchPak 1022) was set. 90 ml of the backing layer solution was set in front of a knife over roll with an opening of 1.5 mm. The solution was then casted on a glass substrate and film dried for 8-9 min. at 130° C. Following the drying step, a 0.14 mm thick reddish film was the result.

Using this procedure, the film may be easily peeled off the substrate after drying, or may be left on the substrate and rolled, to be laminated later, or for use as a substrate for the adhesive layer.

EXAMPLE 2

A 100 ml solution for the non-adhesive backing layer was made using 94.98% by weight water USP, 0.02% by weight FD&C red 40 dye, and 5% by weight hydroxypropyl cellulose. The procedure of example 1 was used, resulting in a 0.16 mm thick film.

EXAMPLE 3

A 100 ml solution for the non-adhesive backing layer was made using 84.98% by weight water USP, 0.02% by weight FD&C red 40 dye, 12% by weight hydroxyethyl cellulose, and 3% by weight hydroxypropyl cellulose. Here, the overall polymeric material was at a 15% concentration in solution. The mixture of two different types of polymeric materials modified the overall mechanical properties and erosion kinetics characteristics of

the backing film. The solution was then casted on a polyester substrate and dried overnight at 90°C. The opening of the knife was set at 3 mm, resulting in a 0.3 mm thick film.

EXAMPLE 4

A 100 ml solution for the non-adhesive backing layer was made using 87.98% by weight water USP, 0.02% by weight FD&C red 40 dye, 10% by weight hydroxyethyl cellulose (Mw 9 x 10^4), and 2% by weight hydroxyethyl cellulose (Mw 7 x 10^5). Here, the mixture of two different types of hydroxyethyl cellulose modified the mechanical properties and erosion kinetics of the backing film. The solution was then cast on a polyester substrate and dried for 12 min. at 135° C. The opening of the knife was set at 3 mm, resulting in a 0.27 mm thick film.

EXAMPLE 5

A 100 ml solution for the non-adhesive backing layer was made using 87.98% by weight water USP, 0.02% by weight FD&C red 40 dye, 11.75% by weight hydroxyethyl cellulose (Mw 9 x 10^4), and 0.25% by weight hydroxyethyl cellulose (Mw 1.3 x 10^6). The procedure of Example 1 was used, resulting in a 0.14 mm thick film.

Here, the mixture of two different grades of hydroxyethyl cellulose modified the mechanical properties and erosion kinetics of the backing film. The ratio may be used to adjust the erosion pattern and residence time of the bioadhesive disk. Compared to the backing layer of Example 1, which was made of 12% by weight hydroxyethyl cellulose (Mw 9 x 10^4), and which had an erosion time of about 21 minutes (See Table 2), the backing layer of this Example, made from a combination of two grades of hydroxyethyl cellulose, had an erosion time of about 69 minutes (See Table 2).

EXAMPLE 6

A 100 ml solution for the non-adhesive backing layer was made using 87.98% by weight water USP, 0.02% by weight FD&C red 40 dye, 11.95% by weight hydroxyethyl

cellulose (Mw 9 x 10^4), and 0.05% by weight of 40% glyoxal aqueous solution. The procedure of Example 1 was used, resulting in a 0.13 mm film.

Here, the glyoxal acted as a crosslinking agent, inducing a slow down in the erosion kinetics of the backing film. Compared to the backing layer of Example 1, which had no glyoxal and which had an erosion time of about 21 minutes (See Table 2), the backing layer of this Example, which incorporated glyoxal, had an erosion time of about 57 minutes (See Table 2).

EXAMPLE 7

A 100 ml solution for the non-adhesive backing layer was made using 87.98% by weight water USP, 0.02% by weight FD&C red 40 dye, 11.8% by weight hydroxyethyl cellulose , 0.1% by weight of 40% glyoxal aqueous solution, and 0.1% sweet peppermint flavor. Here, as in Example 6, the glyoxal acted as a crosslinking agent, inducing a slow down in the erosion kinetics of the backing film, compared with a backing layer with no glyoxal. The sweet peppermint was added as a flavoring agent.

EXAMPLE 8

As described in Example 1, the solutions of Examples 5, 6 and 7 were each casted on a polyester substrate. Instead of using a knife, a meier's bar was used to coat the substrate. The films were dried overnight at 90° C. The dried films were thicker, having a thickness of about 0.17 mm.

EXAMPLE 9

The solution of Example 1 was prepared in a beaker. A microslide was then dipped quickly into the solution until it was fully immersed, removed from the solution, and left at room temperature for about 1 hour. The microslide was then dried overnight at 90° C. The resulting film was heterogeneous and had an average thickness of about 0.2 mm.

EXAMPLE 10

A 100 ml solution for the non-adhesive backing layer was made using 84% by weight water USP, 0.02% by weight FD&C red 40 dye, 11% by weight hydroxyethyl cellulose (Mw 9×10^4), 1% by weight hydroxyethyl cellulose (Mw 7×10^5), 0.1% by weight of a 40% glyoxal aqueous solution, 3% by weight glyoxal, and 1% by weight menthol. Here, the glyoxal acted as a crosslinking agent, inducing a slow down in the erosion kinetics of the backing film. Also, the mixture of two different grades of hydroxyethyl cellulose was used to achieve slow release of the menthol. The film was coated on a polyester film as previously described.

EXAMPLE 11

A 100 ml solution for the adhesive layer was made using 88.6% by weight water USP, 1.8% by weight hydroxyethyl cellulose, Natrosol® 99-250 L NF (Aqualon), 2.6% by weight polyacrylic acid, Noveon® AA1 USP (BF Goodrich), 4.5% sodium carboxymethyl cellulose, cellulose gum 7 LF PH (Aqualon), and 2.5% by weight dyclonine HCl. Upon mixing, a suspension was formed.

Here, dyclonine HCl may be easily substituted with any other active pharmaceutical component. However, chemical characteristics of the active pharmaceutical, such as solubility, counter ions, and melting point, might require minor modifications of the overall process, such as dissolution in a particular solvent, changing the temperature of the solution, etc. The next example illustrates one slight modification.

EXAMPLE 12

A 100 ml solution for the adhesive layer was made using 74.6% by weight water USP, 1.8% by weight hydroxyethyl cellulose, 2.6% by weight polyacrylic acid, 4.5% sodium carboxymethyl cellulose, 2.5% by weight benzocaine, and 14% by weight ethyl alcohol. The use of benzocaine as the active pharmaceutical required that it first be dissolved in ethyl alcohol, given that benzocaine is more soluble in alcohol than water.

In the final solution, the benzocaine tends to precipitate in the form of a very fine powder. However, the film characteristics and bioadhesive properties remain intact.

EXAMPLE 13

A 100 ml solution for the adhesive layer was made using 91% by weight water USP, 2% by weight hydroxyethyl cellulose, 2.5% by weight polyacrylic acid, and 4.5% sodium carboxymethyl cellulose. The composition of the adhesive layer may be modified and may vary according the ranges described in Table 1 below:

TABLE 1

Item #	%w	Material
1	60 to 99.5	Water USP
2	0.05 to 5	Hydroxyethyl cellulose
3	0.5 to 10	Polyacrylic acid
4	0.0 to 15	Sodium Carboxymethyl cellulose
5	0 to 10	Polyvinyl pyrrolidone

The relative part of each components depends of the chemical compatibility of the components and the residence time to be obtained.

EXAMPLE 14

A 100 ml solution for the adhesive layer was made using 90% by weight water USP, 1% by weight butacaine sulfate, 2% by weight hydroxyethyl cellulose, 2.5% by weight polyvinyl pyrrolidone, and 4.5% by weight sodium carboxymethyl cellulose. The solution was coated using a knife over roll on a Mylar substrate.

EXAMPLE 15

A 100 ml solution for the adhesive layer was made. The total composition of the solution was 48.6% water, 40% ethyl alcohol, 1.8% hydroxyethyl cellulose, 2.6% polyacrylic

acid, 4.5% sodium carboxymethyl cellulose, and 2.5% dyclonine HCl. Here, however, the dyclonine HCl was first solubilized in 40 ml ethyl alcohol, and then, 48.6 ml of water were added to the dyclonine HCl/ethyl alcohol solution, followed by the addition of the other components.

The use of ethyl alcohol as an additional solvent resulted in a suspension which was slightly more viscous than that of Example 11, which used water as the only solvent.

EXAMPLE 16

Following the procedure of Example 12, a 100 ml solution for the adhesive layer was prepared. The solution was then coated following the procedure used in Example 1. The resulting film was 0.12 mm thick.

EXAMPLE 17

Following the procedure of Example 12, a 100 ml solution for the adhesive layer was prepared. The solution was coated on top of a backing film prepared according to Example 1. The opening of the knife was adjusted, taking into account the thickness of the backing film. After coating, the layered film was dried at 130°C for 15 minutes. A 0.27 mm layered film of two layers was formed.

EXAMPLE 18

Following the procedure of Example 14, a bioadhesive film was prepared, except that the film was not fully dried. A backing film was prepared according to Example 1. The backing film was peeled off of its substrate and laminated on top of the bioadhesive film while still moist, and pressure was applied to seal the two films together. The pressure applied on the films resulted in a good interfacial adhesion. A 0.38 mm layered film of two layers was formed.

EXAMPLE 19

Following the procedure of Example 1, several solutions for backing films were prepared according to the compositions of Table 2 below. Following film formation, ½ inch disks were die cut and set on a double-sided tape. The tape was then positioned on a micro slide. The kinetics of erosion were evaluated in water: the slide was plunged into a 100 ml beaker of water stirred at a constant speed of 50 rpm. The time for erosion was measured from the moment the disk was fully immersed in the beaker of water. Percentages (%) refer to the concentration in solution.

TABLE 2

Composition	Weight (mg)/ Thickness (mm)	Erosion Time (min.)
12% HEC (Mw 9 x 10^4)	17.1 / 0.14	21
10% HEC (Mw 9 x 10^4) and 2% HEC (Mw 7 x 10^5)	16.9 / 0.13	37
9% HEC (Mw 9 x 10^4) and 3% HEC (Mw 7 x 10^5)	17 / 0.14	75
11.75% HEC ((Mw 9 x 10^4) and 0.25% HEC (Mw 1.3 x 10^6)	17.1 / 0.14	69
11.95% HEC ((Mw 9 x 10^4) and 0.05% glyoxal (40% aq. sol.)	17.2 / 0.13	57
11.99% HEC ((Mw 9 x 10^4) and 0.01% propylene glycol	17.3 / 0.14	65

The results demonstrate that the erosion time varies, depending on the components of the formulation, assuming a similar surface state for each sample. Although water does not mimic the exact composition of saliva, and this experiment cannot precisely replicate *in vivo*

residence times, the experiment provides an *in vitro* comparison of erosion times of various compositions for use in practicing the present invention.

EXAMPLE 20

1/2 inch diameter disks having a thickness of between 0.19 and 0.21 mm were administered to six healthy volunteers. The backing layer was prepared according to Example 1, and the adhesive layer was prepared according to Example 15, some containing dyclonine HCl as the active pharmaceutical component, and others containing benzocaine as a substitute. The adhesive layer was coated on top of the backing layer, forming a layered disk. The layered disk was set in the mouth, and the time for erosion was measured from the moment the disk was set in place.

Participants were asked to evaluate the disk's handling and numbing effect on a scale of 0 to 3, with 3 being very good, 2 good, 1 fair, and 0 poor. Participants also evaluated the time necessary for adhesion; the residence time; the foreign body sensation, if any, and its duration; and the erosion of the disk. Finally, participants were asked to evaluate the overall effectiveness of the disk and their overall impression, as well as which pharmaceutical component, dyclonine HCl (D) or benzocaine (B), they preferred. The results are described in Table 3 below.

TABLE 3

No.	Handling	Adhesion	Residence Time	Foreign Body Sensation	Numb-ing	Disso-lution	Effi-cienc y	Over-all	Pharma-ceutical Pref.
1	3	instant	~ 1 hr	< 5 min.	3	did not notice	+	+	B
2	2	instant	~ 1 hr	< 5 min.	3	did not notice	+	+	B
3	3	instant	~ 45 min.	no	2	did not notice	+	+	D
4	3	instant	~ 45 min.	no	2	at the end	+	-	D
5	2	instant	~ 30 min.	< 5 min.	3	at the end	+	+	D
6	1	difficult	~ 15 min.	< 5 min.	2	did not notice	-	-	D

The results demonstrate that although the handling of the disk may be difficult for first time users, the adhesion is instantaneous, there is only a minor foreign body sensation which disappears after a couple minutes upon swelling of the disk, and numbing is effective.

EXAMPLE 21

A 1 kg preparation of a backing layer was made using 43.49% by weight of water, 43.49.% by weight of ethyl alcohol, 0.02% of FD&C red dye 40, 12% by weight of hydroxyethyl cellulose (Mw 9 x 104) and 1% by weight of 40% glyoxal aqueous solution. . Then another 1 kg batch of the backing solution described at the example 1 was prepared. Using a Werner Mathis Labcoater, the substrate (Mylar 1000D or other polyester films such

as 3M ScotchPak 1022) was set. 90 ml of the backing layer solution prepared according to example 1 was set in front of a knife over roll with an opening of 0.7 mm. The solution was then casted on the substrate and film dried for 8-9 min. at 130° C. Following the drying step, a 0.09 mm thick reddish film was the result. Then, the backing solution first described in this example was casted directly on the top of the first layer with the knife over roll technique using an opening of 0.8 mm. The resulting bilayer backing film was 0.15 mm thick.

EXAMPLE 22

A preparation of a backing layer obtained as described in example 5 was cast using a knife over roll and dried for 8-9 min. at 130° C. Then a preparation of a backing layer using 43.49% by weight of water, 43.49.% by weight of ethyl alcohol, 0.02% of FD&C red dye 40, 12% by weight of hydroxyethyl cellulose (Mw 9 x 104) and 1% by weight of 40% glyoxal aqueous solution was coated directly on the top of the previous dry film (first layer was 0.05 mm thick) The resulting bilayer backing film was 0.12 mm thick.

EXAMPLE 23

When a crosslinking agent is incorporated in the formulation, thermal curing allows to further crosslink the material either before or after the bioadhesive(s) layer(s) have been casted. Thermal curing of the films is performed by exposing the films to a time-temperature cycle. For instance, the film obtained at the end of example 22 might be exposed to 150°C for 5 minutes, 120°C for 10 minutes or any temperature/time which would accommodate the stability requirements of the film's components.

EXAMPLE 24

A preparation of a backing layer obtained as described in example 5 was cast using a knife over roll and dried for 8-9 min. at 130° C. A preparation of a backing layer using 42.49% by weight of water, 42.49.% by weight of ethyl alcohol, 0.02% of FD&C red dye 40, 11% by weight of hydroxyethyl cellulose (Mw 9 x 104), 2% by weight of polyethylene glycol

6000 and 2% by weight of propylene glycol was coated directly on the top of the previous dry film (first layer was 0.06 mm thick) The resulting bilayer backing film was 0.12 mm thick.

EXAMPLE 25

A preparation of a backing layer using 42.49% by weight of water, 42.49.% by weight of ethyl alcohol, 0.02% of FD&C red dye 40, 10% by weight of hydroxyethyl cellulose (Mw 9 x 104), 4% by weight of hydropropylcellulose (Mw 5 105) was coated using a knife over roll technique. Then directly on the top of the previous dry film (first layer was 0.07 mm thick) a backing preparation made from 42.49% by weight of water, 42.49.% by weight of ethyl alcohol, 0.02% of FD&C red dye 40, 12% by weight of hydroxyethyl cellulose (Mw 9 x 104) and 3% by weight of oleic acid, was casted and dried. The resulting bilayer backing film was 0.15 mm thick.

EXAMPLE 26

A preparation for the adhesive layer was made using 45.6% by weight water USP, 45% by weight of ehtyl alcohol, 2% by weight hydroxyethyl cellulose, Natrosol® 99-250 L NF (Aqualon), 2.9% by weight polyacrylic acid, Noveon® AA1 USP (BF Goodrich), and 4.5% by weight of sodium carboxymethyl cellulose, cellulose gum 7 LF PH (Aqualon). This preparation is a bioadhesive preparation but does not contain any pharmaceutical.

EXAMPLE 27

A 100 ml solution for the adhesive layer was made using 45.1% by weight of water USP, 45% by weight of ehtyl alcohol, 1.8% by weight hydroxyethyl cellulose, Natrosol® 99-250 L NF (Aqualon), 2.6% by weight polyacrylic acid, Noveon® AA1 USP (BF Goodrich), 4.5% sodium carboxymethyl cellulose, cellulose gum 7 LF PH (Aqualon), and 1% by weight terbutaline sulfate.

EXAMPLE 28

The film obtained following the example 25 is used as substrate for the final multilayer film of this example. The bioadhesive preparation of example 26 is directly casted on the film of example 25 and dried. Then the preparation of example 27 is cast on the top with a knife over roll system. The final four layer film is 0.240 mm. The composition of this film limits the release of terbutaline in the oral cavity but not completely as the pharmaceutical can still diffuse through the sides. In order to avoid this side diffusion, we have to changed slightly the design has previously mentioned.

EXAMPLE 29

The film obtained following the example 25 is used as substrate for the final multilayer film of this example. The bioadhesive preparation of example 26 is directly casted on the film of example 25 and dried. A trilayer film is thus obtained, the last layer being bioadhesive but not containing any drug. Then the preparation of example 27 is coated using a mask and dried (the mask is a 0.500 mm polyester film in which ellipsoids have been die cut deposited on the trilayer laminate). This step can be repeated if necessary. The mask is then delaminated. The resulting film is tri/four layers film composed of a laminate backing layer and a laminate bioadhesive layer in which the final component includes the pharmaceutical and is of a smaller surface as shown in figure . With this system, diffusion by either the sides or the back side is limited and allows an unidirectional release of the drug into the mucosal tissues.

EXAMPLE 30

Following the previous example but with fluocinonide instead of pilocarpine HCl, the same type of film is constructed using a screen coating technique instead of using a mask. Others techniques such as deposition of, spraying the solution or die cutting off the last layer are satisfactory.

CLAIMS:

1. A pharmaceutical carrier device comprising a layered film having a first water-erodable adhesive layer to be placed in contact with a mucosal surface, and a second, water-erodable non-adhesive backing layer, wherein said device is capable of having a pharmaceutical incorporated within said first layer, said second layer, or both layers.

2. The pharmaceutical carrier device of claim 1, wherein said first water-erodable adhesive layer comprises an alkyl cellulose or hydroxyalkyl cellulose and a bioadhesive polymer.

3. The pharmaceutical carrier device of claim 1, wherein said first water-erodable adhesive layer comprises a film forming polymer selected from hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, hydroxyethyl methyl cellulose, polyvinyl alcohol, polyethylene glycol, polyethylene oxide, ethylene oxide-propylene oxide co-polymers, collagen and derivatives, gelatin, albumin, polyaminoacids and derivatives, polyphosphazenes, polysaccharides and derivatives, or chitin and chitosan, alone or in combination, and a bioadhesive polymer selected from polyacrylic acid, polyvinyl pyrrolidone, or sodium carboxymethyl cellulose, alone or in combination.

4. The pharmaceutical carrier device of claim 1, wherein said second water-erodable non-adhesive backing layer comprises hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxyethylmethyl cellulose, hydroxypropylmethyl cellulose, polyvinyl alcohol, polyethylene glycol, polyethylene oxide, or ethylene oxide-propylene oxide co-polymers, alone or in combination.

5. The pharmaceutical device of claim 1, wherein a pharmaceutical is present in said first water-erodable adhesive layer.

6. The pharmaceutical device of claim 1, wherein said layered film has two layers and a total thickness of from 0.1 mm to 1 mm.

7. The pharmaceutical device of claim 1 which further comprises a third layer between said first adhesive layer and said second backing layer and wherein said third layer is a water-

erodable, adhesive layer which has a surface area sufficient to encompass said first adhesive layer and contact the mucosal surface.

8. The pharmaceutical device of claim 7, wherein a pharmaceutical is present in said first adhesive layer.

9. The pharmaceutical device of claim 1, wherein one or more of the layers further comprises a component which acts to adjust the kinetics of the erodability of the device.

10. The pharmaceutical device of claim 9 wherein the component is a water-based emulsion of polylactide, polyglycolide, lactide-glycolide copolymers, poly-ε-caprolactone and derivatives, polyorthoesters and derivatives, polyanhydrides and derivatives, ethyl cellulose, vinyl acetate, cellulose acetate, or polyisobutylene, alone or in combination.

11. The pharmaceutical device of claim 9 wherein the component is alkyl-glycol, propylene glycol, polyethyleneglycol, oleate, sebacate, stearate or esters of glycerol, or phthalate.

12. The pharmaceutical device of claim 7, wherein one or more of the layers further comprises a component which acts to adjust the kinetics of the erodability of the device.

13. The pharmaceutical device of claim 12 wherein the component is a water-based emulsion of polylactide, polyglycolide, lactide-glycolide copolymers, poly-ε-caprolactone and derivatives, polyorthoesters and derivatives, polyanhydrides and derivatives, ethyl cellulose, vinyl acetate, cellulose acetate, or polyisobutylene, alone or in combination.

14. The pharmaceutical device of claim 12 wherein the component is alkyl-glycol, propylene glycol, polyethyleneglycol, oleate, sebacate, stearate or esters of glycerol, or phthalate.

15. The pharmaceutical device of claim 1, wherein said pharmaceutical capable of being incorporated within said first layer, said second layer, or both layers comprises an anti-inflammatory analgesic agent, a steroidal anti-inflammatory agent, an antihistamine, a local anesthetic, a bactericide, a disinfectant, a vasoconstrictor, a hemostatic, a chemotherapeutic drug, an antibiotic, a keratolytic, a cauterizing agent, an antiviral, an antirheumatic, an

antihypertensive, a bronchodilator, an anticholigernic, an antimenimic compounds, a hormone, a macromolecule, a peptide, a protein, or a vaccine alone or in combination.

16. The pharmaceutical device of claim 1, wherein said first water-erodable adhesive layer comprises hydroxyethyl cellulose, polyacrylic acid, and sodium carboxymethyl cellulose; said second water-erodable non-adhesive backing layer comprises hydroxyethyl cellulose; and said pharmaceutical capable of being incorporated comprises dyclonine HCl.

17. A layered film disk which adheres to mucosal surfaces for the localized delivery of pharmaceutical, comprising a first adhesive layer and a second non-adhesive backing layer, said pharmaceutical or combination of pharmaceuticals present in said first adhesive layer, or said second non-adhesive backing layer, or both said first adhesive layer and said second non-adhesive backing layer, said layered film having a total thickness of from 0.1 mm to 1 mm.

18. The layered film disk of claim 17, wherein said pharmaceutical or combination of pharmaceuticals comprises an anti-inflammatory analgesic agent, a steroidal anti-inflammatory agent, an antihistamine, a local anesthetic, a bactericide, a disinfectant, a vasoconstrictor, a hemostatic, a chemotherapeutic drug, an antibiotic, a keratolytic, a cauterizing agent, an antiviral, an antirheumatic, an antihypertensive, a bronchodilator, an anticholigernic, an antimenimic compounds, a hormone, a macromolecule, a peptide, a protein, or a vaccine, alone or in combination.

19. A method for treating mucosal surfaces, surrounding tissues, and bodily fluids, comprising applying an adherent film at the treatment site for the protection of said treatment site and delivery of pharmaceutical to said mucosal surface, said surrounding tissues, and said bodily fluids, said adherent film comprising a layered pharmaceutical carrier device which is water-erodable.

20. The method of claim 19, wherein said layered pharmaceutical carrier device comprises a first water-erodable adhesive layer and a second water-erodable non-adhesive backing layer, said first and second layers each having a thickness of from 0.01 mm to 0.9 mm.

21. The method of claim 20, wherein said layered carrier device further comprises a pharmaceutical incorporated within said first or second layer.

22. The method of claim 21, wherein said first water-erodable adhesive layer comprises a film forming polymer selected from hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, or hydroxyethylmethyl cellulose, alone or in combination, and a bioadhesive polymer selected from polyacrylic acid, polyvinyl pyrrolidone, or sodium carboxymethyl cellulose, alone or in combination.

23. The method of claim 22, wherein said second water-erodable non-adhesive backing layer comprises hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxyethylmethyl cellulose, hydroxypropylmethyl cellulose, polyvinyl alcohol, polyethylene glycol, polyethylene oxide, or ethylene oxide-propylene oxide co-polymers, alone or in combination.

24. The method of claim 23, wherein said pharmaceutical comprises an anti-inflammatory analgesic agent, a steroidal anti-inflammatory agent, an antihistamine, a local anesthetic, a bactericide, a disinfectant, a vasoconstrictor, a hemostatic, a chemotherapeutic drug, an antibiotic, a keratolytic, a cauterizing agent, an antiviral, an antirheumatic, an antihypertensive, a bronchodilator, an anticholigernic, an antimenimic compounds, a hormone, a macromolecule, a peptide, a protein, or a vaccine alone or in combination.

25. A method for treating wounds or burns of the skin comprising applying an adherent film at the treatment site for the protection of said treatment site and delivery of pharmaceutical to the skin, said adherent film comprising a layered pharmaceutical carrier device which is water-erodable.

26. The method of claim 25, wherein said layered pharmaceutical carrier device comprises a first water-erodable adhesive layer and a second water-erodable non-adhesive backing layer, said first and second layers each having a thickness of from 0.01 mm to 0.9 mm.

27. The method of claim 26, wherein said layered carrier device further comprises a pharmaceutical incorporated within said first or second layer.

28. The method of claim 27, wherein said first water-erodable adhesive layer comprises a film forming polymer selected from hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, or hydroxyethylmethyl cellulose, alone or in combination, and a bioadhesive polymer selected from polyacrylic acid, polyvinyl pyrrolidone, or sodium carboxymethyl cellulose, alone or in combination.

29. The method of claim 28, wherein said second water-erodable non-adhesive backing layer comprises hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxyethylmethyl cellulose, hydroxypropylmethyl cellulose, polyvinyl alcohol, polyethylene glycol, polyethylene oxide, or ethylene oxide-propylene oxide co-polymers, alone or in combination.

30. The method of claim 29, wherein said pharmaceutical comprises an anti-inflammatory analgesic agent, a steroidal anti-inflammatory agent, an antihistamine, a local anesthetic, a bactericide, a disinfectant, a vasoconstrictor, a hemostatic, a chemotherapeutic drug, an antibiotic, a keratolytic, a cauterizing agent, an antiviral, an antirheumatic, an antihypertensive, a bronchodilator, an anticholigernic, an antimenimic compounds, a hormone, a macromolecule, a peptide, a protein, or a vaccine alone or in combination.

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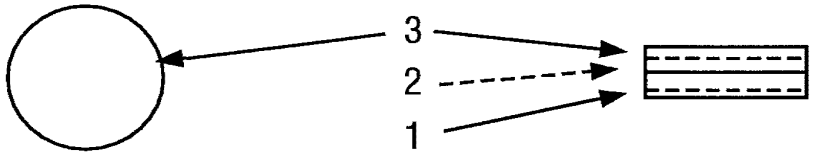

FIG.1

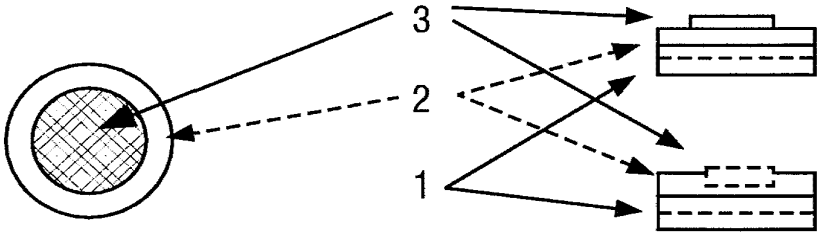

FIG.2

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 97/18605

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 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 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FR 2 582 942 A (YAMANOUCHI TRADING) 12 December 1986 see claims 1,6,7 see page 5, line 1 - line 17 see page 6, line 13 - page 7, line 19 ---	1-6,9, 11,15, 17-30
X	EP 0 262 422 A (TEIKOKU SEIYAKU KABUSHIKI KAISHA) 6 April 1988 see claims 1,2,11,12 see page 3, line 35 - line 41 see examples 3,4 see figure 1 --- -/--	1-3, 9-11,15, 17-21, 25-30

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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1

Date of the actual completion of the international search	Date of mailing of the international search report
18 December 1997	15/01/1998

Name and mailing address of the ISA	Authorized officer
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 159 604 A (TEIKOKU SEIYAKU TOYO BOSEKI KABUSHIKI KAISHA) 30 October 1985 see claim 4 see page 9, paragraph 2 ---	1-5,15, 17-30
A	FR 2 497 098 A (TEIJIN LIMITED) 2 July 1982 see claims 1,3,4,7-9 -----	1-30

1

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No
PCT/US 97/18605

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		JP 61280423 A	11-12-86
		DE 3618553 A	08-01-87
		GB 2177002 A,B	14-01-87
		US 4765983 A	23-08-88
EP 262422 A	06-04-88	JP 2063718 C	24-06-96
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		US 4715369 A	29-12-87

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(54) Title: PHARMACEUTICAL CARRIER DEVICE SUITABLE FOR DELIVERY OF PHARMACEUTICAL COMPOUNDS TO MUCOSAL SURFACES

(57) Abstract

The present invention relates to a pharmaceutical delivery device for application of a pharmaceutical to mucosal surfaces. The device comprises an adhesive layer and a nonadhesive backing layer, and the pharmaceutical may be provided in either or both layers. Upon application, the device adheres to the mucosal surface, providing localized drug delivery and protection to the treatment site. The kinetics of erodability are easily adjusted by varying the number of layers and/or the components.

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PHARMACEUTICAL CARRIER DEVICE SUITABLE FOR DELIVERY OF PHARMACEUTICAL COMPOUNDS TO MUCOSAL SURFACES

FIELD OF THE INVENTION

The present invention relates generally to a water-erodable pharmaceutical carrier which adheres to mucosal surfaces for the localized delivery of pharmaceutical compounds and protection of the treatment site.

BACKGROUND OF THE INVENTION

The localized treatment of body tissues, diseases, and wounds requires that the particular pharmaceutical component be maintained at the site of treatment for an effective period of time. Given the tendency of natural bodily fluids to rapidly wash away topically applied pharmaceutical components, the topical treatment of wet mucosal tissues has been problematic. In the mouth, saliva, natural replacement of the mucosal tissue, as well as, eating, drinking, and speaking movements are some of the problems that have limited the effectiveness and residence time of pharmaceutical carriers.

Bioadhesive carriers are known in the art and include gels, pastes, tablets, and films. These products, however, may lack one or several of the preferred characteristics for an efficient and commercially acceptable pharmaceutical delivery device. Some characteristics which are preferred by users of bioadhesive carriers include water-erodability; ease of handling and application to the treatment site; ease of comfort; minimal foreign body sensation; and unidirectional, specific release into the mucosal tissue. Other preferred characteristics for an effective and user-friendly product for the treatment of mucosal surfaces include the use of pharmaceutically approved components or materials; instantaneous adhesion to mucosal surface upon application; increased residence time for the protection of the affected tissue or the delivery of the pharmaceutical component; and ease of removal of the delivery device from the affected tissue or natural erosion of the delivery device at the delivery site.

Bioadhesive gels which are used for application to mucosal tissues and especially the oral cavity are known in the art. For example, U.S. Patent No. 5,192,802 describes a bioadhesive teething gel made from a blend of sodium carboxymethyl cellulose and xanthan gum. The gel may also have potential use in the treatment of canker sores, fever blisters, and hemorrhoids. However, this type of pharmaceutical carrier has a very limited residence time, given that body fluids such as saliva quickly wash it away from the treatment site. Bioadhesive gels are also described in U.S. Patent Nos. 5,314,915; 5,298,258; and 5,642,749. The gels described in those patents use an aqueous or oily medium and different types of bioadhesive and gelling agents.

Denture adhesive pastes are another type of bioadhesive product known in the art. However, these preparations are used primarily for their adhesive properties, to adhere dentures to the gums, rather than for the protection of tissue or for the topical delivery of pharmaceuticals, although drugs such as local anesthetics may be used in the paste for the relief of sore gums. U.S. Patent Nos. 4,894,232 and 4,518,721 describe denture adhesive pastes. The '721 Patent describes a combination of sodium carboxymethyl cellulose and polyethylene oxide in polyethylene glycol.

Pastes have also been used as film protectants and as drug delivery systems. One such example having film forming and adhesive properties is the product commercialized under the name Orabase®-B, which is a thick gel or paste for the relief of mouth sores. Ingredients include guar gum, sodium carboxymethyl cellulose, tragacanth gum, and pectin. Even though it does provide numbing to the area of application, the film forming behavior and bioadhesion do not last. Thus, this product has a limited residence time.

Bioadhesive tablets are described in U.S. Patent No. 4,915,948. The water-soluble bioadhesive material used in this device is a xanthan gum or a pectin combined with an adhesion enhancing material such as a polyol. Although residence time is improved with the use of bioadhesive tablets, they are not user friendly, especially when used in the oral cavity, given the unpleasant feelings associated with their solidity, bulkiness, and slow erosion time.

Bioadhesive tablets are also described in U.S. Patent Nos. 4,226,848; 4,292,299; and 4,250,163, and are single layer or bilayer devices having an average thickness of 0.2 to 2.5 mm. The bioadhesive tablets described in these patents utilize a non-adhesive component such as cellulose ether, a bioadhesive component such as polyacrylic acid, sodium carboxymethyl cellulose, or polyvinylpyrrolidone, and a binder for tableting purposes. The cellulose derivatives may or may not be water-erodable.

The use of bandages or bioadhesive laminated films, which are thinner and flexible and therefore have a decreased foreign body sensation, is described in U.S. Patent Nos. 3,996,934 and 4,286,592. These products are used to deliver drugs through the skin or mucous. The laminated films usually include an adhesive layer, a reservoir layer, and a backing layer. Bioadhesive devices designed to release drug through the skin at a given rate and over a period of time are usually not water soluble, and thus are not dissolved or washed away by bodily fluids.

In addition to film systems for the delivery of drug through the skin, film delivery systems for use on mucosal surfaces are also known. These types of systems, which are water-insoluble and usually in the form of laminated, extruded or composite films, are described in U.S. Patent Nos. 4,517,173; 4,572,832; 4,713,243; 4,900,554; and 5,137,729. The '173 Patent describes and claims a membrane-adhering film consisting of at least three layers, including a pharmaceutical layer, a poor water soluble layer, and an intermediate layer. The pharmaceutical layer includes the drug and a cellulose derivative selected from hydroxypropyl cellulose, methyl cellulose, and hydroxypropyl methyl cellulose. The poor water soluble layer is made by the combination of one or more cellulose derivatives with a poor water soluble fatty acid, and the intermediate layer is made of cellulose derivatives. The '832 Patent relates to a soft film for buccal delivery, made by the combined use of a water soluble protein, a polyol, and a polyhydric alcohol such as cellulose and polysaccharides, and also teaches the use of coloring or flavoring agents. The '243 Patent describes a single or multi-layered bioadhesive thin film made from 40-95% water soluble hydroxypropyl cellulose,

5-60% water-insoluble ethylene oxide, 0-10% water-insoluble ethyl cellulose, propyl cellulose, polyethylene, or polypropylene, and a medicament. The films are three-layered laminates and include a bioadhesive layer, a reservoir layer, and a non water-soluble outer protective layer. The '729 Patent teaches a soft adhesive film applicable to the oral mucosa containing a systemic drug and comprising a mixture of a vinyl acetate non water-soluble homopolymer, an acrylic acid polymer, and a cellulose derivative. Finally, the '554 Patent describes a device for use in the oral cavity having an adhesive layer including a mixture of an acrylic acid polymer, a water-insoluble cellulose derivative, and a pharmaceutical preparation, and a water-insoluble or sparingly soluble backing layer. The adhesive layer contains the pharmaceutical, and upon application to the mucosal surface, delivers the drug. The '554 Patent also states that "it is impossible to achieve an adhesive device for application to body tissue without all three components, that is, acrylic acid polymer, water insoluble cellulose derivative and a water insoluble or sparingly soluble backing layer."

JP 56-100714 describes a preparation which comprises a coating layer and an active ingredient layer. The coating layer adheres to the mucosal membrane and is comprised of a cellulose ether or an acrylic acid polymer or salt. The active ingredient layer comprises an ointment base comprised of water-insoluble substances such as fats and oils, waxes, hydrocarbons, higher fatty acids, higher alcohols, polyhydric alcohols or glycerol esters. A surfactant and active ingredient are also present in the active ingredient layer. Thus, the active ingredient is mixed with an essentially non-water erodable substance. The previous examples of thin films to be applied in the oral cavity by adhesion onto the mucosal tissues all utilize polymers which are water-insoluble by nature or which are made water-insoluble by crosslinking, and claim a long residence time. Therefore, unfortunately, the above examples of thin films do not provide a water erodable device with good adhesive properties. Therefore, upon release of the desired amount of drug, the thin films of water insoluble polymers must be peeled off the site of application. Such peeling often removes tissue from the mucosal tissue and is painful to the patient. What is needed in the art is a water-erodable

pharmaceutical delivery device which provides good adhesion and localized delivery of a pharmaceutical with minimal discomfort to the patient.

SUMMARY OF THE INVENTION

The present invention relates to a novel water-erodable pharmaceutical carrier device for application to mucosal surfaces to provide protection of and localized delivery of pharmaceutical to the site of application, surrounding tissues, and other bodily fluids such as blood or lymph, having an effective residence time, with minimal discomfort and ease of use. In one embodiment, the pharmaceutical delivery device includes a layered film disk which is water-erodable. The device comprises a layered film disk having an adhesive layer and a backing layer, both water-erodable, having the pharmaceutical in one or more of the layers.

In another embodiment, the pharmaceutical delivery device further comprises a third layer between the first adhesive layer and the second backing layer. The third layer is a water-erodable adhesive layer which has a surface area sufficient to encompass said first adhesive layer and contact the mucosal surface. In this manner, localized delivery of a pharmaceutical may be accomplished in a unidirectional manner toward the mucosal layer.

The adhesive layer(s) comprise(s) a film-forming polymer such as hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, hydroxyethyl methyl cellulose, polyvinyl alcohol, polyethylene glycol, polyethylene oxide, ethylene oxide-propylene oxide co-polymers, collagen and derivatives, gelatin, albumin, polyaminoacids and derivatives, polyphosphazenes, polysaccharides and derivatives, chitin, or chitosan, alone or in combination and a bioadhesive polymer such as polyacrylic acid, polyvinyl pyrrolidone, or sodium carboxymethyl cellulose, alone or in combination.

The non-adhesive backing layer(s) comprise(s) hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxyethylmethyl cellulose, hydroxypropylmethyl

cellulose, polyvinyl alcohol, polyethylene glycol, polyethylene oxide, or ethylene oxide-propylene oxide co-polymers, alone or in combination.

In another embodiment of the invention, one or more of the layers of the device further comprise a component which acts to adjust the kinetics of the erodability and provide a convenient manner of altering the release of the pharmaceutical and the lifespan of the device. A component which acts to adjust the kinetics of the erodability is a water-based emulsion of a polylactide, polyglycolide, lactide-glycolide copolymers, poly-Mcaprolactone and derivatives, polyorthoesters and derivatives, polyanhydrides and derivatives, ethyl cellulose, vinyl acetate, cellulose acetate, and polyisobutylene, alone or in combination. Another component which acts to adjust the kinetics of the erodability is alkyl-glycol, propylene glycol, polyethyleneglycol, oleate, sebacate, stearate or esters of glycerol, or phthalate, alone or in combination.

In another embodiment of the invention, the number of layers of the device further may be varied to adjust the kinetics of the erodability and provide a convenient manner of altering the release of the pharmaceutical and the lifespan of the device.

In a preferred embodiment, the backing layer comprises two or more layers with different erodibility kinetics.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a three layered film disk wherein layers 2 and 3 are bioadhesive layers and layer 1 is a backing layer.

Figure 2 is a three layered film disk wherein two of the layers are bioadhesive layers and the other layer is a backing layer. The bioadhesive layer, layer 3, which will adhere to the mucosal tissue is of smaller surface area and encompassed by the second bioadhesive layer, layer 2, to provide unidirectional delivery. Layer 1 is a backing layer.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, the term "water-erodable" means that the component, device, layer, etc. erodes in water-based media such as saliva, over time. Such erosion in water may be due to factors such as dissolution, dispersion, friction, gravity, etc.

As used herein, the term "kinetics of erodability" or "erosion kinetics" refers to the timing of the release of pharmaceutical from the carrier device (release profile), as well as, the timing of the erosion of the device itself over time (lifespan or residence time of the device). As described herein, kinetics of erodability are based on factors such as type and amount of components in the device, thickness and number of layers in the device, and additives or excipients in the device. In a case in which all the components of the device are very water soluble, the kinetics of erodability will closely parallel the solubility kinetics.

In the present invention, a novel water-erodable pharmaceutical device which adheres to mucosal surfaces is provided. The present invention finds particular use in the localized treatment of body tissues, diseases, or wounds which may have moist surfaces and which are susceptible to bodily fluids, such as the mouth, the vagina, or other types of mucosal surfaces. The device carries a pharmaceutical, and upon application and adherence to the mucosal surface, offers a layer of protection and delivers the pharmaceutical to the treatment site, the surrounding tissues, and other bodily fluids. The device provides an appropriate residence time for effective drug delivery at the treatment site, given the control of erosion in aqueous solution or bodily fluids such as saliva, and the slow, natural erosion of the film concomitant or subsequent to the delivery. In one embodiment, the pharmaceutical delivery device comprises a layered film disk having an adhesive layer and a backing layer, both water-erodable, having the pharmaceutical in either or both layers.

Unlike bioadhesive gels and pastes known in the art, which have a very limited residence time, given the tendency of bodily fluids such as saliva to wash away the gel from the treatment site, the present invention offers an increased residence time because of its filmy consistency and components. A typical

residence time for an aqueous gel or paste, such as Orajel®, Orabase®, or Kanka® is a few minutes. This short residence time is a consequence of a limited or poor adhesion. In a typical aqueous gel, the mucoadhesive components are either in solution, suspension, or swollen. Once applied to the mucosal surface, however, the water based gel does not instantaneously penetrate the lipophilic mucosal surface. The composition and water affinity of these gels results in a tendency to quickly mix with the saliva, rapidly pulling away the different components of the gel, and limiting the residence time. The same tendency is expected with pastes, the increase in viscosity only slightly delaying the timing. The present invention, by its solid form and its instantaneous adhesion to the mucosal surface, allows a lasting contact, a consequence of the entanglement of polymer chains and glycoproteins of the mucosal tissue which assures adhesion. Erosion kinetics in the saliva and other aqueous media are influenced by the physical state of the device. While a gel or solution will readily mix with saliva and/or other bodily fluids, a solid form of the same or similar composition, such as the film of the present invention, dissolves / erodes more slowly.

Also, unlike the bioadhesive tablets which are known in the art, the pharmaceutical device of the present invention minimizes the discomfort associated with application of a foreign substance for a period of time sufficient to provide effective drug delivery to the treatment site. Often, users of the bioadhesive tablets of the prior art experience unpleasant sensations due to their solidity, bulkiness, and slow dissolution time if erodable, especially when used in the oral cavity. Moreover, the typical thickness of bioadhesive tablets, which may or may not be water soluble, is a couple of millimeters, and because of their thickness, the preferred site of application is on the upper gingival area. This site is usually unsatisfactory for local delivery as the type of compounds to be delivered, their bioavailability, and pharmokinetics is limited. In contrast to tablets, the device of the present invention offers the advantages of an effective residence time with minimal discomfort and ease of use, and is an appropriate vehicle for the local, as well as systemic, delivery of pharmaceutical, given its thinner, flexible form.

Finally, unlike the film systems known in the art which are used to deliver pharmaceutical through the skin or mucous, the device of the present invention is made of water-erodable components and thus is bioerodable. The use of water-erodable components allows the device to erode over a period of time, with natural bodily fluids slowly dissolving or eroding away the carrier, while the pharmaceutical remains at the application site. Unlike bandages and other non-water-erodable film systems, the user of the present invention does not have to remove the device following treatment. Nor does the user experience the sensation of the presence of a foreign object at the mucosal surface or within the body cavity, given that upon application, water absorption softens the device, and over time, the device slowly dissolves or erodes away.

The residence time of the device of the present invention depends on the erosion rate of the water-erodable polymers used in the formulation and their respective concentrations. The erosion rate may be adjusted, for example, by mixing together components with different solubility characteristics or chemically different polymers, such as hydroxyethyl cellulose and hydroxypropyl cellulose; by using different molecular weight grades of the same polymer, such as mixing low and medium molecular weight hydroxyethyl cellulose; by using excipients or plasticizers of various lipophilic values or water solubility characteristics (including essentially insoluble components); by using water soluble organic and inorganic salts; by using crosslinking agents such as glyoxal with polymers such as hydroxyethyl cellulose for partial crosslinking; or by post-treatment irradiation or curing, which may alter the physical state of the film, including its crystallinity or phase transition, once obtained. These strategies might be employed alone or in combination in order to modify the erosion kinetics of the device.

Upon application, the pharmaceutical delivery device adheres to the mucosal surface and is held in place. Water absorption softens the device, thereby diminishing the foreign body sensation. As the device rests on the mucosal surface, delivery of the drug occurs. Residence times may be adjusted over a wide range depending upon the desired timing of the delivery of the chosen pharmaceutical and the desired lifespan of the carrier. Generally, however, the

residence time is modulated between about a few seconds to about a few days. Preferably, the residence time for most pharmaceuticals is adjusted from about 30 minutes to about 24 hours. More preferably, the residence time is adjusted from about 1 hour to about 8 hours. In addition to providing drug delivery, once the device adheres to the mucosal surface, it also provides protection to the treatment site, acting as an erodable bandage.

In one embodiment, the present invention comprises a film disc having an adhesive layer and a non-adhesive backing layer which can be comprised of components having a similar or different hydrophilicity. The pharmaceutical component may be included in either layer, although preferably, it is included in the adhesive layer, which is closest to the treatment site and which will have a slower erosion time, given that the backing layer protects the interior, adhesive layer and will typically erode first.

The adhesive layer may comprise at least one film-forming water-erodable polymer (the "film-forming polymer") and at least one pharmacologically acceptable polymer known for its bioadhesive capabilities (the "bioadhesive polymer"). The film forming polymer may comprise hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, hydroxyethyl methyl cellulose, polyvinyl alcohol, polyethylene glycol, polyethylene oxide, ethylene oxide-propylene oxide co-polymers, collagen and derivatives, gelatin, albumin, polyaminoacids and derivatives, polyphosphazenes, polysaccharides and derivatives, chitin and chitosan, alone or in combination. Preferably, the film-forming polymer comprises hydroxyethyl cellulose and hydroxypropyl cellulose. Preferably, in the case of hydroxyethyl cellulose, the average molecular weight (Mw estimated from intrinsic viscosity measurements) is in the range 10^2 to 10^6 and more preferably in the range 10^3 to 10^5, while in the case of hydroxypropyl cellulose, the average molecular weight (Mw obtained from size exclusion chromatography measurements) is in the range 50×10^3 to 1.5×10^6, and more preferably between 80×10^3 to 5×10^5.

The bioadhesive polymer of the adhesive layer may comprise polyacrylic acid (PAA), which may or may not be partially crosslinked, sodium

carboxymethyl cellulose (NaCMC), and polyvinylpyrrolidone (PVP), or combinations thereof. These bioadhesive polymers are preferred because they have good and instantaneous mucoadhesive properties in a dry, film state. In the case of sodium carboxymethyl cellulose, typical average molecular weights comprise 50,000 to 700,000, and preferably 60,000 to 500,000, with a degree of substitution of 0.7. The substitution range varies between 0.5 and 1.5, and preferably between 0.6 and 0.9. The polyvinyl pyrrolidone can be characterized according to its average molecular weight and comprises between 5,000 and 150,000, preferably between 10,000 and 100,000. The simultaneous use of PAA with some grades of PVP may result in the precipitation of one or both components. This precipitation may not be ideal to obtain a homogenous layer and may slightly alter the overall adhesive properties of the device.

While not wishing to bound to a particular theory, it is believed that the adhesion properties of the present invention are the result of the entanglement of polymer chains and interactions with glycoproteins of the mucosal surface. The chemical nature of the bioadhesive polymers, including chain and side groups and crosslinking agents, generates interactions between the mucosal constituents and the polymer or polymers, such as physical entanglement, Van der Waals interactions, and hydrogen bonding. Given that the composition of mucosal tissues differs from one individual to another and changes naturally over time, the use of a combination of bioadhesive polymers or the use of a combination of different grades of the same polymer is preferred. The use of a combination of at least two bioadhesive polymers maximizes the adhesion capabilities of the device, although use of a single bioadhesive polymer is effective as well.

The ratio of the bioadhesive polymer to the film-forming polymer in the adhesive layer may vary, depending on the type of pharmaceutical and the amount of pharmaceutical to be used. However, the content of combined components in the adhesive layer is usually between 5 and 95% by weight, preferably between 10 and 80% by weight. In terms of weight percent of the different bioadhesive polymers PAA, NaCMC, and PVP, some examples are provided below and using the examples one skilled in the art will be able to readily adjust the percentages to

obtain a pharmaceutical device having desired characteristics for a given application. Preferred combinations include PAA and NaCMC, NaCMC and PVP, or PAA and PVP, and also include the use of different grades of the same polymer.

The non adhesive backing layer may comprise a water-erodable, film-forming pharmaceutically acceptable polymer such as hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, hydroxyethylmethyl cellulose, polyvinylalcohol, polyethylene glycol, polyethylene oxide, ethylene oxide-propylene oxide co-polymers, collagen and derivatives, gelatin, albumin, polyaminoacids and derivatives, polyphosphazenes, polysaccharides and derivatives, chitin and chitosan, alone or in combination. The backing layer component may or may not be crosslinked depending on the desired erosion kinetics. In one embodiment, the preferred backing layer component comprises hydroxyethyl cellulose or hydroxypropyl cellulose, and more preferably comprises hydroxyethyl cellulose. Preferably, in the case of hydroxyethyl cellulose, the average molecular weight (Mw estimated from intrinsic viscosity measurements) is in the range 10^2 to 10^6, and more preferably in the range 10^3 to 10^5, while in the case of hydroxypropyl cellulose, the average molecular weight (Mw obtained from size exclusion chromatography measurements) is in the range of 50×10^3 to 1.5×10^6 and more preferably from 80×10^3 to 5×10^5.

Moreover, it has been discovered that a particularly preferable combination for the backing layer comprises hydroxypropyl cellulose and an alkylcellulose such as methylcellulose or ethylcellulose. Such a combination comprises a film-forming amount of alkylcellulose, hydroxypropyl cellulose, and a suitable solvent. Advantageously, the characteristics of the film formed from the gel may be modified depending upon the ratio of hydroxypropyl cellulose to alkylcellulose. Such modifiable characteristics advantageously include the kinetics of erodability.

Typically, the ratio of hydroxypropyl cellulose to alkylcellulose is that necessary to form a suitable film. This ratio may vary based on the other components and the type of alkylcellulose. However, if ethylcellulose is

employed then the ratio of hydroxypropyl cellulose to ethyl cellulose is usually from about 1000:1 to about 3:1, preferably from about 200:1 to about 4:1, more preferably from about 200:1 to about 8:1. Typically, as the ratio of hydroxypropyl cellulose to alkylcellulose increases, the water erodability increases, i.e., the films are more readily washed away. Thus, the ethylcellulose is a component which acts to adjust the kinetics of erodability of the device.

As described above, the erosion kinetics of one or more of the layers (adhesive layer, backing layer, or both) may be altered in many different ways in order to modify the residence time and the release profile of a drug. One way is by crosslinking or plasticizing the film-forming polymer. Crosslinking agents known in the art are appropriate for use in the invention and may include glyoxal, propylene glycol, glycerol, dihydroxy-polyethylene glycol of different sizes, butylene glycol, and combinations thereof. The amount of crosslinking agent used may vary, depending on the particular polymers and crosslinking agent but usually should not exceed 5% molar equivalent of the polymeric material, and preferably comprises 0 to 3% molar equivalent of the polymeric material.

Another way of altering the residence time and release profile is by employing a component in one or more of the layers which acts to adjust the kinetics of the erodability of the layer. While these components will vary widely depending upon the particular pharmaceutical delivery device employed, preferred components include water-based emulsions of polylactide, polyglycolide, lactide-glycolide copolymers, poly-ε-caprolactone and derivatives, polyorthoesters and derivatives, polyanhydrides and derivatives, ethyl cellulose, vinyl acetate, cellulose acetate, silicone, polyisobutylene and derivatives, alone or in combination.

It is also possible to adjust the kinetics of erodability of the devices by adding excipients which are very soluble in water such as water soluble organic and inorganic salts. Suitable such excipients may include the sodium and potassium salts of chloride, carbonate, bicarbonate, citrate, trifluoroacetate, benzoate, phosphate, fluoride, sulfate, or tartrate. The amount added will vary

depending upon how much the erosion kinetics are to be altered as well as the amount and nature of the other components in the device.

Emulsifiers typically used in the water-based emulsions described above are, preferably, either obtained *in situ* if selected from the linoleic, palmitic, myristoleic, lauric, stearic, cetoleic or oleic acids and sodium or potassium hydroxide, or selected from the laurate, palmitate, stearate, or oleate esters of sorbitol and sorbitol anhydrides, polyoxyethylene derivatives including monooleate, monostearate, monopalmitate, monolaurate, fatty alcohols, alkyl phenols, alyl ethers, alkyl aryl ethers, sorbitan monostearate, sorbitan monooleate and sorbitan monopalmitate.

Furthermore, in the case of the water-insoluble polymeric materials such as the polyesteraliphatic family (co-polymers of lactide-glycolide, caprolactone, etc.) the average molecular weight (Mw) is in the range 10^2 to 10^5 and, more preferably, 10^3 to 10^4, while in the case of the cellulosic family (ethyl cellulose, cellulose acetate, etc.), the average molecular weight (Mw estimated from intrinsic viscosity measurements) is in the range 10^2 to 10^6 and more preferably in the range 10^3 to 10^5.

Yet another manner of modifying the erosion kinetics of any layer, is by employing excipients which plasticize the film concomitantly. The excipient or plasticizer often improves the mechanical properties of the device and/or modifies the drug release profile or disintegation time. Suitable excipients or plasticizers modifying the erosion behavior of the layer(s) may include alkyl-glycol such as propylene glycol, polyethyleneglycols, oleate, sebacate, stearate or esters of glycerol, phthalate and others. Other suitable plasticizers include esters such as acetyl citrate, arnyl oleate, myristyl acetate, butyl oleate and stearate, dibutyl sebacate, phthalate esters such as diethyl, dibutyl, and diethoxy ethyl phthalate and the like, fatty acids such as oleic and stearic acid, fatty alcohols such as cetyl, myristyl, and stearyl alcohol. Moreover, in some instances, a polymer, a pharmaceutical, or solvent residual may act as a plasticizer.

It is also possible to modify the erosion kinetics of the device of the instant invention by adjusting the thickness and number of layers. Typically, the thicker

the layers, the slower the release of pharmaceutical and the longer the release profile. Correspondingly, the more layers there are, the slower the release of pharmaceutical and the longer the release profile. In a preferred embodiment, the backing layer comprises two or more layers with different erosion kinetics.

Moreover, combinations of different polymers or similar polymers with definite molecular weight characteristics may be used in order to achieve preferred film forming capabilities, mechanical properties, and kinetics of dissolution in any layer. Some combinations for use in the invention are provided in the examples below and may include ¾ of hydroxyethyl cellulose and ¼ of hydroxypropyl cellulose; 4/5 of low molecular weight hydroxyethyl cellulose and 1/5 of medium molecular weight hydroxyethyl cellulose; and 8/9 of low molecular weight hydroxyethyl cellulose and 1/9 of high molecular weight hydroxyethyl cellulose. As mentioned previously, combinations of water-erodable polymers may be employed in order to modify the erosion kinetics of the device. A particularly preferred combination includes ½ hydroxyethyl cellulose, 1/6 hydroxypropylcellulose, and 2/6 of a pseudolatex, i.e., emulsion of polymer, of lactide-glycolide copolymer.

The pharmaceutical component of the present invention may comprise a single pharmaceutical or a combination of pharmaceuticals, which may be incorporated in the adhesive layer, the backing layer, or both. Pharmaceuticals which may be used, either alone or in combination, include anti-inflammatory analgesic agents, steroidal anti-inflammatory agents, antihistamines, local anesthetics, bactericides and disinfectants, vasoconstrictors, hemostatics, chemotherapeutic drugs, antibiotics, keratolytics, cauterizing agents, antiviral drugs, antirheumatics, antihypertensives, bronchodilators, anticholinergics, antimenimic compounds, hormones and macromolecules, peptides, proteins and vaccines.

Examples of anti-inflammatory analgesic agents include acetaminophen, methyl salicylate, monoglycol salicylate, aspirin, mefenamic acid, flufenamic acid, indomethacin, diclofenac, alclofenac, diclofenac sodium, ibuprofen, ketoprofen, naproxen, pranoprofen, fenoprofen, sulindac, fenclofenac, clidanac,

flurbiprofen, fentiazac, bufexamac, piroxicam, phenylbutazone, oxyphenbutazone, clofezone, pentazocine, mepirizole, tiaramide hydrochloride, etc. Examples of steroidal anti-inflammatory agents include hydrocortisone, predonisolone, dexamethasone, triamcinolone acetonide, fluocinolone acetonide, hydrocortisone acetate, predonisolone acetate, methylpredonisolone, dexamethasone acetate, betamethasone, betamethasone valerate, flumetasone, fluorometholone, beclomethasone diproprionate, fluocinonide, etc.

Examples of antihistamines include diphenhydramine hydrochloride, diphenhydramine salicylate, diphenhydramine, chlorpheniramine hydrochloride, chlorpheniramine maleate isothipendyl hydrochloride, tripelennamine hydrochloride, promethazine hydrochloride, methdilazine hydrochloride, etc. Examples of local anesthetics include dibucaine hydrochloride, dibucaine, lidocaine hydrochloride, lidocaine, benzocaine, p-buthylaminobenzoic acid 2-(die-ethylamino) ethyl ester hydrochloride, procaine hydrochloride, tetracaine, tetracaine hydrochloride, chloroprocaine hydrochloride, oxyprocaine hydrochloride, mepivacaine, cocaine hydrochloride, piperocaine hydrochloride, dyclonine, dyclonine hydrochloride, etc.

Examples of bactericides and disinfectants include thimerosal, phenol, thymol, benzalkonium chloride, benzethonium chloride, chlorhexidine, povidone iode, cetylpyridinium chloride, eugenol, trimethylammonium bromide, etc. Examples of vasoconstrictors include naphazoline nitrate, tetrahydrozoline hydrochloride, oxymetazoline hydrochloride, phenylephrine hydrochloride, tramazoline hydrochloride, etc. Examples of hemostatics include thrombin, phytonadione, protamine sulfate, aminocaproic acid, tranexamic acid, carbazochrome, carbaxochrome sodium sulfanate, rutin, hesperidin, etc.

Examples of chemotherapeutic drugs include sulfamine, sulfathiazole, sulfadiazine, homosulfamine, sulfisoxazole, sulfisomidine, sulfamethizole, nitrofurazone, etc. Examples of antibiotics include penicillin, meticillin, oxacillin, cefalotin, cefalordin, erythromcycin, lincomycin, tetracycline, chlortetracycline, oxytetracycline, metacycline, chloramphenicol, kanamycin, streptomycin, gentamicin, bacitracin, cycloserine, etc.

Examples of keratolytics include salicylic acid, podophyllum resin, podolifox, and cantharidin. Examples of cauterizing agents include the chloroacetic acids and silver nitrate. Examples of antiviral drugs include protease inhibitors, thymadine kinase inhibitors, sugar or glycoprotein synthesis inhibitors, structural protein synthesis inhibitors, attachment and adsorption inhibitors, and nucleoside analogues such as acyclovir, penciclovir, valacyclovir, and ganciclovir.

Examples of proteins, peptides, vaccines, genes and the like include heparin, insulin, LHRH, TRH, interferons, oligonuclides, calcitonin, and octreotide.

Other pharmaceuticals which may be employed include omeprazone, fluoxetine, ethinylestradiol, amiodipine, paroxetine, enalapril, lisinopril, leuprolide, prevastatin, lovastatin, norethindrone, risperidone, olanzapine, albuterol, hydrochlorothiazide, pseudoephridrine, warfarin, terazosin, cisapride, ipratropium, busprione, methylphenidate, levothyroxine, zolpidem, levonorgestrel, glyburide, benazepril, medroxyprogesterone, clonazepam, ondansetron, losartan, quinapril, nitroglycerin, midazolam versed, cetirizine, doxazosin, glipizide, vaccine hepatitis B, salmeterol, sumatriptan, triamcinolone acetonide, goserelin, beclomethasone, granisteron, desogestrel, alprazolam, estradiol, nicotine, interferon beta 1A, cromolyn, fosinopril, digoxin, fluticasone, bisoprolol, calcitril, captorpril, butorphanol, clonidine, premarin, testosterone, sumatriptan, clotrimazole, bisacodyl, dextromethorphan, nitroglycerine In D, nafarelin, dinoprostone, nicotine, bisacodyl, goserelin, and granisetron.

The amount of active pharmaceutical (s) to be used depends on the desired treatment strength and the composition of the layers, although preferably, the pharmaceutical component comprises from about 0.001 to about 99, more preferably from about 0.003 to about 30, and most preferably from about 0.005 to about 20% by weight of the device.

Plasticizers, flavoring and coloring agents, and preservatives may also be included in the pharmaceutical delivery device of the present invention in the adhesive layer, the backing layer, or both. The amounts of each may vary depending on the drug or other components but typically these components

comprise no more than 50, preferably no more than 30, most preferably no more than 15% by total weight of the device.

A permeation enhancer may be added to the device to improve absorption of the drug. Typically, such a permeation enhancer is added to the layer in which the pharmaceutical is to be contained. Suitable permeation enhancers include natural or synthetic bile salts such as sodium fusidate; glycocholate or deoxycholate; fatty acids and derivatives such as sodium laurate, oleic acid, oleyl alcohol, monoolein, and palmitoylcarnitine; chelators such as disodium EDTA, sodium citrate and sodium laurylsulfate, azone, sodium cholate, sodium 5-methoxysalicylate, sorbitan laurate, glyceryl monolaurate, octoxynonyl-9, laureth-9, polysorbates, etc.

The thickness of the device may vary, depending on the thickness of each of the layers and the number of layers. As stated above, both the thickness and amount of layers may be adjusted in order to vary the erosion kinetics. Preferably, if the device has only two layers, the thickness ranges from 0.05 mm to 3mm, preferably from 0.1 to 1 mm, and more preferably from 0.1 to 0.5 mm. The thickness of each layer may vary from 10 to 90% of the overall thickness of the layered device, and preferably varies from 30 to 60%. Thus, the preferred thickness of each layer may vary from 0.01 mm to 0.9 mm, and more preferably from 0.03 to 0.6 mm.

While the device of the invention only requires two layers, i.e., an adhesive layer and a backing layer, it is often preferable to have additional layers. One instance in which this might be advantageous is when specific unidirectional flow of a pharmaceutical is required toward a mucosal layer. The layered device described above provides some directional release, i.e., release will mainly be toward the mucosa and not, for instance, into the oral or vaginal cavity. However, due to the swelling characteristics of the thin film, a small amount of pharmaceutical may also be released through the sides of the device and the backing layer if all the layers are of the approximately the same surface area and are essentially on top of one another. While a preferential, but not specific, release is acceptable, and even desirable, for many pharmaceuticals, other

pharmaceuticals may require unidirectional, specific release into the mucosal tissue.

An example of when unidirectional release may be desirable is when the pharmaceutical to be delivered has a specific therapeutic window or has undesirable side effects if absorbed in the gastrointestinal tract. Furthermore, some pharmaceuticals are enzymatically degraded. Therefore, a bioerodible mucoadhesive system allowing a transmucosal unidirectional delivery and protecting the drug being delivered from enzymes present, for instance, in the oral or vaginal cavities would have advantages.

In such instances when unidirectional release is desired, an additional layer may be placed between the first adhesive layer and the second backing layer. The third layer is a water-erodable adhesive layer which has a surface area sufficient to encompass said first adhesive layer and contact the mucosal surface. The third layer may be comprised of any of the components described above for the first adhesive layer and thus may be the same or different than the first adhesive layer. Figure 2 illustrates a disk having a third layer which encompasses the first adhesive layer.

If a bioadhesive layer is to be of a smaller surface area than the other layers then it is usually between about 5 and about 50, preferably between about 10 and about 30% smaller than the other layers.

In the aforementioned manner, localized delivery of a pharmaceutical may be accomplished in a unidirectional manner. For instance, if pharmaceutical is present in the first adhesive layer then it is prevented from being released through the sides and back of the device. If pharmaceutical is present in the backing layer, then it is prevented from entering the mucosal layer to which the device is adhered. Likewise, if a pharmaceutical is present in the first adhesive layer and the backing layer, they are prevented from mixing.

The pharmaceutical delivery device of the present invention may be prepared by numerous methods known in the art. In one embodiment, the components are dissolved in a biocompatible solvent, preferably an aqueous medium or a combination of water and lower alkanols, to prepare a solution, a gel,

or a suspension that can be used for coating. Solvents for use in the present invention may comprise water, methanol, ethanol, propanol, or low alkyl alcohols such as isopropyl alcohol, or acetone. Other suitable solvents may comprise dimethyl acetamide, N-methyl-2-pyrrolidone, dimethyl sulfoxide, ethoxydiglycol, propylene glycol, polyethylene glycol. The final solvent content or residual solvent content in the film may be the result of either or both layers. Typically, such final solvent content is at least about 10, preferably at least about 5, more preferably at least about 1% by weight of the total device. Similarly, the final solvent content is not more than about 20, preferably not more than about 15, most preferably not more than about 10% by weight of the total device. The solvent may also be used as a plasticizer or an erosion rate-modifying agent.

Each solution is then coated onto a substrate. Eventually, one of the components might be in suspension. Each solution is casted and processed into a thin film by techniques known in the art, such as by film dipping, film coating, film casting, spin coating, or spray drying using the appropriate substrate. The thin film is then allowed to dry. If desired, the drying step can be accomplished in any type of oven in order to facilitate the process. However, as one skilled in the art will appreciate, the solvent residual, which may effect the erosion kinetics, depends on the drying procedure. The film layers may be filmed independently and then laminated together or may be filmed one on the top of the other.

The film obtained after the two layers have been laminated together or coated on top of each other may be cut, if desired, into any type of shape which is suitable for application to the mucosal tissue. Suitable shapes may include disks, ellipses, squares, rectangles, parallepipedes, as well as, shredded, meshed, or porous films depending upon the purpose and location where the device is to be employed. Likewise, the surface area of the device of the present invention will necessarily vary depending on many factors with the major factor being where the device is to be employed. Typically, the surface area may be from about 0.1 to about 30, preferably from 0.5 to about 20 square centimeters.

Methods for treating mucosal surfaces, surrounding tissues, and bodily fluids for localized and systemic drug delivery are also provided. In one

embodiment, the method comprises applying an adherent film of the invention to the treatment site in order to provide protection to the treatment site and drug delivery. The adherent film may comprise any of the layered devices provided herein. In a preferred embodiment, the method comprises application of a layered pharmaceutical carrier device having a first adhesive layer and a second non-adhesive backing layer as described above, each layer having a thickness of from 0.01 mm to 0.9 mm. The pharmaceutical or combination of pharmaceuticals may be present in the adhesive layer, the non-adhesive backing layer, or both layers.

As one skilled in the art will appreciate, when systemic delivery, e.g., transmucosal or transdermal delivery, is desired the treatment site may include any area in which the adherent film of the invention is capable of maintaining a desired level of pharmaceutical in the blood, lymph, or other bodily fluid. Typically, such treatment sites include the oral, anal, nasal, and vaginal mucosal tissue, as well as, the skin. If the skin is to be employed as the treatment site, then usually larger areas of the skin wherein movement will not disrupt the adhesion of the device, such as the upper arm or thigh, are preferred.

While the pharmaceutical carrier described in this application readily adheres to mucosal tissues, which are wet tissues by nature, it can also be used on other surfaces such as skin or wounds. The water-soluble film of the present invention will adhere to the skin if prior to application the skin is wet with an aqueous-based fluid such as water, saliva, or perspiration. The film will typically adhere to the skin until it erodes due contact with water by, for example, showering, bathing or washing. The film may also be readily removed by peeling without significant damage to tissue.

While it is in contact with the skin, the film may act as a washable, erodable bandage to protect the area where it has been applied. It is also possible to employ the film as a transdermal drug delivery system to facilitate the healing process and keep the wound or burn free of germs and debris. A significant advantage of the instant invention over conventional alternatives is that not only is the film washable, but also, perspiration helps the adhesion of the device instead of preventing or reducing it as with conventional transdermal patches.

The pharmaceutical carrier of the present invention can also be used as a wound dressing. By offering a physical, compatible, oxygen and moisture permeable, flexible barrier which can be washed away, the film can not only protect a wound but also deliver a pharmaceutical in order to promote healing, asepty, scarification, to ease the pain or to improve globally the condition of the sufferer. Some of the examples given below are well suited for an application to the skin or a wound. As one skilled in the art will appreciate, the formulation might require incorporating a specific hydrophilic / hygroscopic excipient which would help in maintaining good adhesion on dry skin over an extended period of time. Another advantage of the present invention when utilized in this manner is that if one does not wish that the film be noticeable on the skin, then no dyes or colored substances need be used. If, on the other hand, one desires that the film be noticeable, a dye or colored substance may be employed.

The following examples are provided to illustrate pharmaceutical carrier devices, as well as, methods of making and using, pharmaceutical carrier devices of the present invention.

EXAMPLE 1

A 100 ml solution for the non-adhesive backing layer was made using 87.98% by weight water USP, 0.02% by weight FD&C red 40 dye, and 12% by weight hydroxyethyl cellulose (Mw 9 x 10^4). Using a Werner Mathis Labcoater, the substrate (Mylar 1000D or other polyester films such as 3M ScotchPak 1022) was set. 90 ml of the backing layer solution was set in front of a knife over roll with an opening of 1.5 mm. The solution was then casted and the film dried for 8-9 min. at 60°C. Following the drying step, a 0.14 mm thick reddish film was the result.

Using this procedure, the film may be easily peeled off the substrate after drying, or may be left on the substrate and rolled, to be laminated later, or for use as a substrate for the adhesive layer.

EXAMPLE 2

A 100 ml solution for the non-adhesive backing layer was made using 94.98% by weight water USP, 0.02% by weight FD&C red 40 dye, and 5% by weight hydroxypropyl cellulose. The procedure of Example 1 was used, resulting in a 0.16 mm thick film.

EXAMPLE 3

A 100 ml solution for the non-adhesive backing layer was made using 84.98% by weight water USP, 0.02% by weight FD&C red 40 dye, 12% by weight hydroxyethyl cellulose, and 3% by weight hydroxypropyl cellulose. Here, the overall polymeric material was at a 15% concentration in solution. The mixture of two different types of polymeric materials modified the overall mechanical properties and erosion kinetics characteristics of the backing film. The solution was then casted on a polyester substrate and dried overnight at 90°C. The opening of the knife was set at 3 mm, resulting in a 0.3 mm thick film.

EXAMPLE 4

A 100 ml solution for the non-adhesive backing layer was made using 87.98% by weight water USP, 0.02% by weight FD&C red 40 dye, 10% by weight hydroxyethyl cellulose (Mw 9 x 10^4), and 2% by weight hydroxyethyl cellulose (Mw 7 x 10^5). Here, the mixture of two different types of hydroxyethyl cellulose modified the mechanical properties and erosion kinetics of the backing film. The solution was then cast on a polyester substrate and dried for 12 min. at 135°C. The opening of the knife was set at 3 mm, resulting in a 0.27 mm thick film.

EXAMPLE 5

A 100 ml solution for the non-adhesive backing layer was made using 87.98% by weight water USP, 0.02% by weight FD&C red 40 dye, 11.75% by

weight hydroxyethyl cellulose (Mw 9 x 10^4), and 0.25% by weight hydroxyethyl cellulose (Mw 1.3 x 10^6). The procedure of Example 1 was used, resulting in a 0.14 mm thick film.

Here, the mixture of two different grades of hydroxyethyl cellulose modified the mechanical properties and erosion kinetics of the backing film. The ratio may be used to adjust the erosion pattern and residence time of the bioadhesive disk. Compared to the backing layer of Example 1, which was made of 12% by weight hydroxyethyl cellulose (Mw 9 x 10^4), and which had an erosion time of about 21 minutes (See Table 2), the backing layer of this example, made from a combination of two grades of hydroxyethyl cellulose, had an erosion time of about 69 minutes (See Table 2).

EXAMPLE 6

A 100 ml solution for the non-adhesive backing layer was made using 87.98% by weight water USP, 0.02% by weight FD&C red 40 dye, 11.95% by weight hydroxyethyl cellulose (Mw 9 x 10^4), and 0.05% by weight of 40% glyoxal aqueous solution. The procedure of Example 1 was used, resulting in a 0.13 mm film.

Here, the glyoxal acted as a crosslinking agent, inducing a slow down in the erosion kinetics of the backing film. Compared to the backing layer of Example 1, which had no glyoxal and which had an erosion time of about 21 minutes (See Table 2), the backing layer of this example, which incorporated glyoxal, had an erosion time of about 57 minutes (See Table 2).

EXAMPLE 7

A 100 ml solution for the non-adhesive backing layer was made using 87.98% by weight water USP, 0.02% by weight FD&C red 40 dye, 11.8% by weight hydroxyethyl cellulose , 0.1% by weight of 40% glyoxal aqueous solution, and 0.1% sweet peppermint flavor. Here, as in Example 6, the glyoxal acted as a crosslinking agent, inducing a slow down in the erosion kinetics of the backing

film, compared with a backing layer with no glyoxal. The sweet peppermint was added as a flavoring agent.

EXAMPLE 8

As described in Example 1, the solutions of Examples 5, 6 and 7 were each casted on a polyester substrate. Instead of using a knife, a meier's bar was used to coat the substrate. The films were dried overnight at 90°C. The dried films were thicker, having a thickness of about 0.17 mm.

EXAMPLE 9

The solution of Example 1 was prepared in a beaker. A microslide was then dipped quickly into the solution until it was fully immersed, removed from the solution, and left at room temperature for about 1 hour. The microslide was then dried overnight at 90°C. The resulting film was heterogeneous and had an average thickness of about 0.2 mm.

EXAMPLE 10

A 100 ml solution for the non-adhesive backing layer was made using 84% by weight water USP 0.02% by weight FD&C red 40 dye, 11% by weigh hydroxyethyl cellulose (Mw 9 x 10^4), 1% by weight hydroxyethyl cellulose (Mw 7 x 10^5), 0.1% by weight of a 40% glyoxal aqueous solution, 3% by weight glyoxal, and 1% by weight menthol. Here, the glyoxal acted as a crosslinking agent, inducing a slow down in the erosion kinetics of the backing film. Also, the mixture of two different grades of hydroxyethyl cellulose was used to achieve slow release of the menthol. The film was coated on a polyester film as previously described.

EXAMPLE 11

A 100 ml solution for the adhesive layer was made using 88.6% by weight water USP, 1.8% by weight hydroxyethyl cellulose, Natrosol® 99-250 L NF (Aqualon), 2.6% by weight polyacrylic acid, Noveon® AAl USP (BF Goodrich), 4.5% sodium carboxymethyl cellulose, cellulose gum 7 LF PH (Aqualon), and 2.5% by weight dyclonine HC1. Upon mixing, a suspension was formed.

Here, dyclonine HC1 may be easily substituted with any other active pharmaceutical component. However, chemical characteristics of the active pharmaceutical, such as solubility, counter ions, and melting point, might require minor modifications of the overall process, such as dissolution in a particular solvent, changing the temperature of the solution, etc. The next example illustrates one slight modification.

EXAMPLE 12

A 100 ml solution for the adhesive layer was made using 74.6% by weight water USP, 1.8% by weight hydroxyethyl cellulose, 2.6% by weight polyacrylic acid, 4.5% sodium carboxymethyl cellulose, 2.5% by weight benzocaine, and 14% by weight ethyl alcohol. The use of benzocaine as the active pharmaceutical required that it first be dissolved in ethyl alcohol, given that benzocaine is more soluble in alcohol than water.

In the final solution, the benzocaine tends to precipitate in the form of a very fine powder. However, the film characteristics and bioadhesive properties remain intact.

EXAMPLE 13

A 100 ml solution for the adhesive layer was made using 91% by weight water USP, 2% by weight hydroxyethyl cellulose, 2.5% by weight polyacrylic acid, and 4.5% sodium carboxymethyl cellulose. The composition of the adhesive

layer may be modified and may vary according the ranges described in Table 1 below:

TABLE 1

Item	%w	Material
1	60 to 99.5	Water USP
2	0.05 to 5	Hydroxyethyl cellulose
3	0.5 to 10	Polyacrylic acid
4	0.0 to 15	Sodium Carboxymethyl cellulose
5	0 to 10	Polyvinyl pyrrolidone

The relative part of each components depends of the chemical compatibility of the components and the residence time to be obtained.

EXAMPLE 14

A 100 ml solution for the adhesive layer was made using 90% by weight water USP, 1% by weight butacaine sulfate, 2% by weight hydroxyethyl cellulose, 2.5% by weight polyvinyl pyrrolidone, and 4.5% by weight sodium carboxymethyl cellulose. The solution was coated using a knife over roll on a Mylar substrate.

EXAMPLE 15

A 100 ml solution for the adhesive layer was made. The total composition of the solution was 48.6% water, 40% ethyl alcohol, 1.8% hydroxyethyl cellulose, 2.6% polyacrylic acid, 4.5% sodium carboxymethyl cellulose, and 2.5% dyclonine HC1. Here, however, the dyclonine HC1 was first solubilized in 40 ml ethyl alcohol, and then, 48.6 ml of water were added to the dyclonine HC1/ethyl alcohol solution, followed by the addition of the other components.

The use of ethyl alcohol as an additional solvent resulted in a suspension which was slightly more viscous than that of Example 11, which used water as the only solvent.

EXAMPLE 16

Following the procedure of Example 12, a 100 ml solution for the adhesive layer was prepared. The solution was then coated following the procedure used in Example 1. The resulting film was 0.12 mm thick.

EXAMPLE 17

Following the procedure of Example 12, a 100 ml solution for the adhesive layer was prepared. The solution was coated on top of a backing film prepared according to Example 1. The opening of the knife was adjusted, taking into account the thickness of the backing film. After coating, the layered film was dried at 130°C for 15 minutes. A 0.27 mm layered film of two layers was formed.

EXAMPLE 18

Following the procedure of Example 14, a bioadhesive film was prepared, except that the film was not fully dried. A backing film was prepared according to Example 1. The backing film was peeled off of its substrate and laminated on top of the bioadhesive film while still moist, and pressure was applied to seal the two films together. The pressure applied on the films resulted in a good interfacial adhesion. A 0.38 mm layered film of two layers was formed.

EXAMPLE 19

Following the procedure of Example 1, several solutions for backing films were prepared according to the compositions of Table 2 below. Following film formation, ½ inch disks were die cut and set on a double-sided tape. The tape was then positioned on a micro slide. The kinetics of erosion were evaluated in water:

the slide was plunged into a 100 ml beaker of water stirred at a constant speed of 50 rpm. The time for erosion was measured from the moment the disk was fully immersed in the beaker of water. Percentages (%) refer to the concentration in solution.

TABLE 2

Composition	Weight (mg)/ Thickness (mm)	Erosion Time (min.)
12% HEC (Mw 9 x 10^4	17.1 / 0.14	21
10% HEC (Mw 9 x 10^4) and 2% HEC (Mw 7 x 10^5)	16.9 / 0.13	37
9% HEC (MW 9 X 10^4) and 3% HEC (Mw 7 x 10^5)	17 / 0.14	75
11.75% HEC (Mw 9 x 10^4) and 0.25% HEC (Mw 1.3 x 10^6)	17.1/ 0.14	69
11.95% HEC (Mw 9 x 10^4) and 0.05% glyoxal (40% aq. sol.)	17.2 / 0.13	57
11.99% HEC (Mw 9 x 10^4) and 0.01% propylene glycol	17.3 / 0.14	65

The results demonstrate that the erosion time varies, depending on the components of the formulation, assuming a similar surface state for each sample. Although water does not mimic the exact composition of saliva, and this experiment cannot precisely replicate *in vivo* residence times, the experiment provides an *in vitro* comparison of erosion times of various compositions for use in practicing the present invention.

EXAMPLE 20

½ inch diameter disks having a thickness of between 0.19 and 0.21 mm were administered to six healthy volunteers. The backing layer was prepared according to Example 1, and the adhesive layer was prepared according to Example 15, some containing dyclonine HCl as the active pharmaceutical component, and others containing benzocaine as a substitute. The adhesive layer was coated on top of the backing layer, forming a layered disk. The layered disk was set in the mouth, and the time for erosion was measured from the moment the disk was set in place.

Participants were asked to evaluate the disk's handling and numbing effect on a scale of 0 to 3, with 3 being very good, 2 good, 1 fair, and 0 poor. Participants also evaluated the time necessary for adhesion; the residence time; the foreign body sensation, if any, and its duration; and the erosion of the disk. Finally, participants were asked to evaluate the overall effectiveness of the disk and their overall impression, as well as which pharmaceutical component, dyclonine HCl (D) or benzocaine (B), they preferred. The results are described in Table 3 below.

TABLE 3

No.	Hand ling	Adhesion	Residence Time	Foreign Body Sensation	Numbing	Dissolution	Efficiency	Overall	Pharma ceutical Pref.
1	3	instant	~ 1 hr	<5 min	3	did not notice	+	+	B
2	2	instant	~ 1 hr	<5 min	3	did not notice	+	+	B
3	3	instant	~ 45 min	no	2	did not notice	+	+	D
4	3	instant	~ 45 min	no	2	at the end	+	-	D

No.	Hand ling	Adhesion	Residence Time	Foreign Body Sensation	Numbing	Dissolution	Efficiency	Overall	Pharma ceutical Pref.
5	2	instant	~ 30 min	<5 min	3	at the end	+	+	D
6	1	difficult	~ 15 min	<5 min	2	did not notice	-	-	D

The results demonstrate that although the handling of the disk may be difficult for first time users, the adhesion is instantaneous, there is only a minor foreign body sensation which disappears after a couple minutes upon swelling of the disk, and numbing is effective.

EXAMPLE 21

A 1 kg preparation of a backing layer was made using 43.49% by weight of water, 43.49% by weight of ethyl alcohol, 0.02% of FD&C red dye 40, 12% by weight of hydroxyethyl cellulose (Mw 9 x 10^4) and 1% by weight of 40% glyoxal aqueous solution. Then another 1 kg batch of the backing solution described at the Example 1 was prepared. Using a Wemer Mathis Labcoater, the substrate (Mylar 1000D or other polyester films such as 3M ScotchPak 1022) was set. 90 ml of the backing layer solution prepared according to Example 1 was set in front of a knife over roll with an opening of 0.7 mm. The solution was then casted on the substrate and film dried for 8-9 min. at 130°C. Following the drying step, a 0.09 mm thick reddish film was the result. Then, the backing solution first described in this example was casted directly on the top of the first layer with the knife over roll technique using an opening of 0.8 mm. The resulting bilayer backing film was 0.15 mm thick.

EXAMPLE 22

A preparation of a backing layer obtained as described in Example 5 was cast using a knife over roll and dried for 8-9 min. at 130°C. Then a preparation of a backing layer using 43.49% by weight of water, 43.49% by weight of ethyl alcohol, 0.02% of FD&C red dye 40, 12% by weight of hydroxyethyl cellulose (Mw 9 x 10^4) and 1% by weight of 40% glyoxal aqueous solution was coated directly on the top of the previous dry film (first layer was 0.05 mm thick). The resulting bilayer backing film was 0.12 mm thick.

EXAMPLE 23

When a crosslinking agent is incorporated in the formulation, thermal curing allows to further crosslink the material either before or after the bioadhesive(s) layer(s) have been casted. Thermal curing of the films is performed by exposing the films to a time-temperature cycle. For instance, the film obtained at the end of Example 22 might be exposed to 150°C for 5 minutes, 120°C for 10 minutes or any temperature/time which would accommodate the stability requirements of the film's components.

EXAMPLE 24

A preparation of a backing layer obtained as described in Example 5 was cast using a knife over roll and dried for 8-9 min. at 130°C. A preparation of a backing layer using 42.49% by weight of water, 42.49% by weight of ethyl alcohol, 0.02% of FD&C red dye 40, 11% by weight of hydroxyethyl cellulose (Mw9 x 10^4), 2% by weight of polyethylene glycol 6000 and 2% by weight of propylene glycol was coated directly on the top of the previous dry film (first layer was 0.06 mm thick). The resulting bilayer backing film was 0.12 mm thick.

EXAMPLE 25

A preparation of a backing layer using 42.49% by weight of water, 42.49% by weight of ethyl alcohol, 0.02% of FD&C red dye 40, 10% by weight of hydroxyethyl cellulose (Mw 9 x 10^4), 4% by weight of hydropropylcellulose (Mw 5 x 10^5) was coated using a knife over roll technique. Then directly on the top of the previous dry film (first layer was 0.07 mm thick) a backing preparation made from 42.49% by weight of water, 42.49% by weight of ethyl alcohol, 0.02% of FD&C red dye 40, 12% by weight of hydroxyethyl cellulose (Mw 9 x 10^4) and 3% by weight of oleic acid, was casted and dried. The resulting bilayer backing film was 0.15 mm thick.

EXAMPLE 26

A preparation for the adhesive layer was made using 45.6% by weight water USP, 45% by weight of ethyl alcohol, 2% by weight hydroxyethyl cellulose, Natrosol® 99-250 L NF (Aqualon), 2.9% by weight polyacrylic acid, Noveon® AA1 USP (BF Goodrich), and 4.5% by weight of sodium carboxymethyl cellulose, cellulose gum 7 LF PH (Aqualon). This preparation is a bioadhesive preparation but does not contain any pharmaceutical.

EXAMPLE 27

A 100 ml solution for the adhesive layer was made using 45.1 % by weight of water USP, 45% by weight of ethyl alcohol, 1.8% by weight hydroxyethyl cellulose, Natrosol® 99-250 L NF (Aqualon), 2.6% by weight polyacrylic acid, Noveon® AA1 USP (BF Goodrich), 4.5% sodium carboxymethyl cellulose, cellulose gum 7 LF PH (Aqualon), and 1% by weight terbutaline sulfate.

EXAMPLE 28

The film obtained following the Example 25 is used as substrate for the final multilayer film of this example. The bioadhesive preparation of Example 26 is directly casted on the film of Example 25 and dried. Then the preparation of Example 27 is cast on the top with a knife over roll system. The final four layer film is 0.240 mm. The composition of this film limits the release of terbutaline in the oral cavity but not completely as the pharmaceutical can still diffuse through the sides. In order to avoid this side diffusion, we have to changed slightly the design has previously mentioned.

EXAMPLE 29

The film obtained following the Example 25 is used as substrate for the final multilayer film of this example. The bioadhesive preparation of Example 26 is directly casted on the film of Example 25 and dried. A trilayer film is thus obtained, the last layer being bioadhesive but not containing any drug. Then the preparation of Example 27 is coated using a mask and dried (the mask is a 0.500 mm polyester film in which ellipsoids have been die cut deposited on the trilayer laminate). This step can be repeated if necessary. The mask is then delaminated. The resulting film is tri/four layers film composed of a laminate backing layer and a laminate bioadhesive layer in which the final component includes the pharmaceutical and is of a smaller surface as shown in figure. With this system, diffusion by either the sides or the back side is limited and allows an unidirectional release of the drug into the mucosal tissues.

EXAMPLE 30

Following the previous example but with fluocinonide instead of pilocarpine HC1, the same type of film is constructed using a screen coating technique instead of using a mask. Others techniques such as deposition of,

spraying the solution or die cutting off the last layer, slot coating, or gravure coating, are satisfactory.

EXAMPLE 31

A 200 gram (g) backing solution (or backing collodion) for coating the backing layer was made by using 84.865% by weight ethyl alcohol 190F, 0.01% by weight of FD&C Red dye 40, 13.75% by weight of hydroxypropyl cellulose, 1.25% by weight ethylcellulose and 0.125% by weight of diethyl phathalate. This solution was prepared at ambient temperature by adding the ethyl cellulose to the solution of ethyl alcohol, dye, and diethyl phathalate. The hydroxypropyl cellulose was then added and the collodion stirred for two hours.

A two layered film was subsequently obtained using a labcoater/dryer. On a Rexam 8024 substrate, 50 mL of the solution above was set in front of a knife-over-roll-coating device. The wet film was then dried for 6 minutes at 60°C. A second layer was directly coated on the top and the wet film was dried for an additional 6 minutes at 60°C. The final film thickness was measured to be 130 microns.

EXAMPLE 32

A 200 g backing solution (or backing collodion) for coating the backing layer was prepared as in Example 31 except that 84.74% by weight ethyl alcohol 190F, 0.01% by weight FD&C Red dye 40, 12.5% by weight hydroxypropyl cellulose, 2.5% by weight of ethylcellulose, and 0.25% by weight diethyl phathalate was used.

A film was obtained as in Example 31 except that the film thickness was 135 microns.

EXAMPLE 33

A 120 micron thick film was made in a similar manner as in Example 32 except that a higher molecular weight grade of ethyl cellulose was employed.

EXAMPLE 34

A 200 g backing solution (or backing collodion) for coating the backing layer was prepared as in Example 31 except that 84.74% by weight ethyl alcohol 190F, 0.01% by weight FD&C Red dye 40, 10% by weight hydroxypropyl cellulose, 5% by weight of ethylcellulose, and 0.5% by weight diethyl phathalate was used.

A film was obtained as in Example 31 except that the film thickness was 115 microns.

EXAMPLE 35

A 200 g backing solution (or backing collodion) for coating the backing layer was prepared as in Example 31 except that 81.99% by weight ethyl alcohol 190F, 0.01% by weight FD&C Red dye 40 and 18% by weight hydroxypropyl cellulose was used.

A film was obtained as in Example 31 except that the film thickness was 170 microns.

EXAMPLE 36

The disintegration time in water for the films of Examples 31 to 35 was measured by placing the films in a bath of water at 37±2 °C. As the results in Table 4 show, the disintegration time varies with the ratio of hydroxypropyl cellulose to ethylcellulose.

Table 4

	Example 31	Example 32	Example 33	Example 34	Example 35
Thickness (microns)	130	135	120	115	170
Disintegration time (min)	20-25	25-30	35-40	>60	15-20

EXAMPLE 37

A gel for the backing layers was prepared which contained 79.74% water, 0.01% FD&C red dye 40, 0.05% sodium benzoate, 2.5% peppermint flavor, 13.5% hydroxyethyl cellulose, and 4.5% hydroxypropyl cellulose by weight. The gel was then made into a two layer flexible backing film of 0.17 mm in thickness by first coating a 0.8 mm thick layer of the formulation on a substrate and then drying it at 80°C for 8 minutes. A second 0.8 mm thick layer was then coated directly on top of the first layer and dried at 80°C for 8 minutes. A sample of the two layer film was found to disintegrate in water within 10 minutes. While not wishing to be bound to any theory, it was believed that the hydrophilic salt modified the disintegration time and the hydroxypropyl cellulose improved the tensile strength of the film.

A gel for the bioadhesive layers was prepared which contained 45.2% water USP, 45.3% ethyl alcohol, 1.6% hydroxyethyl cellulose, 0.6% hydroxypropyl cellulose, 2.8% polyacrylic acid Noveon® AA1 USP, 2.5% sodium carboxymethyl cellulose, 0.1% titanium dioxide, and 1.9% albuterol sulfate by weight. Using the gel, a first bioadhesive layer of 0.5 mm was coated directly on top of the two layer flexible backing film and dried at 60°C for 8 minutes. A second bioadhesive layer of 0.7 mm was then coated directly on top of the first bioadhesive layer and dried at 60°C for 20 minutes. The final film was 0.330 mm in thickness, contained 5.92% water by weight, disintegrated in water in 15 ± 3 minutes, and contained 1.46mg/cm^2 albuterol sulfate. The final film also exhibited excellent tensile strength.

EXAMPLE 38

A gel for the backing layers was prepared which contained 42.49% water, 42.49% ethyl alcohol, 0.02% of FD&C red dye 40, 14% hydroxyethyl cellulose (Mw 9 x 10^4), and 1% sweet peppermint by weight. Using the gel, a first backing layer of 0.7 mm was coated onto a substrate using a knife over roll technique. The layer was dried at 60°C for 8 minutes. A second backing layer of 0.8 mm was then coated directly on top of the first backing layer and dried at 60°C for 8 minutes. The final two layer film backing was 0.20 mm in thickness.

A gel for the bioadhesive layers was prepared which contained 45.95% water USP, 45.95% ethyl alcohol, 1.6% hydroxyethyl cellulose Natrosol® 99-250 L NF (Aqualon), 2.2% polyacrylic acid Noveon® AA1 USP (BF Goodrich), 3.4% sodium carboxymethyl cellulose cellulose gum 7 LF PH (Aqualon), and 0.9% albuterol sulfate by weight. Using the gel, a first bioadhesive layer of 0.5 mm was coated onto the two backing layers and dried at 60°C for 10 minutes. A second bioadhesive layer of 0.8 mm was coated onto the first bioadhesive layer and dried at 60°C for 20 minutes. The final film was 0.260 mm thick, disintegrated in water in 20 ± 5 minutes, contained 5.6% water by weight and about 0.71 mg/cm^2 of albuterol sulfate.

EXAMPLE 39

A gel for the backing layers was prepared which contained 42.49% water, 42.49% ethyl alcohol, 0.02% of FD&C red dye 40, 14% hydroxyethyl cellulose (Mw 9 x 10^4), and 1% sweet peppermint by weight. Using the gel, a first backing layer of 0.7 mm was coated onto a substrate using a knife over roll technique. The layer was dried at 60°C for 8 minutes. A second backing layer of 0.8 mm was then coated directly on top of the first backing layer and dried at 60°C for 8 minutes. The final two layer film backing was 0.20 mm in thickness.

A suspension for the bioadhesive layers was prepared which contained 45.95% water USP, 45.95% ethyl alcohol, 1.6% hydroxyethyl cellulose

Natrosol® 99-250 L NF (Aqualon), 2.2% polyacrylic acid Noveon® AA1 USP (BF Goodrich), 3.4% sodium carboxymethyl cellulose cellulose gum 7 LF PH (Aqualon), and 0.9% testosterone by weight. The testosterone is insoluble in the formulation and is added as a micronized powder which stays in suspension. The viscosity of the formulation was lowered to facilitate the coating step by adding 10% by weight of alcohol:water in a 1:1 ratio. Using the suspension, a first bioadhesive layer of 0.5 mm was coated onto the two backing layers and dried at 60°C for 10 minutes. A second bioadhesive layer of 0.9 mm was coated onto the first bioadhesive layer and dried at 60°C for 20 minutes. The final film was 0.310 mm thick, disintegrated in water in 20 ± 5 minutes, contained 5.3% of water by weight and about 0.64 mg/cm^2 of testosterone.

EXAMPLE 40

The films obtained via Examples 38 and 39 are die-cut in ½ inch diameter discs to be characterized and to be used for a systemic availability study in three dogs (20-25 kg spayed female bred hounds). One disc of the film to be evaluated is applied to the inside of the mouth on the buccal mucosa. A slight pressure is applied for 10 seconds. Then, the oral cavity is examined to assure adherence of the film to the mucosa and over the course of the study, to monitor the erosion of the discs. Using an indwelling jugular catheter, blood samples are collected at specific intervals. The serum is characterized by an ELISA assay in the case of albuterol sulfate and by an RIA method for the testosterone study. Mucosal tissues at the end of the studies did not show any sign of irritation.

After application of ½ inch diameter discs, systemic plasma levels obtained at different intervals are given in nanograms per milliliter for the mean of the three dogs. Drug loadings are 0.9 mg albuterol sulfate per disc and 0.8 mg testosterone per disc. Results are shown in Table 5 for the albuterol sulfate and in Table 6 for the testosterone.

Table 5 (albuterol sulfate)

Time (minutes)	Mean (ng/ml)	Standard deviation
0	0.12	0.01
5	0.15	0.12
10	0.22	0.07
15	0.57	0.54
30	1.51	1.61
60	6.01	4.75
90	8.90	3.99
120	11.66	2.97
150	11.22	3.49
180	9.90	1.21
240	6.30	2.21
360	6.29	2.23
480	3.75	0.62
720	1.00	1.05

Table 6 (testosterone)

Time (minutes)	Mean (ng/ml)	Standard deviation
0	0.00	0
5	2.21	1.48
10	4.68	2.55
15	3.81	2.06
30	2.87	2.32
60	3.73	3.31
90	4.82	3.53
120	7.14	0.51
150	3.20	0.03
180	0.62	0.18
240	0.18	0.20
360	0.12	0.18
480	0.02	0.04
720	0.01	0.01

These results illustrate that systemic delivery can be achieved with the pharmaceutical carrier devices of the invention. Moreover, the pharmaceutical carrier devices of the invention yield fast onset of activity, excellent bioavailability, and sustained delivery.

CLAIMS:

1. A pharmaceutical carrier device comprising a layered film having a first water-erodable adhesive layer to be placed in contact with a mucosal surface, and a second, water-erodable non-adhesive backing layer comprising hydroxypropyl cellulose and an alkyl cellulose, wherein said device is capable of having a pharmaceutical incorporated within said first layer, said second layer, or both layers.

2. The device of claim 1 wherein the alkyl cellulose is methyl cellulose or ethyl cellulose.

3. The device of claim 1 wherein the alkyl cellulose is ethyl cellulose.

4. The device of claim 3 wherein the ratio of hydroxypropyl cellulose to ethyl cellulose is from 1000:1 to 3:1.

5. The device of claim 3 wherein the ratio of hydroxypropyl celluose to ethyl celluose is from 200:1 to 4:1.

6. The device of claim 3 wherein the ratio of hydroxypropyl cellulose to ethyl cellulose is from 200:1 to 8:1.

7. A pharmaceutical carrier device comprising a layered film having a first water-erodable adhesive layer to be placed in contact with a mucosal surface, and a second, water-erodable non-adhesive backing layer, at least one of said layers containing an erosion kinetics altering amount of a water soluble non-plasticizing excipient, wherein said device is capable of having a pharmaceutical incorporated within said first layer, said second layer, or both layers.

8. The device of claim 7 wherein the excipient is a water soluble salt.

9. The device of claim 8 wherein the salt is the sodium or potassium salt of chloride, carbonate, bicarbonate, citrate, trifluoroacetate, benzoate, phosphate, fluoride, sulfate, or tartrate.

10. The device of claim 8 wherein the salt is sodium benzoate.

11. The device of any of claims 7-10 wherein the backing layer contains said excipient.

12. The device of any of claims 1-6 wherein the backing layer contains an erosion kinetics altering amount of a water soluble non-plasticizing excipient.

13. The device of claim 12 wherein the excipient is a water-soluble salt.

14. The device of claim 12 wherein the excipient is sodium benzoate.

15. The device of any of claims 1-14, wherein said first water-erodable adhesive layer comprises an alkyl cellulose or hydroxyalkyl cellulose and a bioadhesive polymer.

16. The device of claim 15, wherein said first water-erodable adhesive layer comprises a film forming polymer selected from hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, hydroxyethyl methyl cellulose, polyvinyl alcohol, polyethylene glycol, polyethylene oxide, ethylene oxide-propylene oxide co-polymers, collagen and derivatives, gelatin, albumin, polyaminoacids and derivatives, polyphosphazenes, polysaccharides and derivatives, or chitin and chitosan, alone or in combination, and a bioadhesive polymer selected from polyacrylic acid, polyvinyl pyrrolidone, or sodium carboxymethyl cellulose, alone or in combination.

17. The device of any of claims 1 to 16, wherein said layered film has two layers and a total thickness of from 0.1 mm to 1 mm.

18. The device of any of claims 1 to 17 which further comprises a third layer between said first adhesive layer and said second backing layer and wherein said third layer is a water-erodable, adhesive layer which has a surface area sufficient to encompass said first adhesive layer and contact the mucosal surface.

19. The device of any of claims 1 to 18, wherein said pharmaceutical capable of being incorporated within said first layer, said second layer, or both layers comprises an anti-inflammatory analgesic agent, a steroidal anti-inflammatory agent, an antihistamine, a local anesthetic, a bactericide, a disinfectant, a vasoconstrictor, a hemostatic, a chemotherapeutic drug, an antibiotic, a keratolytic, a cauterizing agent, an antiviral, an antirheumatic, an antihypertensive, a bronchodilator, an anticholigernic, an antimenimic compounds, a hormone, a macromolecule, a peptide, a protein, or a vaccine alone or in combination.

1/1

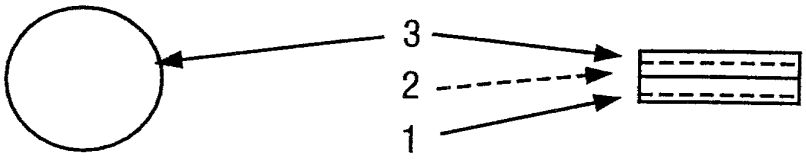

FIG.1

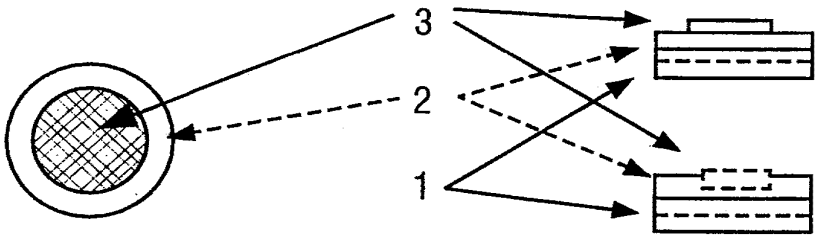

FIG.2

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(57) Abstract

The present invention relates to a pharmaceutical delivery device for application of a pharmaceutical to mucosal surfaces. The device comprises an adhesive layer and a nonadhesive backing layer, and the pharmaceutical may be provided in either or both layers. Upon application, the device adheres to the mucosal surface, providing localized drug delivery and protection to the treatment site. The kinetics of erodability are easily adjusted by varying the number of layers and/or the components.

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 781 546 A (SANWA KAGAKU KENKYUSHO) 2 July 1997 (1997-07-02) the whole document	1-19
A	EP 0 250 187 A (JOHNSON & JOHNSON) 23 December 1987 (1987-12-23) cited in the application the whole document	1-19
A	EP 0 050 480 A (ONO PHARM. CO. LTD.,JP) 28 April 1982 (1982-04-28) the whole document	1-19
A	EP 0 381 194 A (NITTO DENKO) 8 August 1990 (1990-08-08) cited in the application the whole document	1-19

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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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	Scarponi, U

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte onal Application No
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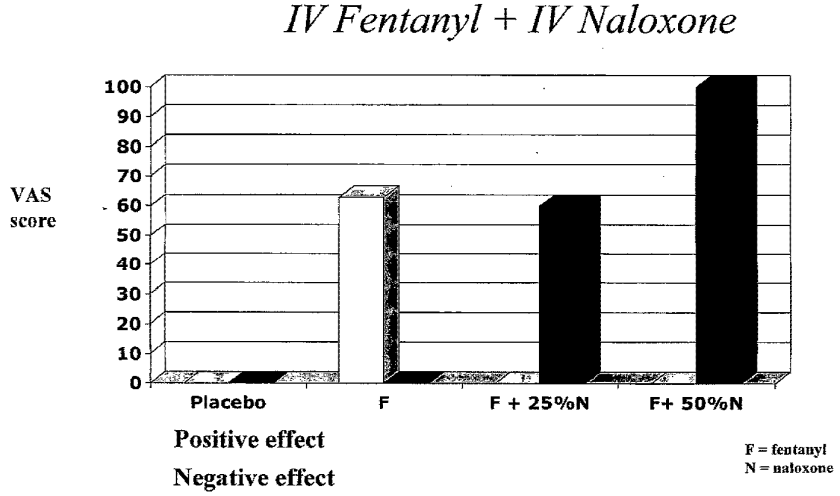
(54) Title: ABUSE RESISTANT TRANSMUCOSAL DRUG DELIVERY DEVICE



(57) Abstract: The present invention relates to a solid pharmaceutical dosage form for abusable drug delivery with reduced illicit abuse potential. The dosage form is presented as a bioerodable transmucosal delivery device that includes an abusable drug and an antagonist to the abusable drug associated with an abuse-resistant matrix. The devices of the invention may be in the form of a layered film or a tablet. Upon application in a non-abusive manner, the device adheres to the mucosal surface, providing transmucosal drug delivery of the drug with minimal absorption of the antagonist into systemic circulation.

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ABUSE RESISTANT TRANSMUCOSAL DRUG DELIVERY DEVICE

RELATED APPLICATIONS

[001] This application claims the benefit of and priority to U.S. Provisional Application No. 60/750,191, filed on December 13, 2005 and U.S. Provisional Application No. 60/764,619, filed on February 2, 2006. The contents of these applications are hereby incorporated by this reference in their entireties.

BACKGROUND OF THE INVENTION

[002] Opioids, or opioid agonists, refer generally to a group of drugs that exhibit opium or morphine-like properties. Opioids can be employed as moderate to strong analgesics, but have other pharmacological effects as well, including drowsiness, respiratory depression, changes in mood and mental clouding without a resulting loss of consciousness. Opium contains more than twenty distinct alkaloids. Morphine, codeine and papaverine are included in this group. With the advent of totally synthetic entities with morphine-like actions, the term "opioid" was generally retained as a generic designation for all exogenous substances that bind stereo-specifically to any of several subspecies of opioid receptors and produce agonist actions.

[003] The potential for the development of tolerance and physical dependence with repeated opioid use is a characteristic feature of all the opioid drugs, and the possibility of developing psychological dependence (*i.e.*, addiction) is one of the major concerns in the treatment of pain with opioids. Another major concern associated with the use of opioids is the diversion of these drugs from the patient in pain to another (non-patient) for recreational purposes, *e.g.*, to an addict.

[004] While opioids are highly successful in relieving and preventing moderate to severe pain, they are subject to abuse to achieve a state of narcosis or euphoria. Oral intake of such drugs by abusers, however, does not usually give rise to the euphoric result desired by the abuser, even when taken in an abusively large quantity, because of poor uptake of such drugs through the GI tract.

[005] Because a particular dose of an opioid analgesic is typically more potent when administered parenterally as compared to the same dose administered orally, one mode of abuse of oral medications involves the extraction of the opioid from the dosage

form, and the subsequent injection of the opioid (using any suitable vehicle for injection) in order to achieve a "high." Such extraction is generally as easy as dissolving the dosage form using an aqueous liquid or a suitable solvent. Oral opioid formulations, however, are not only being abused by the parenteral route, but also via the oral route when the patient or addict orally self-administers more than the prescribed oral dose during any dosage interval. In another mode of abuse, the corresponding dosage forms are comminuted, for example ground, by the abuser and administered, for example, by inhalation. In still another form of abuse, the opioid is extracted from the powder obtained by comminution of the dosage form (optionally dissolving in a suitable liquid) and inhaling the (dissolved or powdered) opioid. These forms of administration give rise to an accelerated rise in levels of the abusable drug, relative to oral administration, providing the abuser with the desired result.

[006] Some progress has been made in the attempt to alleviate or lessen the problem of opioid abuse. For example, U.S. Patent No. 5,866,164 proposes an oral osmotic therapeutic system with a two-layer core, wherein the first layer of the core, facing towards the opening of the system comprises an opioid analgesic and the second layer comprises an antagonist for this opioid analgesic and simultaneously effects the push function, *i.e.*, expelling the analgesic from the corresponding layer out of the opening of the system. U.S. Patent No. 6,228,863 describes an oral dosage form containing a combination of an opioid agonist and an opioid antagonist, the formulation of which has been selected such that the two compounds can in each case only be extracted together from the dosage form and then an at least two-stage process is required to separate them.

[007] U.S. Patent No. 4,582,835 describes a method of treating pain by administering a sublingually effective dose of buprenorphine with naloxone. U.S. Patent No. 6,277,384 also discloses a dosage form containing a combination of an opioid agonist and an opioid antagonist in a specific ratio that brings about a negative effect on administration to an addicted person. U.S. Application Publication No. 2004/0241218 discloses a transdermal system which includes an inactivating agent, *e.g.*, a substance which crosslinks the opioid drug, to prevent abuse. Such transdermal formulations may also include an antagonist.

SUMMARY OF THE INVENTION

[008] The present invention provides a bioerodable abuse resistant transmucosal drug delivery device and method of treatment using such devices. The drug delivery devices of the present invention provide reduced illicit abuse potential and are particularly useful in, *e.g.*, opioid transmucosal drug delivery. The transmucosal drug delivery devices of the present invention generally include a drug and its antagonist contained within the device such that abuse of the drug is impeded.

[009] Thus, for example, illicit use efforts to extract an abusable drug from the transmucosal devices of the present invention for parenteral injection (*e.g.*, by extraction of the drug by dissolving some or all of the transmucosal device in water or other solvent), are thwarted by the co-extraction of an antagonist. The amount of antagonist contained in the product is chosen to block any psychopharmacological effects that would be expected from parenteral administration of the drug alone. The antagonist is generally associated with an abuse-resistant matrix, and does not interfere with the transmucosal delivery of the drug.

[0010] One of the advantages of the devices of the present invention is that the devices generally include an abuse-resistant matrix that does not effectively release the antagonist when the device is used in a non-abusive manner. The dosage forms described in U.S. Patent No. 4,582,384 and U.S. Patent No. 6,227,384, even when correctly administered, release the corresponding antagonist into the mucosa along with the opioid. This impairs the activity of the opioid analgesic and it often becomes necessary to increase the quantity thereof required in the dosage form for satisfactory treatment of the patient. The risk of the occurrence of undesirable accompanying symptoms is also increased in comparison to dosage forms which contain no opioid antagonists. Moreover, it is desirable not to further increase the stress on the patient by releasing a large proportion of opioid antagonist when such a dosage form is correctly administered.

[0011] One of the advantages of the devices of the present invention is that the devices are bioerodable, such that the devices do not have to be removed after use.

[0012] Accordingly, in one aspect, the present invention includes a bioerodable abuse-resistant drug delivery device. The device generally includes transmucosal drug delivery composition and an abuse-resistant matrix. The transmucosal drug delivery composition includes an abusable drug and the abuse-resistant matrix includes an

antagonist to the abusable drug. The delivery device can be, for example, a mucoadhesive drug delivery device, a buccal delivery device, and/or a sublingual delivery device. In some embodiments, the antagonist is substantially transmucosally unavailable. In other embodiments, the device is substantially free of inactivating agents.

[0013] In some embodiments, the abuse-resistant matrix is a layer or coating, *e.g.*, a water-erodable coating or layer at least partially disposed about the antagonist. In some embodiments, the abuse-resistant matrix is a water-hydrolysable, water-erodable or water-soluble matrix, *e.g.*, an ion exchange polymer. In some embodiments, the delivery device is in the form of a tablet, a lozenge, a film, a disc, a capsule or a mixture of polymers.

[0014] In some embodiments, the device includes a mucoadhesive layer. In some embodiments, the device includes a mucoadhesive layer and a non-adhesive backing layer. In other embodiments, the device includes a third layer disposed between the mucoadhesive layer and the backing layer. In some embodiments, either or both of the abusable drug and the abuse-resistant matrix are incorporated into a mucoadhesive layer. In some embodiments, the abuse-resistant matrix is incorporated into the backing layer. In some embodiments, either or both of the abusable drug and the abuse-resistant matrix are incorporated into the third layer. In some embodiments, the abuse-resistant matrix is the third layer. In some embodiments, either or both of the abusable drug and the abuse-resistant matrix are incorporated into any combination of layers discussed herein. In some embodiments, the abusable drug is incorporated into the mucoadhesive layer and the abuse-resistant matrix is incorporated into the backing layer.

[0015] In some embodiments, the abuse-resistant matrix erodes at a slower rate than the backing layer, the mucoadhesive layer, the third layer, or any combination thereof.

[0016] In some embodiments, the abusable drug can be, but is not limited to opiates and opioids, *e.g.*, alfentanil, allylprodine, alphaprodine, apomorphine, anileridine, apocodeine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, cyclorphan, cyprenorphine, desomorphine, dextromoramide, dextropropoxyphene, dezocine, diampromide, diamorphone, dihydrocodeine, dihydromorphine, dimenoxadol, eptazocine, ethylmorphine, etonitazene, etorphine, fentanyl, fencamfamine, fenethylline, hydrocodone, hydromorphone, hydroxymethylmorphinan, hydroxypethidine, isomethadone, levomethadone,

levophenacylmorphan, levorphanol, lofentanil, mazindol, meperidine, metazocine, methadone, methylmorphine, modafinil, morphine, nalbuphene, necomorphine, normethadone, normorphine, opium, oxycodone, oxymorphone, pholcodine, profadol remifentanil, sufentanil, tramadol, corresponding derivatives, physiologically acceptable compounds, salts and bases.

[0017] In some embodiments, the antagonist includes, but is not limited to opiate or opioid antagonists, *e.g.*, naloxone, naltrexone, nalmefene, nalide, nalmexone, nalorphine, naluphine, cyclazocine, levallorphan and physiologically acceptable salts and solvates thereof.

[0018] In some embodiments, the abuse-resistant matrix includes, but is not limited to, partially crosslinked polyacrylic acid, polycarbophil™, providone™, cross-linked sodium carboxymethylcellulose, gelatin, chitosan, Amberlite™ IRP69, Duolite™ AP143, AMBERLITE™ IRP64, AMBERLITE™ IRP88, and combinations thereof. In other embodiments, the abuse-resistant matrix includes, but is not limited to, alginates, polyethylene oxide, poly ethylene glycols, polylactide, polyglycolide, lactide-glycolide copolymers, poly-epsilon-caprolactone, polyorthoesters, polyanhydrides and derivatives, methyl cellulose, ethyl cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxyethylmethyl cellulose, hydroxypropylmethyl cellulose, polyacrylic acid, and sodium carboxymethyl cellulose, poly vinyl acetate, poly vinyl alcohols, polyethylene glycol, polyethylene oxide, ethylene oxide-propylene oxide co-polymers, collagen and derivatives, gelatin, albumin, polyaminoacids and derivatives, polyphosphazenes, polysaccharides and derivatives, chitin, or chitosan bioadhesive polymers, polyacrylic acid, polyvinyl pyrrolidone, sodium carboxymethyl cellulose, and combinations thereof.

[0019] In some embodiments, the device is less susceptible to abuse than an abusable drug alone. In other embodiments, less than 30% of the efficacy of the abusable drug is retained when used in an abusive manner. In some embodiments, the antagonist and the abusable drug are released at substantially the same rate when abusively dissolved. In some embodiments, the antagonist and the abusable drug are released at substantially the same rate when dissolved in water. In other embodiments, the ratio of released antagonist to released abusable drug is not less than about 1:20.

[0020] In some aspects, the present invention provides a method for treating pain in a subject. The method includes administering any device described herein such that pain is treated. In some embodiments, the extent of the absorption into systemic circulation

of the antagonist by the subject is less than about 15% by weight. In some embodiments, the dosage of the abusable drug is between about 50μg and about 10 mg.

[0021] In some aspects, the bioerodable abuse-resistant drug delivery device comprising: a layered film having at least one bioerodable, mucoadhesive layer to be placed in contact with a mucosal surface, and at least one bioerodable non-adhesive backing layer, wherein at least one abusable drug is incorporated in at least the mucoadhesive layer, and an abuse-resistant matrix comprising an antagonist to the abusable drug is incorporated in any or all of the layers.

BRIEF DESCRIPTION OF THE FIGURES

[0022] *Figure 1* graphically depicts the measure of positive and negative effects felt by a subject who was administered placebo, fentanyl only, and varying ratios of fentanyl and naloxone.

DETAILED DESCRIPTION OF THE INVENTION

[0023] Subjects with pain, *e.g.*, cancer pain, are typically opioid tolerant because of the chronic narcotic use required to control such pain. Moreover, the dose of transmucosal opioid drug, *e.g.*, fentanyl, required to treat breakthrough pain (for example, pain associated with unusual movement) can be high because of the opioid tolerance. In fact, doses in excess of one mg, a dose that would be fatal for a subject that was not opioid tolerant, are often used. This amount of a potent narcotic in a device makes it potentially subject to diversion and abuse by the intended route of administration as well as through extraction of the fentanyl for injection or inhalation.

[0024] Abuse by injection can be prevented or reduced by the inclusion of an antagonist, such as naloxone, in the formulation, which would block any psychopharmacologic effect of injected opioid drug.

[0025] Accordingly, the present invention relates to novel drug delivery devices that provide for the transmucosal delivery of an abusable drug while reducing, and, in some embodiments, eliminating abuse potential. The drug delivery devices generally include an abusable drug and at least one antagonist for the drug incorporated into a device (*e.g.*, a multilayered transmucosal delivery device) that impedes abuse of the drug. Abuse of the drug can be impeded by use of the present invention in many, non-limiting ways. In some embodiments, the antagonist impedes abuse of the drug because attempts to extract

the drug from the transmucosal delivery device results in co-extraction of the antagonist which blocks the expected effect of the drug. In other embodiments, the abusable drug and the antagonist are incorporated into the same layer or indistinguishable layers of a delivery device of the present invention, so that they can not be separated from one another, *e.g.*, by peeling one layer off of the device.

[0026] When used as intended, however, the abusable drug will be delivered through the mucosa, *e.g.*, by application to the mucous membrane of the mouth, and thus into the systemic circulation. The antagonist is associated with an abuse-resistant matrix, *e.g.*, dispersed within coated-microparticles or chemically-bound to a polymer that impedes or prevents mucoabsorption, *e.g.*, a high molecular weight polymer or an ion exchange polymer. In some embodiments, the antagonist is substantially transmucosally unavailable when used in a non-abusive manner. Without wishing to be bound by any particular theory, it is believed that when used in a non-abusive manner, the opioid antagonist will be swallowed, *e.g.*, as an unbound antagonist in a layer or matrix not contacting the mucosa and/or as an intact microcapsule, polymer bound particle or in some other form not amenable to mucosal administration. Because the opioid antagonist is poorly absorbed from the gastrointestinal tract, the amount in the systemic circulation is below a level that would produce a significant pharmacologic effect against the drug, and therefore it is relatively inactive under these conditions.

[0027] In order to more clearly and concisely describe the subject matter of the claims, the following definitions are intended to provide guidance as to the meaning of terms used herein.

[0028] The terms "abusable drug" or "drug" as used interchangeably herein, refers to any pharmaceutically active substance or agent that has the ability to promote abuse, high tolerance with extended use, and/or chemical or physical dependency. Abusable drugs include, but are not limited to, drugs for the treatment of pain such as an opioid analgesic, *e.g.*, and opioid or an opiate.

[0029] As used herein, the term "antagonist" refers to a moiety that renders the active agent unavailable to produce a pharmacological effect, inhibits the function of an agonist, *e.g.*, an abusable drug, at a specific receptor, or produces an adverse pharmacological effect. For example, in some embodiments, when used in an abusive manner, the antagonist is released in an amount effective to attenuate a side effect of said opioid agonist or to produce adverse effect such as anti-analgesia, hyperalgesia,

hyperexcitability, physical dependence, tolerance, or any combination thereof. Without wishing to be bound by any particular theory, it is believed that antagonists generally do not alter the chemical structure of the abusable drug itself, but rather work, at least in part, by an effect on the subject, *e.g.*, by binding to receptors and hindering the effect of the agonist. Antagonists can compete with an agonist for a specific binding site (competitive antagonists) and/or can bind to a different binding site from the agonist, hindering the effect of the agonist via the other binding site (non-competitive antagonists). Non-limiting examples of antagonists include opioid-neutralizing antibodies; narcotic antagonists such as naloxone, naltrexone and nalmefene; dysphoric or irritating agents such as scopolamine, ketamine, atropine or mustard oils; or any combinations thereof. In one embodiment, the antagonist is naloxone or naltrexone.

[0030] The term "bioerodable" as used herein refers to the property of the devices of the present invention which allow the solid or semisolid portion of the device to sufficiently degrade by surface erosion, bioerosion, and/or bulk degradation such that it is small enough to be swallowed. Bulk degradation is the process in which a material, *e.g.*, a polymer, degrades in a fairly uniform manner throughout the matrix. This results in a reduction of molecular weight (M_n) without immediate change in physical properties, followed by fragmentation due to faster penetration of saliva or water into the device than conversion of the device into saliva- or water-soluble form. Bioerosion or surface erosion generally occurs when the rate at which saliva or water penetrates the material is slower than the rate of the conversion of the material into saliva- or water-soluble substances. Bioerosion generally results in a thinning of the material over time, though the bulk integrity is maintained. It is to be understood that "bioerodable" refers to the device as a whole, and not necessarily to its individual components. For example, if the antagonist is microencapsulated or coated, the microcapsules or coating may or may not be bioerodable, but the device as a whole may be bioerodable such that as the device is eroded the intact microcapsules or coated antagonist is swallowed. This can be advantageous because the device will erode and the microcapsules or coated antagonist can be delivered to the GI tract intact, *i.e.*, without crossing the mucosa. The term "bioerodable" is intended to encompass many modes of material removal, such as enzymatic and non-enzymatic hydrolysis, oxidation, enzymatically-assisted oxidation, wear, degradation and/or dissolution.

[0031] Bioerodable materials are generally selected on the basis of their degradation characteristics to provide a sufficient functional lifespan for the particular application. In the case of applications of the present invention, a functional lifespan of between 1 minute and 10 hours may be suitable. In some embodiments, the functional lifespan is about 2 minutes. In some embodiments, the functional lifespan is about 5 minutes. In some embodiments, the functional lifespan is about 10 minutes. In some embodiments, the functional lifespan is about 15 minutes. In some embodiments, the functional lifespan is about 20 minutes. In some embodiments, the functional lifespan is about 30 minutes. In some embodiments, the functional lifespan is about 45 minutes. In some embodiments, the functional lifespan is about 60 minutes. In some embodiments, the functional lifespan is about 2 hours. In some embodiments, the functional lifespan is about 3 hours. In some embodiments, the functional lifespan is about 4 hours. In some embodiments, the functional lifespan is about 5 hours. In some embodiments, the functional lifespan is about 10 hours. All ranges and values which fall between the ranges and values listed herein are meant to be encompassed by the present invention. For example, lifespans of between about 5 minutes and about 45 minutes, between about 6 minutes and about 53 minutes, between about 13 minutes and about 26 minutes, etc. are all encompassed herein. Shorter or longer periods may also be appropriate.

[0032] Bioerodable materials include, but are not limited to, polymers, copolymers and blends of polyanhydrides (*e.g.*, those made using melt condensation, solution polymerization, or with the use of coupling agents, aromatic acids, aliphatic diacids, amino acids, *e.g.*, aspartic acid and glutamic acid, and copolymers thereof); copolymers of epoxy terminated polymers with acid anhydrides; polyorthoesters; homo- and copolymers of α-hydroxy acids including lactic acid, glycolic acid, ϵ-caprolactone, γ-butyrolactone, and δ-valerolactone; homo- and copolymers of α-hydroxy alkanoates; polyphosphazenes; polyoxyalkylenes, *e.g.*, where alkene is 1 to 4 carbons, as homopolymers and copolymers including graft copolymers; poly(amino acids), including pseudo poly(amino acids); polydioxanones; and copolymers of polyethylene glycol with any of the above.

[0033] As used herein, the articles "a" and "an" mean "one or more" or "at least one," unless otherwise indicated. That is, reference to any element of the present invention by the indefinite article "a" or "an" does not exclude the possibility that more than one of the element is present.

[0034] The term "abuse-resistant matrix" refers generally to a matrix with which an antagonist to an abusable drug is associated. An abuse resistant matrix is a matrix that effectively releases the antagonist when the device is used in an abusive manner (*e.g.*, dissolved in water in an attempt to extract the drug, solubilized, opened, chewed and/or cut apart) so that, *e.g.*, the antagonist is co-extracted and alters or blocks the effect the drug. However, when used as intended, *e.g.*, in a non-abusive manner, the abuse-resistant matrix does not effectively release the antagonist. *E.g.*, the antagonist instead is retained within the matrix and is delivered to the gastrointestinal tract where it is not readily absorbed such that any amount of antagonist delivered systemically through the mucosa and/or the GI tract does not significantly block or alter the effect of the drug.

[0035] When used in reference to the antagonist, the phrase "substantially transmucosally unavailable" refers to the fact that the antagonist in the compositions and devices of the present invention is available transmucosally in amounts that do not effect, or negligibly effect, the efficacy of the abusable drug when employed in a non-abusive manner. Without wishing to be bound by any particular theory, it is believed that the antagonist is prevented or slowed from entering the system transmucosally while still being available for other routes of administration (*e.g.*, swallowing or dissolution), thus allowing the abusable drug to act efficaciously in a transmucosal composition, but hindering the use of the composition in an abusive manner. That is, it is to be understood that the antagonist effects the efficacy of the abusable drug when the compositions of the present invention are abused. In non-abusive situations, the antagonist provides no or negligible effect, *e.g.*, is swallowed. In some embodiments, less than about 25% antagonist (by weight versus abusable drug) can be delivered non-abusively, *e.g.*, transmucosally. In other embodiments, less than about 15% antagonist is delivered transmucosally. In still other embodiments, less than 5% of antagonist is delivered transmucosally. In some embodiments, less than 2% antagonist is delivered transmucosally. In still other embodiments, less than 1% antagonist is delivered transmucosally.

[0036] Accordingly, in some embodiments, when the device is a multilayer disc or film, the abuse-resistant matrix is a layer or is incorporated into a layer which is disposed between a mucoadhesive layer and a backing layer. In other embodiments, the abuse-resistant matrix is incorporated into a backing layer. Without wishing to be bound by any particular theory, it is believed that the antagonist would not able to enter

systemic circulation through the mucosa in any significant amount because it would be washed into the GI tract, *e.g.*, swallowed. In some embodiments, the abuse resistant matrix is a coating or water-hydrolysable matrix, *e.g.*, an ion-exchange polymer. The coating or water-hydrolysable matrix can be chosen such that it dissolves more slowly than a backing layer as described above. The coating or water-hydrolysable matrix can additionally or alternatively be chosen such that they dissolve slowly enough not to release the antagonist at all. Without limiting the invention, it is believed that the antagonist would be washed into the GI tract as either free-antagonist or as a coated or otherwise entrapped, *e.g.*, by the ion-exchange polymer, moiety. It is to be understood that layers, coatings, and water-hydrolyzable matrices are exemplary, and that additional abuse-resistant matrices can be envisioned using the teachings of the present invention.

[0037] As used herein, the term "abusive manner" refers to the use of the delivery device in a manner not intended, *e.g.*, in a non-transmucosal manner or in a manner not otherwise prescribed by a physician. In some embodiments, the abusive manner includes extraction of the drug from the delivery device for oral or parenteral administration. As used herein, "non-abusive manner" refers to the use of the delivery device for its intended purpose, *e.g.*, transmucosal administration of the drug. In some cases, a portion of the drug will unintentionally be delivered non-transmucosally, *e.g.*, orally through the dissolution of a portion of the device. Such inadvertent or unintentional delivery is not indicative of use in an abusive manner.

[0038] Accordingly, in some embodiments, the devices of the present invention are less susceptible to abuse than an abusable drug alone. For example, when used in an abusive manner, the abusable drug may only retain about 50%, 40%, 30%, 20%, 10%, 5%, 2%, 1% or 0% of its efficacy, *e.g.*, as a pain reliever. Accordingly, when used in an abusive manner, it is believed that the effectiveness of the abusable drug, *e.g.*, the ability to produce a "high" in an addict, would be reduced by a corresponding amount, *e.g.*, by 50%, 60%, 70%, 80%, 90%, 95%, 98%, 99% or 100%.

[0039] As used herein, "treatment" of a subject includes the administration of a drug to a subject with the purpose of preventing, curing, healing, alleviating, relieving, altering, remedying, ameliorating, improving, stabilizing or affecting a disease or disorder, or a symptom of a disease or disorder (*e.g.*, to alleviate pain).

[0040] The term "subject" refers to living organisms such as humans, dogs, cats, and other mammals. Administration of the drugs included in the devices of the present

invention can be carried out at dosages and for periods of time effective for treatment of a subject. An "effective amount" of a drug necessary to achieve a therapeutic effect may vary according to factors such as the age, sex, and weight of the subject. Dosage regimens can be adjusted to provide the optimum therapeutic response. For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation. Similarly, effective amounts of antagonist to a drug will vary according to such factors such as the amount of drug included in the devices.

[0041] In some embodiments, the antagonist and the abusable drug are incorporated into a delivery device such as the devices described in US Patent No. 5,800,832 and/or US Patent No. 6,585,997, the entireties of which are incorporated herein by this reference. In other embodiments, the antagonist and the abusable drug are incorporated into a delivery device that is dissimilar to the devices described in US Patent No. 5,800,832 and/or US Patent No. 6,585,997. It is to be understood that any transmucosal drug delivery device can be used with the teachings of the present invention to provide an abuse-resistant device of the present invention.

[0042] In some embodiments, the antagonist and the abusable drug are incorporated into a narcotic drug product. In other embodiments, the antagonist and the abusable drug are incorporated into an antagonist drug product. In one embodiment, the antagonist drug product is a naloxone drug product.

[0043] In some embodiments, the antagonist and the abusable drug are incorporated into a delivery device such as the devices described in U.S. Patent No. 6,200,604 (incorporated herein in its entirety by this reference) and/or U.S. Patent No. 6,759,059 (incorporated herein in its entirety by this reference). In other embodiments, the antagonist and the abusable drug can be combined in a sublingual or buccal monolayer or multilayer tablets. In some embodiments, the antagonist and the abusable drug are incorporated into a mucoadhesive liquid and/or a mucoadhesive solid formulation. It is to be understood that any sublingual tablet, buccal tablet, mucoadhesive liquid formulation and/or mucoadhesive solid formulation can be used with the teachings of the present invention to provide an abuse-resistant device of the present invention.

[0044] In some embodiments, the antagonist and the abusable drug are incorporated into a delivery device such as a transdermal drug device, for example, a transdermal patch. In some embodiments, the transdermal drug device is a transdermal analgesic

drug device. It is to be understood that any transdermal drug device can be used with the teachings of the present invention to provide an abuse-resistant device of the present invention.

[0045] In some embodiments, the abuse-resisitant drug delivery device is in the form of a disc, patch, tablet, solid solution, lozenge, liquid, aerosol or spray or any other form suitable for transmucosal delivery.

[0046] As used herein, the term "incorporated" as used with respect to incorporation of a drug and/or an antagonist into the devices of the present invention or any layer of the devices of the present invention, refers to the drug or antagonist being disposed within, associated with, mixed with, or otherwise part of a transmucosal device, *e.g.*, within one or more layers of a multilayered device or existing as a layer or coating of the device. It is to be understood that the mixture, association or combination need not be regular or homogeneous.

[0047] In some embodiments, the delivery devices of the present invention are substantially free of inactivating agents. As used herein, the term "inactivating agent" refers to a compound that inactivates or crosslinks the abusable drug, in order to decrease the abuse potential of the dosage form. Examples of inactivating agents include polymerizing agents, photoinitiators, and formalin. Examples of polymerizing agents include diisocyanates, peroxides, diimides, diols, triols, epoxides, cyanoacrylates, and UV activated monomers.

[0048] Accordingly, in some embodiments, the present invention is directed to devices and methods for treating pain in a subject, *e.g.*, a human, with a dosage of an abusable drug while reducing the abuse potential. The methods can employ any of the devices enumerated herein with any of the desired release profiles herein, *e.g.*, absorption of less than 10% of the antagonist through the mucosa into systemic circulation.

[0049] In the present invention, a novel device is employed for application to mucosal surfaces to provide transmucosal delivery of an abusable drug, *e.g.*, an opioid analgesic into the systemic circulation providing rapid onset with minimal discomfort and ease of use. Accordingly, in one aspect, the devices of the present invention include an abusable drug and an antagonist to the abusable drug associated with an abuse-resistant matrix. The delivery device can be a mucoadhesive drug delivery device, a buccal delivery device, and/or a sublingual delivery device.

[0050] The devices of the present invention may include any number of layers, including but not limited to mucoadhesive layers, non-adhesive layers, backing layers and any combination thereof. In some embodiments, the device includes a mucoadhesive layer. In some embodiments, the device includes a mucoadhesive layer and a non-adhesive backing layer. In other embodiments, the device includes a third layer disposed between the mucoadhesive layer and the backing layer. In some embodiments, either or both of the abusable drug and the abuse-resistant matrix are incorporated into a mucoadhesive layer. In some embodiments, the abuse-resistant matrix is incorporated into the backing layer. In some embodiments, either or both of the abusable drug and the abuse-resistant matrix are incorporated into the third layer. In some embodiments, the abuse-resistant matrix is the third layer. Furthermore, where the device contains a third layer between the mucoadhesive layer and the backing layer, this third layer can be indistinguishable from the mucoadhesive layer. Such an embodiment can be useful because it prevents the removal of layers from the device in an effort to extract the drug. The third layer may also be co-extractable with the abusable drug. In some embodiments, the third layer is a non-adhesive layer. In some embodiments, either or both of the abusable drug and the abuse-resistant matrix are incorporated into any combination of layers discussed herein. Any or all of the layers of the transmucosal delivery device can be water-soluble.

[0051] In some embodiments, the antagonist is incorporated in the backing layer. This embodiment can be employed to allow the antagonist to release quickly in a situation when one may try to abuse the product. In this embodiment, the antagonist would be substantially swallowed upon erosion of the backing layer such that there is minimum transmucosal adsorption of the antagonist. In another embodiment, the antagonist is incorporated into a layer which is disposed between the adhesive drug layer and the backing layer. This allows delayed or sustained release of the antagonist. By separating the antagonist and the drug in separate indistinguishable layers, the antagonist does not interfere with the transmucosal delivery of the drug. In yet another embodiment, the antagonist may be commingled with the drug in the mucoadhesive layer. This aspect allow the drug and the antagonist to be physically in the same layer thus providing superior abuse resistance, in that the drug and the antagonist will be inseparable when used in an abusive manner.

[0052] In some embodiments, the abusable drug is included in a mucoadhesive layer, generally closest to the treatment site, and the backing layer protects the mucoadhesive layer from contact with saliva or other fluid resulting in slower dissolution of the mucoadhesive layer and longer contact of the mucoadhesive layer and drug with the treatment site. In such embodiments, the placement of the abusable drug in the mucoadhesive layer allows the abusable pharmaceutically active substance to unidirectionally diffuse through the buccal mucosa of the mouth and into the systemic circulation, while avoiding first pass metabolism by the liver.

[0053] The mucoadhesive layer, *e.g.*, a bioerodible mucoadhesive layer, is generally comprised of water-soluble polymers which include, but are not limited to, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, hydroxyethylmethyl cellulose, polyacrylic acid (PAA) which may or may not be partially crosslinked, sodium carboxymethyl cellulose (NaCMC), and polyvinylpyrrolidone (PVP), or combinations thereof. Other mucoadhesive water-soluble polymers may also be used in the present invention.

[0054] The backing layer, *e.g.*, a bioerodible non-adhesive backing layer, is generally comprised of water-soluble, film-forming pharmaceutically acceptable polymers which include, but are not limited to, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, hydroxyethylmethyl cellulose, polyvinylalcohol, polyethylene glycol, polyethylene oxide, ethylene oxide-propylene oxide co-polymers, or combinations thereof. The backing layer may comprise other water-soluble, film-forming polymers as known in the art. Exemplary mucoadhesive and non-adhesive layers, including polymers suitable for such layers are also described, *e.g.*, in U.S. Patent Nos. 5,800,832 and 6,159,498, the entireties of which are incorporated by this reference.

[0055] The devices of the present invention can provide, when desired, a longer residence time than those devices known in the art. In some embodiments, this is a result of the selection of the appropriate backing layer formulation, providing a slower rate of erosion of the backing layer. Thus, the non-adhesive backing layer is further modified to render controlled erodibility which can be accomplished by coating the backing layer film with a more hydrophobic polymer selected from a group of FDA approved Eudragit™ polymers, ethyl cellulose, cellulose acetate phthalate, and hydroxyl propyl methyl cellulose phthalate, that are approved for use in other pharmaceutical

dosage forms. Other hydrophobic polymers may be used, alone or in combination with other hydrophobic or hydrophilic polymers, provided that the layer derived from these polymers or combination of polymers erodes in a moist environment. Dissolution characteristics may be adjusted to modify the residence time and the release profile of a drug when included in the backing layer.

[0056] In some embodiments, any of the layers in the devices of the present invention may also contain a plasticizing agent, such as propylene glycol, polyethylene glycol, or glycerin in a small amount, 0 to 15% by weight, in order to improve the "flexibility" of this layer in the mouth and to adjust the erosion rate of the device. In addition, humectants such as hyaluronic acid, glycolic acid, and other alpha hydroxyl acids can also be added to improve the "softness" and "feel" of the device. Finally, colors and opacifiers may be added to help distinguish the resulting non-adhesive backing layer from the mucoadhesive layer. Some opacifers include titanium dioxide, zinc oxide, zirconium silicate, *etc.*

[0057] The device according to the invention may comprise one or more opioid analgesics with potential for abuse and one or more antagonists. However, in some embodiments, the device according to the invention comprises only one active opioid analgesic and only one antagonist for this active opioid analgesic.

[0058] The abusable drug, *e.g.*, an opioid analgesic, agonist, or partial agonist according to the invention, include, but are not limited to, alfentanil, allylprodine, alphaprodine, apomorphine, anileridine, apocodeine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, cyclorphan, cyprenorphine, desomorphine, dextromoramide, dextropropoxyphene, dezocine, diampromide, diamorphone, dihydrocodeine, dihydromorphine, dimenoxadol, eptazocine, ethylmorphine, etonitazene, etorphine, fentanyl, fencamfamine, fenethylline, hydrocodone, hydromorphone, hydroxymethylmorphinan, hydroxypethidine, isomethadone, levomethadone, levophenacylmorphan, levorphanol, lofentanil, mazindol, meperidine, metazocine, methadone, methylmorphine, modafinil, morphine, nalbuphene, necomorphine, normethadone, normorphine, opium, oxycodone, oxymorphone, pholcodine, profadol remifentanil, sufentanil, tramadol, and corresponding derivatives, and/or their physiologically acceptable compounds, in particular salts and bases, stereoisomers thereof, ethers and esters thereof, and mixtures thereof.

[0059] Pharmaceutically acceptable salts include inorganic salts and organic salts, *e.g.*, hydrobromides, hydrochlorides, mucates, succinates, n-oxides, sulfates, malonates, acetates, phosphate dibasics, phosphate monobasics, acetate trihydrates, bi(heplafluorobutyrates), maleates, bi(methylcarbamates), bi(pentafluoropropionates), mesylates, bi(pyridine-3-carboxylates), bi(trifluoroacetates), hemitartrates, (bi)tartrates, chlorhydrates, fumarates and/or sulfate pentahydrates.

[0060] In some embodiments, the present invention includes devices having at least one opioid analgesic in a dosage range of about 1μg to about 50mg. In some embodiments, the present invention includes devices having at least one opioid analgesic in a dosage range of about 10μg to about 25mg. In still other embodiments, the devices of the present invention have at least one opioid analgesic in a dosage range of about 50μg to about 10mg. It is to be understood that all values and ranges between these values and ranges are meant to be encompassed by the present invention.

[0061] The amount of abusable drug to be used depends on the desired treatment strength, although preferably, the abusable drug comprises between about 0.001 and about 30% by weight of the device. It is to be understood that all values and ranges between the listed values and ranges are to be encompassed by the present invention.

[0062] The antagonist to the abusable drug can be an opioid antagonist. Opioid antagonists are known to those skilled in the art and are known to exist in various forms, *e.g.*, as salts, bases, derivatives, or other corresponding physiologically acceptable forms. The opioid antagonists can be, but are not limited to, antagonists selected from the group consisting of naloxone, naltrexone, nalmefene, nalide, nalmexone, nalorphine, naluphine, cyclazocine, levallorphan and/or their physiologically acceptable salts, bases, stereoisomers, ethers and esters thereof and mixtures thereof.

[0063] In some embodiments, the devices of the present invention include an opioid antagonist in a dosage range of about 1μg to about 20mg. In some embodiments, the devices of the present invention include an opioid antagonist in a dosage range of about 1.0μg to about 20mg. In still other embodiments, the devices of the present invention include an opioid antagonist in a dosage range of about 10μg and about 10mg. It is to be understood that all values and ranges between these values and ranges are meant to be encompassed by the present invention. In some embodiments, the amount of antagonist used is such that the likelihood of abuse of the abusable drug is lessened and/or reduced without diminishing the effectiveness of the abusable drug as a pharmaceutical.

[0064] In some embodiments, the antagonist is absorbed into systemic circulation through the mucosa only to a certain desired extent. For example, in some embodiments, the extent of absorption of the antagonist is less than about 15%. In some embodiments, the extent of absorption of the antagonist is less than about 10%. In some embodiments, the extent of absorption of the antagonist is less than about 5%, 4%, 3%, 2% or 1%.

[0065] The amount of antagonist which is useful to achieve the desired result can be determined at least in part, for example, through the use of "surrogate" tests, such as a VAS scale (where the subject grades his/her perception of the effect of the dosage form) and/or via a measurement such as pupil size (measured by pupillometry). Such measurements allow one skilled in the art to determine the dose of antagonist relative to the dose of agonist which causes a diminution in the opiate effects of the agonist. Subsequently, one skilled in the art can determine the level of opioid antagonist that causes aversive effects in physically dependent subjects as well as the level of opioid antagonist that minimizes "liking scores" or opioid reinforcing properties in non-physically dependent addicts. Once these levels of antagonist are determined, it is then possible to determine the range of antagonist dosages at or below this level which would be useful in achieving the desired results.

[0066] The antagonist is associated with an abuse-resistant matrix. The abuse-resistant matrix can be, but is not limited to a layer or coating, *e.g.*, a water-erodable coating or a water-hydrolysable matrix, *e.g.*, an ion exchange polymer, or any combination thereof. Thus, in one embodiment of the invention, the antagonist is associated with the matrix in a manner such that it is not released in the mouth. In another embodiment of the invention, the antagonist is adequately taste masked. The entrapment and/or taste masking may be achieved by physical entrapment by methods, such as microencapsulation, or by chemical binding methods, *e.g.*, by the use of a polymer that prevents or inhibits mucoabsorption of the antagonist, *e.g.*, ion exchange polymers. Without wishing to be bound by any particular theory, it is believed that the optimum formulation for the particular antagonist may be determined by understanding the ratios needed to prevent abuse, evaluating the possible binding mechanism, and evaluating the physico-chemical properties of the antagonists.

[0067] In some embodiments, the antagonist is microencapsulated in an enteric polymer, polysaccharide, starch or polyacrylate. Without wishing to be bound by a

particular theory, it is believed that microencapsulation will substantially prevent transmucosal absorption of the antagonist, and allow the subject to swallow the microencapsulated antagonist. The coating of the microcapsules can be designed to offer delayed release characteristics, but will release when the article or composition are placed in an aqueous environment, such as when the dosage form is chewed or subject to extraction. Delayed release can be accomplished, for example, by the use of starches or pH dependent hydrolysis polymers as coating materials for the microencapsulated antagonist. Starches, for example, would be susceptible to any enzymes that are present in the saliva, such as salivary amylase.

[0068] In some embodiments, the antagonist is microencapsulated in a microcapsule or microsphere and then incorporated in the abuse resistant matrix. Such a microcapsule or microsphere containing antagonist may be comprised of polymers such as polyacrylates, polysaccharides, starch beads, polyactate beads, or liposomes. In a further embodiment, the microspheres and microcapsules are designed to release in specific parts of the small intestine.

[0069] In another embodiment, the devices of the present invention include the antagonist in a micromatrix with complexing polymers such that the micromatrix is incorporated in the abuse resistant matrix. In yet another embodiment, the antagonist is incorporated in a slowly hydrolysable or slowly eroding polymer which is then incorporated in the abuse resistant matrix.

[0070] In some embodiments, the opioid resides in the mucoadhesive layer, which is in contact with the mucosa, while the antagonist resides in the backing layer, which is non-adhesive and erodes over time. When present, a layer disposed between the mucoadhesive layer and the backing layer may also include an antagonist. This may provide a lower driving force for the antagonist absorption in the transmucosal space, while still being swallowed upon release. The antagonist will also be released promptly from the layer disposed between the mucoadhesive layer and the backing layer, thus hindering abuse.

[0071] In one embodiment, the abuse-resistant matrix comprises water soluble polymers, *e.g.*, polymers similar to those described for the mucoadhesive and/or backing layers, but is associated with the device such that the antagonist is not mucosally absorbed to a significant extent. For example, the matrix can be a third layer disposed between a mucoadhesive layer and a backing layer.

[0072] In one embodiment of an exemplary layered device, the drug can be placed in the mucoadhesive layer along with an antagonist which is chemically bound to a polymer, *e.g.*, pharmaceutically acceptable ion-exchange polymer and/or which is physically entrapped in a microcapsule within a water soluble polymer coating. Upon extraction in water, both the drug and the antagonist are extracted simultaneously, eliminating the abuse potential of the extracted drug. In some embodiments, the chemical bond between the polymer, *e.g.*, the ion-exchange polymer, and the antagonist is also hydrolysable.

[0073] In an exemplary three layered device configuration, the drug can be placed in the mucoadhesive layer, while the antagonist is placed in an indistinguishable, sandwiched third layer either in a physically or chemically bound state as described herein. Again, upon extraction in water, both the drug and its antagonist are extracted reducing or eliminating the abuse potential of the extracted drug.

[0074] In some embodiments, the abuse-resistant matrix is a water-hydrolysable matrix. The term "water-hydrolysable matrix" as used herein, refers to a controlled release matrix that allows water hydrolysis of the matrix at a desired rate, thus also effecting release of the material within the matrix at the desired rate. In some embodiments, the water-hydrolysable matrix is an ion-exchange polymer. In some embodiments, the water-hydrolysable matrix, *e.g.*, the ion-exchange polymer is chosen such that it erodes at a rate slower than the erosion rate of the mucoadhesive layer. In other embodiments, the water-hydrolysable matrix is chosen such that it erode at a rate slower than the erosion rate of the mucoadhesive layer but quicker than the erosion rate of the non-adhesive backing layer. In some embodiments, the rate of dissociation of the antagonist from the ion-exchange polymer is slower than the rate of erosion of the layer in which it is incorporated.

[0075] In some embodiments, chemical binding of the antagonist by ion exchange polymers can also facilitate taste masking and will delay the release of the antagonist allowing the antagonist to be swallowed. Under triggered ionic change induced by ionic molecules (*e.g.*, defined by the Hofmeister's series) or a shift in pH, the drug can be hydrolyzed from the ionic polymer.

[0076] In some embodiments, the abuse-resistant matrix includes materials used for chemical binding, *e.g.*, in ion-exchange polymers. Such materials include, but are not limited to, polyanhydrides, poly(hydroxyethyl methacrylate), polyacrylic acid, sodium

acrylate, sodium carboxymethyl cellulose, poly vinyl acetate, poly vinyl alcohols, poly(ethylene oxide), ethylene oxide-propylene oxide co-polymers, poly(N-vinyl pyrrolidone), poly(methyl methacrylate), polyacrylamide, poly(ethylene-co-vinyl acetate), poly(ethylene glycol), poly(methacrylic acid), gelatin, chitosan, collagen and derivatives, albumin, polyaminoacids and derivatives, polyphosphazenes, polysaccharides and derivatives and commercial polymers such as, but not limited to, noveon AA1 POLYCARBOPHIL™, PROVIDONE™, AMBERLITE™ IRP69, DUOLITE™ AP143, AMBERLITE™ IRP64, and AMBERLITE™ IRP88, and any combinations thereof. A cationic polymer such as AMBERLITE™ IR-122 or an anion exchange resin such as AMBERLITE™ IRA-900 may also be used, depending upon the pKa of the drug. Functional groups may include, but are not limited to $R—CH_2N^+(CH_3)_3$, $R—CH_2N^+(CH_3)_2C_2H_4OH$, $R—SO_3—$, $R—CH_2N^+H(CH_3)_2$, $R—CH_2COO—$, $R—COO—$, and $R—CH_2N(CH_2COO)_2$.

[0077] The selection of the ion exchange polymer depends on the pKa of the antagonist, and functional groups attached to the drug moiety such as –COOH, -OH or amine functionalities on its backbone which could be used to bind to an ion exchange polymer. The amount of the drug loaded on to the ion exchange polymer depends on the molecular weight of the opioid antagonist, the type of ion exchange polymer used, and its ionic stoichiometric ratio. In some embodiments, the antagonist to ion exchange polymer ratios range from about 1:99 to about 99:1. In other embodiments, the antagonist to ion exchange polymer ratios range from about 1:9 to about 9:1. In other embodiments, the antagonist to ion exchange polymer ratios range from about 1:3 to about 3:1.

[0078] In some embodiments, the abuse-resistant matrix is a layer coating, *e.g.*, a water-erodable coating. That is, physical entrapment of the antagonist in the device, *e.g.*, the mucoadhesive layer, can be facilitated by a barrier layer which is coated with a water soluble polymer which erodes slowly. That is, antagonists may be at least partially coated or disposed within water-erodable coating. Methods of microencapsulation and particle coating have been defined in the literature.

[0079] In some embodiments, the abuse-resistant matrix includes materials used for physical entrapment. Such materials include, but are not limited to, alginates, polyethylene oxide, poly ethylene glycols, polylactide, polyglycolide, lactide-glycolide copolymers, poly-epsilon-caprolactone, polyorthoesters, polyanhydrides and derivatives,

methyl cellulose, ethyl cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxyethylmethyl cellulose, hydroxypropylmethyl cellulose, polyacrylic acid, and sodium carboxymethyl cellulose, poly vinyl acetate, poly vinyl alcohols, polyethylene glycol, polyethylene oxide, ethylene oxide-propylene oxide co-polymers, collagen and derivatives, gelatin, albumin, polyaminoacids and derivatives, polyphosphazenes, polysaccharides and derivatives, chitin, chitosan bioadhesive polymers, polyacrylic acid, polyvinyl pyrrolidone, sodium carboxymethyl cellulose and combinations thereof.

[0080] Other exemplary water-erodable coatings and water-hydrolysable matrices are known in the art, *e.g.*, in U.S. Pat. Nos. 6,228,863 and 5,324,351.

[0081] In some embodiments, the device provides an appropriate residence time for effective opioid analgesic delivery at the treatment site, given the control of solubilization in aqueous solution or bodily fluids such as saliva, and the slow, natural dissolution of the film concomitant to the delivery. The residence time can also be tailored to provide a range from minutes to hours, dependent upon the type of opioid used and therapeutic indication. In some embodiments, residence times of between about 20 to 30 minutes and about 3 to 4 hours are achieved with the devices of the present invention. In other embodiments, residence times of between about 1 hour and about 2 hours are achieved. The residence time of the device of the present invention depends on the dissolution rate of the water-soluble polymers used. The dissolution rate may be adjusted by mixing together chemically different hydrophilic and hydrophobic polymers or by using different molecular weight grades of the same polymer. Such adjustments are well described in the art of controlled release.

[0082] As the materials used in the devices of the present invention are soluble in water, illicit use efforts to extract the opioid from the adhesive layer for parenteral injection, are thwarted by the co-extraction of the opioid antagonist. The amount of opioid antagonist contained in the product is designed to block any psychopharmacological effects that would be expected from parenteral administration of the opioid alone.

[0083] In some embodiments, upon use of the device in an abusive manner, the antagonist is generally released (*e.g.*, dissolved in water or some other appropriate solvent) at substantially the same rate as the abusable drug. For example, in some embodiments, the antagonist to the abusable drug is released at substantially the same time as the opioid when abusively dissolved. As used herein, the term "abusively

dissolved" refers to dissolution in a solvent other than saliva, for example, water, ethanol or the like. In other embodiments, the antagonist is released at a slower rate as the abusable drug when abusively dissolved. In such cases, the amount of antagonist released would be sufficient to hinder the use of the abusable drug, *e.g.*, by producing unwanted side effects. In some embodiments, the released antagonist to opioid ratio is not less than 1:20. In other embodiments, the released antagonist to opioid ratio is not less than 1:10. In still other embodiments, the released antagonist to opioid ratio is not less than 1:5. In yet other embodiments, the released antagonist to opioid ratio is at least about 1:10. In yet other embodiments, the released antagonist to opioid ratio is at least about 1:20. In yet other embodiments, the released antagonist to opioid ratio is at least about 1:50. Any values and ranges between the listed values are intended to be encompassed by the present invention.

[0084] If desired, flavoring agents known in the art may be added to mask the taste of the active compound. Penetration enhancers may also be included in the adhesive layer to help reduce the resistance of the mucosa to drug transport. Typical enhancers known in the art include ethylenediamine tetracetic acid, chitosan, *etc.* Ingredients to enhance drug solubility and/or stability of the drug may also be added to the layer or layers containing the abusable drug. Examples of stabilizing and solubilizing agents are cyclodextrins.

[0085] In some embodiments, the devices and methods of the present invention further include one or more drugs in addition to the abusable drug and antagonist. In some embodiments, a combination of two abusable drugs may be included in the formulation. Two such drugs may, *e.g.*, have different properties, such as half-life, solubility, potency, etc. Additional drugs can provide additional analgesia, and include, but are not limited to, aspirin; acetaminophen; non-sterioidal antiinflammatory drugs ("NSAIDS"), N-methyl-D-aspartate receptor antagonists, cycooxygenase-II inhibitors and/or glycine receptor antagonists. Such additional drugs may or may not act synergistically with the opioid analgesic. Further drugs include antiallergic compounds, antianginal agents, anti-inflammatory analgesic agents, steroidal anti-inflammatory agents, antihistamines, local anesthetics, bactericides and disinfectants, vasoconstrictors, hemostatics, chemotherapeutic drugs, antibiotics, keratolytics, cauterizing agents, hormones, growth hormones, growth hormone inhibitors, analgesic narcotics and antiviral drugs.

[0086] In one aspect, the present invention includes methods for treating pain in a subject. The method can include administering any of the devices described herein such that pain is treated.

[0087] The pharmaceutical delivery device of the present invention may be prepared by various methods known in the art. For example, in one embodiment, the components are dissolved in the appropriate solvent or combination of solvents to prepare a solution. Solvents for use in the present invention may comprise water, methanol, ethanol, or lower alkyl alcohols such as isopropyl alcohol, acetone, ethyl acetate, tetrahydrofuran, dimethyl sulfoxide, or dichloromethane, or any combination thereof. The residual solvent content in the dried, multilayered film may act as a plasticizer, an erosion- or dissolution -rate-modifying agent or may provide some pharmaceutical benefit. Desired residual solvent may reside in either or both layers.

[0088] Each solution is then coated onto a substrate. Each solution is cast and processed into a thin film by techniques known in the art, such as film coating, film casting, spin coating, or spraying using the appropriate substrate. The thin film is then dried. The drying step can be accomplished in any type of oven. However, the solvent residual depends on the drying procedure. The film layers may be filmed independently and then laminated together or may be filmed one on the top of the other. The film obtained after the layers have been laminated together or coated on top of each other may be cut into any type of shape, for application to the mucosal tissue. Some shapes include disks, ellipses, squares, rectangles, and parallepipedes.

EXEMPLIFICATION

[0089] Example 1: Effect of Naloxone on Efficacy of Fentanyl

[0090] The purpose of this study is to determine the dose range over which IV naloxone administered in combination with IV fentanyl, would precipitate opioid withdrawal signs and symptoms and attenuate any pleasurable effects from intravenous injection in subjects with a moderate level of opioid dependence. It is believed that the addition of this ratio of naloxone to a transmucosal formulation of fentanyl would hinder or prevent abuse.

[0091] The trial was a randomized, double-blind, placebo controlled, within-subject crossover study in opioid-dependent volunteers. Subjects were maintained on methadone prior to inpatient admission and throughout the 9-day study period. Subjects

received each of the 5 study doses and evaluated the psychopharmacologic effects of each.

[0092] The subjects included males or non-pregnant and non-lactating females; 18 to 55 years of age; free from any significant clinical abnormalities on the basis of medical history and physical examination, ECG, and screening laboratory tests; weighing at least 50kg (110 lbs); with an opioid positive urine sample (> 300 ng/ml) and an alcohol-free breath sample (< .002%).

[0093] Subjects were not eligible for the study if they exhibited certain indications or illnesses. For example, subjects with certain psychiatric illness, neurological disease, cardiovascular disease, pulmonary disease, systemic disease, were ineligible. Additionally, subjects with alcohol or sedative abuse and/or dependence, subjects who were cognitively impaired, subjects concurrently being treated for opioid dependence with methadone, buprenorphine, LAAM, or naltrexone, subjects on any medication other than oral or depot contraceptives and subjects with an injection phobia were excluded from the study. Furthermore, women candidates who were pregnant, lactating, or heterosexually active not using medically approved birth control measures were not eligible.

[0094] Opioid-dependent males and females, ages 18 to 55 years, were recruited. Volunteers were not concurrently seeking treatment for their drug use, and were willing to participate in a short-term study involving methadone maintenance and detoxification, and a consecutive 8-night (9-day) inpatient stay with experimental sessions involving intravenous drug administrations. Each subject who was eligible to participate in the study was assigned a study number.

[0095] A complete medical and drug history was taken and a complete physical examination was performed on each subject, including a measurement of height and weight. Respiration rate, oxygen saturation, heart rate, and blood pressure were measured during all test sessions using a Welch Allyn Noninvasive Patient Monitor. Vital signs including respiration rate, heart rate, systolic and diastolic blood pressure and oxygen saturation were measured prior to each dose and at 5, 10, 15, 30, 45 and 60 minutes after each dose. Each subject's oxyhemoglobin saturation was closely monitored. If the subject's oxyhemoglobin saturation remained below 90% for more than 1 minute, oxygen was administered to the subject via a nasal cannula, an adverse event was documented and the subject was monitored. Subjects requiring oxygen

administration were excluded from further study participation. A 12-lead electrocardiogram was obtained for each subject at screening. Females of childbearing potential had a urine pregnancy test performed according to the study schedule. A positive result at any time during the study excluded the subject from participating in the trial. All adverse events were recorded.

[0096] The laboratory tests listed in the following table were obtained according to the study schedule for each subject. All clinically significant laboratory abnormal values were specifically noted.

HEMATOLOGY	BLOOD CHEMISTRY	OTHER
Hemoglobin	Sodium	Urinalysis
Hematocrit	Potassium	Urine drug screen
Platelet Count	Chloride	Urinary beta-HCG
RBC Count	Bicarbonate	(females only)
White Blood Cell	Calcium	
Count Differential,	Phosphorus (inorganic)	
including:	Glucose	
Neutrophils	Urea Nitrogen	
Lymphocytes	Creatinine	
Monocytes	Uric Acid	
Eosinophils	Cholesterol	
Basophils	Bilirubin (total)	
	Protein (total)	
	Albumin	
	SGOT (AST)	
	SGPT (ALT)	
	Alkaline Phosphatase	

[0097] A Mantoux/PPD tuberculosis skin test was administered into the epidermis of the inner forearm of the subjects and the site of injection was marked. Forty-eight to 72 hours after the test was administered, the test results were read to determine if the test site was raised and felt hard to the touch. Subjects with a positive PPD test were referred to the community health program (CHP) to receive a chest X-ray. If the X-ray was positive (definition of having tuberculosis), the subject was informed and referred for treatment.

[0098] Subjects were asked to complete certain questionnaires, for example, an Injection Phobia Questionnaire, questions regarding the Shipley Institute of Living Scale (used to derive IQ), an Opioid Symptom Questionnaire, a Visual analog scale (VAS) rating of subjective drug effect, questions regarding a Drug reinforcing value (*e.g.*, to

make independent choices between drug and money), and an observer-rated withdrawal assessment

[0099] *Treatment*

[00100] All experimental doses were administered by intravenous injection in a double-blind manner. The starting IV fentanyl dose was 0.6 mg (600 μg) in combination with 0.15, 0.3 and 0.6 mg naloxone. This fentanyl dose corresponded to an intermediate-sized transmucosal formulation of fentanyl, thereby providing a reasonable test of a potentially abusable dose. Depending on the initial results, the fentanyl was adjusted either upward (to a maximum of 0.8 mg) or downward (to a minimum of 0.2 mg). If dose adjustments were made, the naloxone dose was adjusted according to the following ratios: (1) placebo, (2) fentanyl $\leq$ 0.8 mg + naloxone placebo, (3) fentanyl $\leq$ 0.8 mg + naloxone at 25% of the dose of fentanyl, (4),fentanyl $\leq$ 0.8 mg + naloxone at 50% of the dose of fentanyl, and (5) fentanyl $\leq$ 0.8 mg + naloxone at 100% of the dose of fentanyl.

[00101] Subjects were maintained on a target dose of methadone for 10 days prior to the first experimental session. Subjects also received methadone maintenance (50 mg daily) on days without experimental procedures.

[00102] Beginning on the first day of the study period and continuing each day, subjects received one of the 5 study treatments by intravenous injection at the same time each day. The timeline below indicates the times at which drug was administered and assessments were performed.

Time ->	-30 min (0930)	0 min (1000)	+5 min (1005)	+15 min (1015)	+30 min (1030)	+45 min (1045)	+60 min (1100)
IV drug		*x*					
Observer	*x*		*x*	*x*	*x*		
Vitals	*x*		*x*	*x*	*x*	*x*	*x*
VAS	*x*		*x*	*x*	*x*	*x*	*x*
OSQ	*x*		*x*	*x*	*x*	*x*	*x*
MCP							*x*

[00103] Prior to the subjects' discharge on the last day, an evaluation of adverse events, a complete physical examination, laboratory tests and administration of first methadone detoxification dose are all performed.

[00104] Results from initial subjects are shown in Figure 1. As can be seen in Figure 1, there was no positive or negative effects from the placebo, there was only a

positive effect from the fentanyl alone, there was no positive and some significant negative effects with fentanyl plus 25% naloxone, and there was major negative effects with fentanyl plus 50% naloxone.

[0021] Example 2: Extraction of Fentanyl and Naloxone in Water and Ethanol

[0022] A 3.11 cm^2 bilayered transmucosal disc was placed in 100 mL of 0.1N HCl and 0.1N NaOH. The disc was allowed to dissolve over a period of 30 minutes, and the amount of naloxone was measured using a high performance liquid chromatography. At 30 minutes, 100% naloxone and 100% fentanyl was extracted under acidic conditions, while 15% naloxone and 2% fentanyl was measured at a pH 12. The remaining amount was expected to settle at the bottom of the flask with other insoluble excipients.
A 3.11 cm^2 bilayered transmucosal disc as described herein was placed in 100 mL of ethanol. HPLC results show both naloxone and fentanyl present.

[00105] Example 3: Extraction of Buprenorphine and Naloxone in an Aqueous Solvent

A 2.3 cm^2 disc containing buprenorphine in the mucoadhesive layer and naloxone in the backing layer was prepared and placed in pH 7.4 Phosphate buffered solution in a Van Henkel USP dissolution apparatus at 50 RPM. The result of the dissolution experiment is shown in the table below.

Number of Minutes in Aqueous Solvent	Buprenorphine	Naloxone
5	18.0%	20.3%
15	38.5%	48.0%
30	60.5%	72.1%
45	84.1%	83.2%
60	100.2%	86.2%
75	106.7%	86.2%
120	108.9%	85.8%
180	109.4%	87.4%

[00106] As can be seen in the table, naloxone and buprenorphine extract simultaneously up to 180 minutes. Thus, they can not be extracted separately via dissolution.

Claims

1. A bioerodable abuse-resistant drug delivery device comprising:
   a transmucosal delivery composition comprising an abusable drug; and
   an abuse-resistant matrix comprising an antagonist to the abusable drug.

2. The delivery device of claim 1, wherein the antagonist is substantially transmucosally unavailable.

3. The delivery device of claim 1, wherein the device is substantially free of inactivating agents.

4. The delivery device of claim 1, wherein the device is a mucoadhesive drug delivery device.

5. The delivery device of claim 1, wherein the device is a buccal delivery device.

6. The delivery device of claim 1, wherein the device is a sublingual delivery device.

7. The delivery device of any of the foregoing claims, wherein the abuse-resistant matrix is a coating or layer at least partially disposed about the antagonist.

8. The delivery device of any of the foregoing claims, wherein the device is in a form selected from the group consisting of a tablet, a lozenge, a film, a disc, a capsule or a mixture of polymers.

9. The delivery device of claim 7, wherein the coating or layer is a water-erodable coating or layer.

10. The delivery device of any of the foregoing claims, wherein the abuse-resistant matrix is a water-hydrolysable, water-erodable or water-soluble matrix.

11. The delivery device of claim 10, wherein the matrix is an ion exchange polymer.

12. The delivery device of any of the foregoing claims, comprising a mucoadhesive layer.

13. The delivery device of claim 12, wherein either or both of the abusable drug and the abuse-resistant matrix are incorporated into the mucoadhesive layer.

14. The drug delivery device of any of the preceding claims, comprising a mucoadhesive layer and a non-adhesive backing layer.

15. The delivery device of claim 14, wherein the abusable drug is incorporated into a third layer disposed between the mucoadhesive layer and the backing layer.

16. The delivery device of claim 14, wherein the abuse-resistant matrix is incorporated into in a third layer disposed between the mucoadhesive layer and the backing layer.

17. The delivery device of claim 14, wherein the abuse-resistant matrix is a third layer disposed between the mucoadhesive layer and the backing layer.

18. The delivery device of claim 14, wherein the abuse-resistant matrix is incorporated into the mucoadhesive layer and/or the backing layer.

19. The delivery device of claim 14, wherein the abusable drug is incorporated into the mucoadhesive layer and the abuse-resistant matrix is incorporated into the backing layer.

20. The delivery device of any of claims 13-19, wherein the abuse-resistant matrix erodes at a slower rate than the backing layer, the mucoadhesive layer, the third layer, or any combination thereof.

21. The delivery device according to any of the foregoing claims, wherein the abusable drug is selected from the group consisting of opiates and opioids.

22. The delivery device according to any of the foregoing claims, wherein the device comprises at least one abusable drug selected from the group consisting of: alfentanil, allylprodine, alphaprodine, apomorphine, anileridine, apocodeine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, cyclorphan, cyprenorphine, desomorphine, dextromoramide, dextropropoxyphene, dezocine, diampromide, diamorphone, dihydrocodeine, dihydromorphine, dimenoxadol, eptazocine, ethylmorphine, etonitazene, etorphine, fentanyl, fencamfamine, fenethylline, hydrocodone, hydromorphone, hydroxymethylmorphinan, hydroxypethidine, isomethadone, levomethadone, levophenacylmorphan, levorphanol, lofentanil, mazindol, meperidine, metazocine, methadone, methylmorphine, modafinil, morphine, nalbuphene, necomorphine, normethadone, normorphine, opium, oxycodone, oxymorphone, pholcodine, profadol remifentanil, sufentanil, tramadol, corresponding derivatives, physiologically acceptable compounds, salts and bases.

23. The delivery device according to any of the foregoing claims, wherein the antagonist comprises at least one opiate or opioid antagonist selected from the group consisting of naloxone, naltrexone, nalmefene, nalide, nalmexone, nalorphine, naluphine, cyclazocine, levallorphan and physiologically acceptable salts and solvates thereof.

24. The delivery device of any of the foregoing claims, where the abuse-resistant matrix comprises at least one material selected from the group consisting of partially crosslinked polyacrylic acid, polycarbophil™, providone™, cross-linked sodium carboxymethylcellulose, gelatin, chitosan, Amberlite™ IRP69, Duolite™ AP143, AMBERLITE™ IRP64, AMBERLITE™ IRP88, and combinations thereof.

25. The delivery device of any of the foregoing claims, wherein the abuse-resistant matrix comprises at least one material selected from the group consisting of alginates, polyethylene oxide, poly ethylene glycols, polylactide, polyglycolide, lactide-glycolide copolymers, poly-epsilon-caprolactone, polyorthoesters,

polyanhydrides and derivatives, methyl cellulose, ethyl cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxyethylmethyl cellulose, hydroxypropylmethyl cellulose, polyacrylic acid, and sodium carboxymethyl cellulose, poly vinyl acetate, poly vinyl alcohols, polyethylene glycol, polyethylene oxide, ethylene oxide-propylene oxide co-polymers, collagen and derivatives, gelatin, albumin, polyaminoacids and derivatives, polyphosphazenes, polysaccharides and derivatives, chitin, or chitosan bioadhesive polymers, polyacrylic acid, polyvinyl pyrrolidone, sodium carboxymethyl cellulose, and combinations thereof.

26. The delivery device according to any of the preceding claims, wherein less than 30% of the efficacy of the abusable drug is retained when used in an abusive manner.

27. The abuse-resistant drug delivery device of claim 1, wherein the antagonist and the abusable drug are released at substantially the same rate when abusively dissolved.

28. The abuse-resistant drug delivery device of claim 1, wherein the antagonist and the abusable drug are released at substantially the same rate when dissolved in water.

29. The abuse-resistant drug delivery device of claim 27 and 28, wherein the ratio of released antagonist to released abusable drug is not less than about 1:20.

30. A method for treating pain in a subject comprising administering a device according to any one of the preceding claims such that pain is treated.

31. The method of claim 30, wherein the extent of the absorption into systemic circulation of the antagonist by the subject is less than about 15% by weight.

32. The method of claim 30 or 31, wherein the dosage of the abusable drug is between about 50μg and about 10 mg.

33. A bioerodable abuse-resistant drug delivery device comprising:

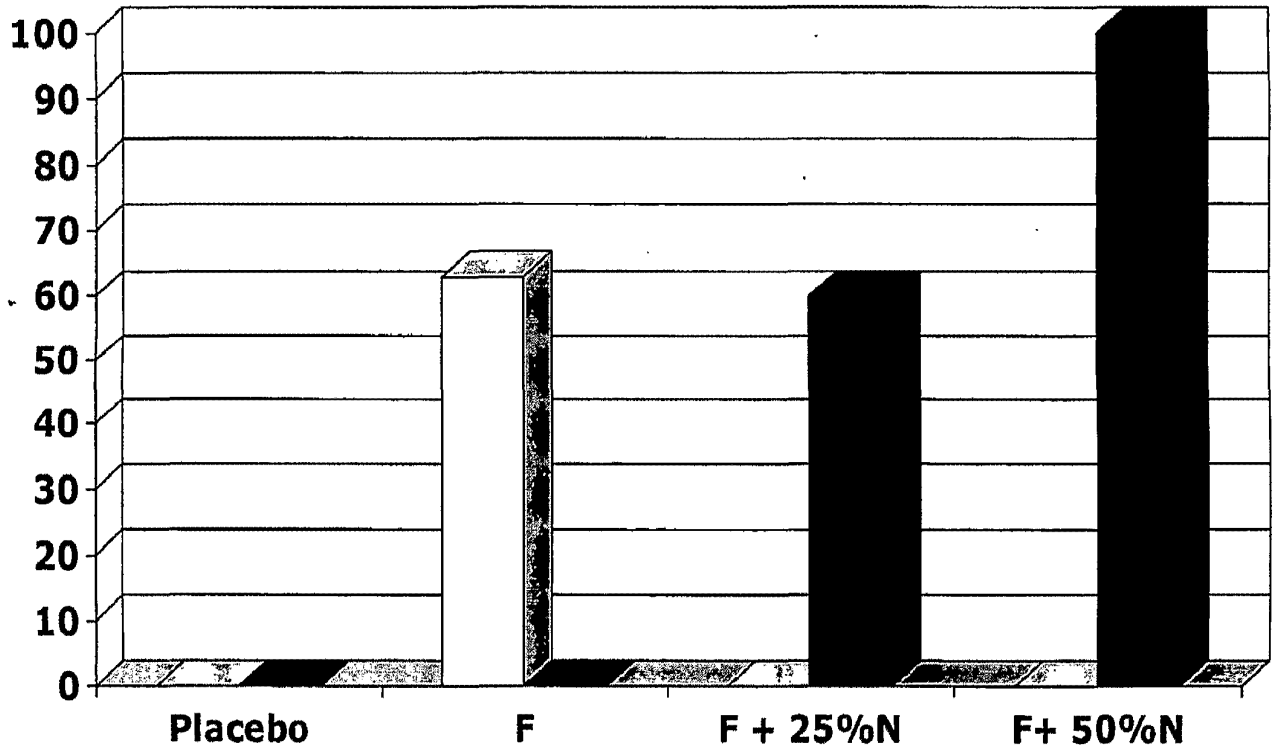
a layered film having

at least one bioerodable, mucoadhesive layer to be placed in contact with a mucosal surface, and

at least one bioerodable non-adhesive backing layer,

wherein at least one abusable drug is incorporated in at least the mucoadhesive layer, and an abuse-resistant matrix comprising an antagonist to the abusable drug is incorporated in any or all of the layers.

Figure 1:IV Fentanyl + IV Naloxone



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(74) Agent: **HANLEY, Elizabeth, A.**; LAHIVE & COCKFIELD, LLP, One Post Office Square, Boston, MA 02109-2127 (US).

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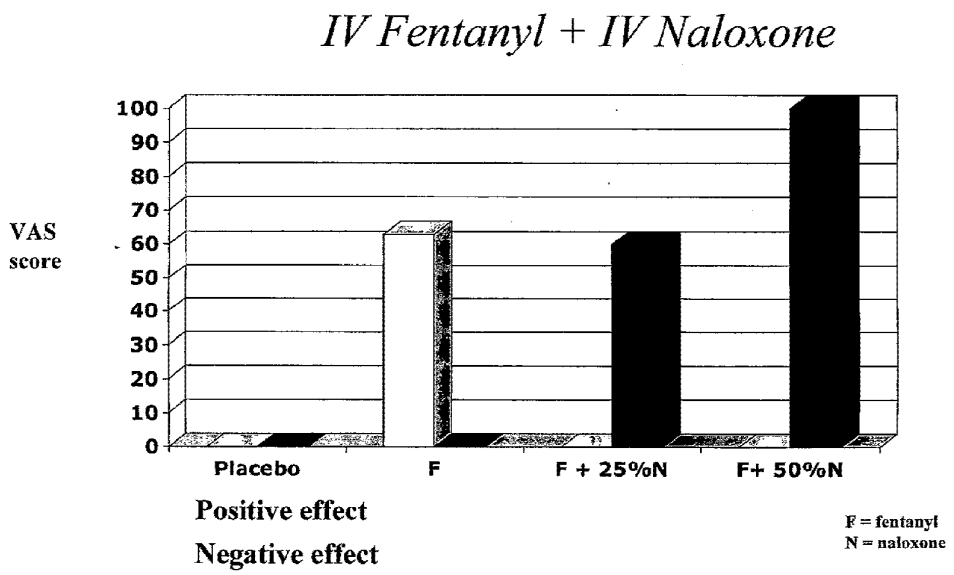
[Continued on next page]

(54) Title: ABUSE RESISTANT TRANSMUCOSAL DRUG DELIVERY DEVICE



(57) Abstract: The present invention relates to a solid pharmaceutical dosage form for abusable drug delivery with reduced illicit abuse potential. The dosage form is presented as a bioerodable transmucosal delivery device that includes an abusable drug and an antagonist to the abusable drug associated with an abuse-resistant matrix. The devices of the invention may be in the form of a layered film or a tablet. Upon application in a non-abusive manner, the device adheres to the mucosal surface, providing transmucosal drug delivery of the drug with minimal absorption of the antagonist into systemic circulation.

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— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

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A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/00 A61K45/06 A61K31/4468 A61K31/485

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

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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)
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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 August 2007	13/08/2007

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	GLIKMAN, J

INTERNATIONAL SEARCH REPORT

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2006/047686

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 30-32 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 composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2006/047686

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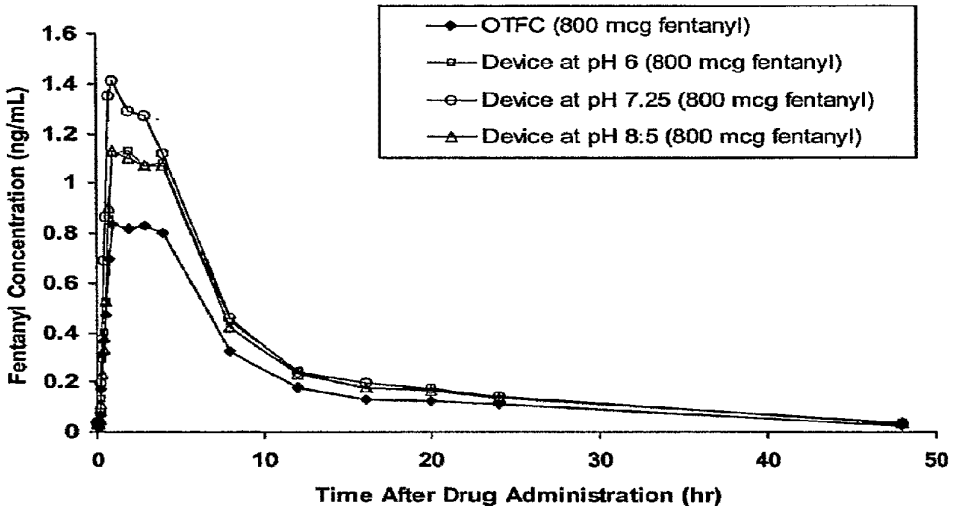
(54) Title: TRANSMUCOSAL DELIVERY DEVICES WITH ENHANCED UPTAKE

Mean Fentanyl Concentration-Time Plots For Three Exemplary Devices of the Invention and OTFC



(57) Abstract: The present invention provides methods for enhancing transmucosal uptake of a medicament, e.g., fentanyl or buprenorphine, to a subject and related devices. The method includes administering to a subject a transmucosal drug delivery device comprising the medicament. Also provided are devices suitable for transmucosal administration of a medicament to a subject and methods of their administration and use. The devices include a medicament disposed in a mucoadhesive polymeric diffusion environment and a barrier environment.

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TRANSMUCOSAL DELIVERY DEVICES WITH ENHANCED UPTAKE

RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 60/832,725, filed July 21, 2006, U.S. Provisional Application No. 60/832,726, filed July 21, 2006, and U.S. Provisional Application No. 60/839,504, filed August 23, 2006. The entire contents of these applications are incorporated herein by this reference. This application is also related to U.S. Serial No. 11/639,408, filed December 13, 2006, and PCT/US2006/47686, also filed December 13, 2006, both of which claim priority to US Provisional Application No. 60/750,191, filed December 13, 2005, and 60/764,618, filed February 2, 2006. The entire contents of these applications are also incorporated herein by this reference.

BACKGROUND

[0002] US Patent No. 6,264,981 (Zhang *et al.*) describes delivery devices, *e.g.*, tablets of compressed powders that include a solid solution micro-environment formed within the drug formulation. The micro-environment includes a solid pharmaceutical agent in solid solution with a dissolution agent that that facilitates rapid dissolution of the drug in the saliva. The micro-environment provides a physical barrier for preventing the pharmaceutical agent from being contacted by other chemicals in the formulation. The micro-environment may also create a pH segregation in the solid formulation. The pH of the micro-environment is chosen to retain the drug in an ionized form for stability purposes. The rest of the formulation can include buffers so that, upon dissolution in the oral cavity, the pH is controlled in the saliva such that absorption of the drug is controlled.

[0003] US Publication 2004/0253307 also describes solid dosage forms that include buffers that upon dissolution of the solid dosage form maintains the pharmaceutical agent at a desired pH to control absorption, *i.e.*, to overcome the influence of conditions in the surrounding environment, such as the rate of saliva secretion, pH of the saliva and other factors.

BRIEF SUMMARY OF THE INVENTION

[0004] The present invention provides transmucosal devices for enhanced uptake of a medicament and methods of making and using the same. In some embodiments, the devices generally include a mucoadhesive polymeric diffusion environment that facilitates not only the absorption of the medicament across the mucosal membrane to which it is applied, but additionally, the permeability and/or motility of the medicament through the mucoadhesive polymeric diffusion environment to the mucosa.

[0005] Accordingly, in one embodiment, the present invention is directed to methods for enhancing direct transmucosal delivery of a fentanyl or fentanyl derivative to a subject. The method generally includes administering a bioerodable drug delivery device to an oral mucosal surface of the subject, the device comprising: a fentanyl or fentanyl derivative disposed in a mucoadhesive polymeric diffusion environment; and a barrier environment disposed relative to the polymeric diffusion environment such that a unidirectional gradient is created upon application to the mucosal surface and the fentanyl or fentanyl derivative is delivered to the subject.

[0006] In another embodiment, the present invention is directed to methods for treating pain in a subject. The method generally includes transmucosally administering to a subject a therapeutically effective amount of a fentanyl or fentanyl derivative disposed in a mucoadhesive polymeric diffusion environment such that the effective amount of the fentanyl or fentanyl derivative is delivered in less than about 30 minutes. In some embodiments, chronic pain is alleviated in the subject. In other embodiments, acute pain is alleviated in the subject. In other embodiments, the pain is breakthrough cancer pain.

[0007] In yet another embodiment, the present invention is directed to mucoadhesive delivery devices suitable for direct transmucosal administration of an effective amount of a fentanyl or fentanyl derivative to a subject. The mucoadhesive device generally includes a fentanyl or fentanyl derivative disposed in a polymeric diffusion environment; and a barrier environment disposed relative to the polymeric diffusion environment such that a unidirectional gradient is upon application to a mucosal surface.

[0008] In another embodiment, the present invention is directed to transmucosal delivery devices that deliver a fentanyl or fentanyl derivative with at least 50% direct buccal absorption and an absolute bioavailability of at least about 70%. In yet another embodiment, the present invention is directed to transmucosal delivery devices that

deliver a fentanyl or fentanyl derivative directly to the mucosa to achieve onset of pain relief (T_{first}) of about 0.20 hours or less and time to peak plasma concentration (T_{max}) of about 1.6 hours or more. In still another embodiment, the present invention is directed to devices comprising about 800 μg of fentanyl, which exhibit upon transmucosal administration to a subject at least one *in vivo* plasma profile as follows: a C_{max} of about 1.10 ng/mL or more; a T_{first} of about 0.20 hours or less; and an AUC_{0-24} of about 10.00 hr·ng/mL or more. In yet another embodiment, the present invention is directed to transmucosal delivery devices which include a fentanyl or fentanyl derivative that delivers the fentanyl or fentanyl derivative in an amount effective to treat pain, wherein oral irritation, oral ulceration and/or constipation associated with the delivery of the fentanyl or fentanyl derivative is insignificant or eliminated. In one embodiment, the pH of the mucoadhesive polymeric diffusion environment is between about 6.5 and about 8, *e.g.*, about 7.25. In one embodiment, the device comprises about 800 μg of fentanyl. In another embodiment, the device further comprises at least one additional layer that facilitates unidirectional delivery of the fentanyl or fentanyl derivative to the mucosa. In another embodiment, the fentanyl is fentanyl citrate.

[0009] In one embodiment, more than 30% of the fentanyl, *e.g.*, more than 55% of the fentanyl, in the device becomes systemically available via mucosal absorption.

[0010] In one embodiment, the present invention is directed to methods for enhancing direct transmucosal delivery of buprenorphine to a subject. The method generally includes administering a bioerodable drug delivery device to an oral mucosal surface of the subject, the device comprising: buprenorphine disposed in a mucoadhesive polymeric diffusion environment; and a barrier environment disposed relative to the polymeric diffusion environment such that a unidirectional gradient is created upon application to the mucosal surface, and the buprenorphine is delivered to the subject.

[0011] In another embodiment, the present invention is directed to methods for treating pain in a subject. The method generally includes transmucosally administering to a subject a therapeutically effective amount of buprenorphine disposed in a mucoadhesive polymeric diffusion environment such that the effective amount of the buprenorphine is delivered in less than about 30 minutes. In some embodiments, chronic pain is alleviated in the subject. In other embodiments, acute pain is alleviated in the subject. In other embodiments, the pain is breakthrough cancer pain.

[0012] In yet another embodiment, the present invention is directed to mucoadhesive delivery devices suitable for direct transmucosal administration of an effective amount of buprenorphine to a subject. The mucoadhesive device generally includes buprenorphine disposed in a polymeric diffusion environment; and a barrier environment disposed relative to the polymeric diffusion environment such that a unidirectional gradient is created upon application to a mucosal surface. In one embodiment, the pH is between about 4.0 and about 7.5, *e.g.*, about 6.0 or about 7.25. In another embodiment, the device further comprises at least one additional layer that facilitates unidirectional delivery of the buprenorphine to the mucosa.

[0013] In one embodiment of the methods and devices of the present invention, the device comprises a pH buffering agent. In one embodiment of the methods and devices of the present invention, the device is adapted for buccal administration or sublingual administration.

[0014] In one embodiment of the methods and devices of the present invention, the device is a mucoadhesive disc. In one embodiment of the methods and devices of the present invention, the medicament is formulated as a mucoadhesive film formed to delineate different dosages. In one embodiment of the methods and devices of the present invention, the device comprises a backing layer disposed adjacent to the mucoadhesive polymeric diffusion environment.

[0015] In one embodiment of the methods and devices of the present invention, the device further comprises an opioid antagonist. In one embodiment of the methods and devices of the present invention, the device further comprises naloxone.

[0016] In one embodiment of the methods and devices of the present invention, the device is a layered, flexible device. In one embodiment of the methods and devices of the present invention, the mucoadhesive polymeric diffusion environment has a buffered environment for the transmucosal administration.

[0017] In one embodiment of the methods and devices of the present invention, there is substantially no irritation at the site of transmucosal administration. In one embodiment of the methods and devices of the present invention, the subject experienced about a 50% decrease in pain over about 30 minutes.

[0018] In one embodiment of the methods and devices of the present invention, the polymeric diffusion environment comprises at least one ionic polymer system, *e.g.*, polyacrylic acid (optionally crosslinked), sodium carboxymethylcellulose and mixtures

thereof. In one embodiment, the polymeric diffusion environment comprises a buffer system, *e.g.*, citric acid, sodium benzoate or mixtures thereof. In some embodiments, the device has a thickness such that it exhibits minimal mouth feel. In some embodiments, the device has a thickness of about 0.25 mm.

[0019] In some embodiments, the present invention provides a flexible, bioerodable mucoadhesive delivery device suitable for direct transmucosal administration of an effective amount of a fentanyl, fentanyl derivative, buprenorphine or buprenorphine derivative to a subject. The mucoadhesive device includes a mucoadhesive layer comprising a fentanyl, fentanyl derivative, buprenorphine or buprenorphine derivative disposed in a polymeric diffusion environment, wherein the polymeric diffusion environment has a pH of about 7.25 for the fentanyl or fentanyl derivative or a pH of about 6 for the buprenorphine or buprenorphine derivative; and a backing layer comprising a barrier environment which is disposed adjacent to and coterminous with the mucoadhesive layer. The device has no or minimal mouth feel and is able to transmucosally deliver the effective amount of the , fentanyl derivative, buprenorphine or buprenorphine derivative in less than about 30 minutes; and wherein a unidirectional gradient is created upon application of the device to a mucosal surface.

BRIEF DESCRIPTION OF THE DRAWINGS

[0020] The foregoing and other aspects, embodiments, objects, features and advantages of the invention can be more fully understood from the following description in conjunction with the accompanying figures.

[0021] *Figures 1 and 2* are graphs comparing fentanyl citrate uptake in humans over 2 days post-administration, and 1 hour post-administration, respectively, for exemplary embodiments of the present invention and a commercially available delivery device (Actiq ® Oral Transmucosal Fentanyl Citrate) as described in Examples 1 and 2.

[0022] *Figure 3* is a graph comparing buprenorphine uptake in humans over 16 hours post-administration, respectively, for exemplary embodiments of the present invention and a commercially available delivery devices as described in Examples 3 and 4.

[0023] *Figures 4A-C* are schematic representations of exemplary embodiments of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

[0024] The present invention is based, at least in part, on the discovery that transmucosal uptake of medicaments can be enhanced by employing a novel polymeric diffusion environment. Such a polymeric diffusion environment is advantageous, *e.g.*, because the absolute bioavailability of the medicament contained therein is enhanced, while also providing a rapid onset. Additionally, less medicament is needed in the device to deliver a therapeutic effect versus devices of the prior art. This renders the device less abusable, an important consideration when the medicament is a controlled substance, such as an opioid. The polymeric diffusion environment described in more detail herein, provides an enhanced delivery profile and more efficient delivery of the medicament. Additional advantages of a polymeric diffusion environment are also described herein.

[0025] In order to more clearly and concisely describe the subject matter of the claims, the following definitions are intended to provide guidance as to the meaning of terms used herein.

[0026] As used herein, the articles "a" and "an" mean "one or more" or "at least one," unless otherwise indicated. That is, reference to any element of the present invention by the indefinite article "a" or "an" does not exclude the possibility that more than one of the element is present.

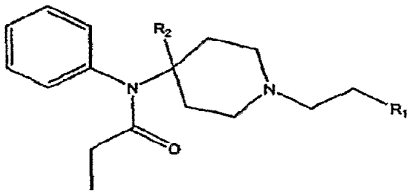
[0027] As used herein, the term "acute pain" refers to pain characterized by a short duration, e.g., three to six months. Acute pain is typically associated with tissue damage, and manifests in ways that can be easily described and observed. It can, for example, cause sweating or increased heart rate. Acute pain can also increase over time, and/or occur intermittently.

[0028] As used herein, the term "chronic pain" refers to pain which persists beyond the usual recovery period for an injury or illness. Chronic pain can be constant or intermittent. Common causes of chronic pain include, but are not limited to, arthritis, cancer, Reflex Sympathetic Dystrophy Syndrome (RSDS), repetitive stress injuries, shingles, headaches, fibromyalgia, and diabetic neuropathy.

[0029] As used herein, the term "breakthrough pain" refers to pain characterized by frequent and intense flares of moderate to severe pain which occur over chronic pain, even when a subject is regularly taking pain medication. Characteristics of breakthrough pain generally include: a short time to peak severity (*e.g.*, three to five minutes);

excruciating severity; relatively short duration of pain (*e.g.*, 15 to 30 minutes); and frequent occurrence (*e.g.*, one to five episodes a day). Breakthrough pain can occur unexpectedly with no obvious precipitating event, or it can be event precipitated. The occurrence of breakthrough pain is predictable about 50% to 60% of the time. Although commonly found in patients with cancer, breakthrough pain also occurs in patients with lower back pain, neck and shoulder pain, moderate to severe osteoarthritis, and patients with severe migraine.

[0030] As used herein, unless indicated otherwise, the term "fentanyl", includes any pharmaceutically acceptable form of fentanyl, including, but not limited to, salts, esters, and prodrugs thereof. The term "fentanyl" includes fentanyl citrate. As used herein, the term "fentanyl derivative" refers to compounds having similar structure and function to fentanyl. In some embodiments, fentanyl derivatives include those of the following formula:

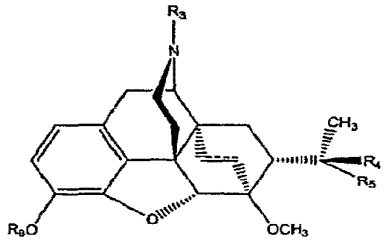


or pharmaceutically acceptable salts or esters thereof, wherein

R_1 is selected from an aryl group, a heteroaryl group or a –COO-C_{1-4} alkyl group; and R_2 is selected from –H, a -C_{1-4} alkyl-O-C_{1-4} alkyl group or a –COO-C_{1-4} alkyl group.

Fentanyl derivatives include, but are not limited to, alfentanil, sufentanil, remifentanil and carfentanil.

[0031] As used herein, unless indicated otherwise, the term "buprenorphine", includes any pharmaceutically acceptable form of buprenorphine, including, but not limited to, salts, esters, and prodrugs thereof. As used herein, the term "buprenorphine derivative" refers to compounds having similar structure and function to buprenorphine. In some embodiments, fentanyl derivatives include those of the following formula:



or pharmaceutically acceptable salts or esters thereof, wherein

 is a double or single bond; R_3 is selected from a -C_{1-4} alkyl group or a cycloalkyl-substituted-C_{1-4} alkyl group; R_4 is selected from a -C_{1-4} alkyl; R_5 is –OH, or taken together, R_4 and R_5 form a =O group; and R_6 is selected from –H or a -C_{1-4} alkyl group.

Buprenorphine derivatives include, but are not limited to, etorphine and diprenorphine.

[0032] As used herein, "polymeric diffusion environment" refers to an environment capable of allowing flux of a medicament to a mucosal surface upon creation of a gradient by adhesion of the polymeric diffusion environment to a mucosal surface. The flux of a transported medicament is proportionally related to the diffusivity of the environment which can be manipulated by, *e.g.*, the pH, taking into account the ionic nature of the medicament and/or the ionic nature polymer or polymers included in the environment and.

[0033] As used herein, "barrier environment" refers to an environment in the form of, *e.g.*, a layer or coating, capable of slowing or stopping flux of a medicament in its direction. In some embodiments, the barrier environment stops flux of a medicament, except in the direction of the mucosa. In some embodiments, the barrier significantly slows flux of a medicament, *e.g.*, enough so that little or no medicament is washed away by saliva.

[0034] As used herein, the term "unidirectional gradient" refers to a gradient which allows for the flux of a medicament (*e.g.*, fentanyl or buprenorphine) through the device, *e.g.*, through a polymeric diffusion environment, in substantially one direction, *e.g.*, to the mucosa of a subject. For example, the polymeric diffusion environment may be a mucoadhesive polymeric diffusion environment in the form of a layer or film disposed adjacent to a backing layer or film. Upon mucoadministration, a gradient is created between the mucoadhesive polymeric diffusion environment and the mucosa, and the medicament flows from the mucoadhesive polymeric diffusion environment, substantially in one direction towards the mucosa. In some embodiments, some flux of the medicament is not entirely unidirectional across the gradient; however, there is typically not free flux of the medicament in all directions. Such unidirectional flux is described in more detail herein, *e.g.*, in relation to Figure 4.

[0035] As used herein, "treating" or "treatment" of a subject includes the administration of a drug to a subject with the purpose of preventing, curing, healing, alleviating, relieving, altering, remedying, ameliorating, improving, stabilizing or affecting a disease or disorder, or a symptom of a disease or disorder (e.g., to alleviate pain).

[0036] The term "subject" refers to living organisms such as humans, dogs, cats, and other mammals. Administration of the medicaments included in the devices of the present invention can be carried out at dosages and for periods of time effective for treatment of a subject. In some embodiments, the subject is a human. In some embodiments, the pharmacokinetic profiles of the devices of the present invention are similar for male and female subjects. An "effective amount" of a drug necessary to achieve a therapeutic effect may vary according to factors such as the age, sex, and weight of the subject. Dosage regimens can be adjusted to provide the optimum therapeutic response. For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation.

[0037] The term "transmucosal," as used herein, refers to any route of administration via a mucosal membrane. Examples include, but are not limited to, buccal, sublingual, nasal, vaginal, and rectal. In one embodiment, the administration is buccal. In one embodiment, the administration is sublingual. As used herein, the term "direct transmucosal" refers to mucosal administration via the oral mucosa, *e.g.*, buccal and/or sublingual.

[0038] As used herein, the term "water erodible" or "at least partially water erodible" refers to a substance that exhibits a water erodibility ranging from negligible to completely water erodible. The substance may readily dissolve in water or may only partially dissolve in water with difficulty over a long period of time. Furthermore, the substance may exhibit a differing erodibility in body fluids compared with water because of the more complex nature of body fluids. For example, a substance that is negligibly erodible in water may show an erodibility in body fluids that is slight to moderate. However, in other instances, the erodibility in water and body fluid may be approximately the same.

[0039] The present invention provides transmucosal delivery devices that uniformly and predictably deliver a medicament to a subject. The present invention also

provides methods of delivery of a medicament to a subject employing devices in accordance with the present invention. Accordingly, in one embodiment, the present invention is directed to mucoadhesive delivery devices suitable for direct transmucosal administration of an effective amount of a medicament, *e.g.*, fentanyl or fentanyl derivative or buprenorphine to a subject. The mucoadhesive device generally includes a medicament disposed in a polymeric diffusion environment; and a having a barrier such that a unidirectional gradient is created upon application to a mucosal surface, wherein the device is capable of delivering in a unidirectional manner the medicament to the subject. The present invention also provides methods of delivery of a medicament to a subject employing the devices in accordance with the present invention.

[0040] In another embodiment, the present invention is directed to methods for enhancing direct transmucosal delivery of a medicament, *e.g.*, fentanyl, fentanyl derivatives and/or buprenorphine, to a subject. The method generally includes administering a bioerodable drug delivery device to an oral mucosal surface of the subject, the device comprising: a medicament disposed in a mucoadhesive polymeric diffusion environment; and a barrier environment disposed relative to the polymeric diffusion environment such that a unidirectional gradient is created upon application to the mucosal surface, wherein an effective amount of the medicament is delivered to the subject.

[0041] In another embodiment, the present invention is directed to methods for treating pain in a subject. The method generally includes transmucosally administering to a subject a therapeutically effective amount of a medicament, *e.g.*, fentanyl, fentanyl derivatives and/or buprenorphine, disposed in a mucoadhesive polymeric diffusion environment having a thickness such that the effective amount of the medicament is delivered in less than about 30 minutes and such that pain is treated. In some embodiments, the medicament is delivered in less than about 25 minutes. In some embodiments, the medicament is delivered in less than about 20 minutes.

[0042] In some embodiments of the above methods and devices, an effective amount is delivered transmucosally. In other embodiments, an effective amount is delivered transmucosally and by gastrointestinal absorption. In still other embodiments, an effective amount is delivered transmucosally, and delivery though the gastrointestinal absorption augments and/or maintains treatment, *e.g.*, pain relief for a desired period of time, *e.g.*, at least 1, 1.5, 2, 2.5, 3, 3.5, or 4 or more hours.

[0043] In yet another embodiment, the present invention is directed to transmucosal delivery devices that deliver a fentanyl or fentanyl derivative directly to the mucosa to achieve onset of pain relief (T_{first}) of about 0.20 hours or less and time to peak plasma concentration (T_{max}) of about 1.6 hours or more. The combination of a rapid onset with a delayed maximum concentration is particularly advantageous when treating pain, *e.g.*, relief for breakthrough cancer pain (BTP) in opioid tolerant patients with cancer, because immediate relief is provided to alleviate a flare of moderate to severe pain but persistence is also provided to alleviate subsequent flares. Conventional delivery systems may address either the immediate relief or subsequent flare-ups, but the devices of this embodiment are advantageous because they address both.

Table 1: Selected Pharmacokinetic properties of transmucosal devices.

	T_{first}	T_{max}	Total Bioavailability
BEMA pH 7.25	0.15 hours	1.61 hours	70%
Actiq®	0.23 hours	2.28 hours	47%
Fentora®	0.25 hours*	0.50 hours	65%

* - reported as onset of main relief, first time point measured.

[0044] The devices of the present invention may have a number of additional or alternative desirable properties, as described in more detail herein. Accordingly, in another embodiment, the present invention is directed to transmucosal delivery devices that deliver a fentanyl or fentanyl derivative with at least 50% direct buccal absorption and an absolute bioavailability of at least about 70%. In still another embodiment, the present invention is directed to devices comprising about 800 μg of fentanyl, which exhibit upon transmucosal administration to a subject at least one *in vivo* plasma profile as follows: a C_{max} of about 1.10 ng/mL or more; a T_{first} of about 0.20 hours or less; and an AUC_{0-24} of about 10.00 hr·ng/mL or more.

[0045] The pain can be any pain known in the art, caused by any disease, disorder, condition and/or circumstance. In some embodiments, chronic pain is alleviated in the subject using the methods of the present invention. In other embodiments, acute pain is alleviated in the subject using the methods of the present invention. Chronic pain can arise from many sources including, cancer, Reflex Sympathetic Dystrophy Syndrome (RSDS), and migraine. Acute pain is typically directly related to tissue damage, and lasts for a relatively short amount of time, *e.g.*, three to six months. In other embodiments, the pain is breakthrough cancer pain. In some embodiments, the methods and devices of the present invention can be used to

alleviate breakthrough pain in a subject. For example, the devices of the present invention can be used to treat breakthrough pain in a subject already on chronic opioid therapy. In some embodiments, the devices and methods of the present invention provide rapid analgesia and/or avoid the first pass metabolism of fentanyl, thereby resulting in more rapid breakthrough pain relief than other treatments, *e.g.*, oral medications.

[0046] In one embodiment of the methods and devices of the present invention, the subject experienced about a 50% decrease in pain over about 30 minutes. In one embodiment of the methods and devices of the present invention, the subject experienced about a 60% decrease in pain over about 30 minutes. In one embodiment of the methods and devices of the present invention, the subject experienced about a 70% decrease in pain over about 30 minutes. In one embodiment of the methods and devices of the present invention, the subject experienced about a 80% decrease in pain over about 30 minutes. In one embodiment of the methods and devices of the present invention, the subject experienced about a 90% decrease in pain over about 30 minutes. In one embodiment of the methods and devices of the present invention, the subject experienced about a 100% decrease in pain over about 30 minutes. In one embodiment of the methods and devices of the present invention, the subject experienced about a 50% decrease in pain over about 25 minutes. In one embodiment of the methods and devices of the present invention, the subject experienced about a 50% decrease in pain over about 20 minutes.

[0047] Without wishing to be bound by any particular theory, it is believed that delivery of the medicament is particularly effective because the mucoadhesive polymeric diffusion environment (*e.g.*, the pH and the ionic nature of the polymers) is such that the medicament (*e.g.*, a weakly basic drug such as fentanyl or buprenorphine) can rapidly move through the mucoadhesive polymeric diffusion environment to the mucosa, while also allowing efficient absorption by the mucosa. For example, in some embodiments, the pH is low enough to allow movement of the medicament, while high enough for absorption.

[0048] In some embodiments, the mucoadhesive polymeric diffusion environement is a layer with a buffered pH such that a desired pH is maintained at the mucosal administration site. Accordingly, the effect of any variation in pH encountered

in a subject or between subjects (*e.g.*, due to foods or beverages recently consumed), including any effect on uptake, is reduced or eliminated.

[0049] Accordingly, one advantage of the present invention is that variability in the properties of the device (*e.g.*, due to changes in the pH of the ingredients) between devices, and from lot to lot is reduced or eliminated. Without wishing to be bound by any particular theory, it is believed that the polymeric diffusion environment of the present invention reduces variation, *e.g.*, by maintaining a buffered pH. Yet another advantage is pH variability at the administration site (e.g., due to what food or drink or other medications was recently consumed) is reduced or eliminated, such that, *e.g.*, the variability of the devices is reduced or eliminated.

[0050] A medicament for use in the present invention includes any medicament capable of being administered transmucosally. The medicament can be suitable for local delivery to a particular mucosal membrane or region, such as the buccal and nasal cavities, throat, vagina, alimentary canal or the peritoneum. Alternatively, the medicament can be suitable for systemic delivery via such mucosal membranes.

[0051] In one embodiment, the medicament can be an opioid. Opioids suitable for use in the present invention include, *e.g.*, alfentanil, allylprodine, alphaprodine, apomorphine, anileridine, apocodeine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, cyclorphan, cyprenorphine, desomorphine, dextromoramide, dextropropoxyphene, dezocine, diampromide, diamorphone, dihydrocodeine, dihydromorphine, dimenoxadol, eptazocine, ethylmorphine, etonitazene, etorphine, fentanyl, fencamfamine, fenethylline, hydrocodone, hydromorphone, hydroxymethylmorphinan, hydroxypethidine, isomethadone, levomethadone, levophenacylmorphan, levorphanol, lofentanil, mazindol, meperidine, metazocine, methadone, methylmorphine, modafinil, morphine, nalbuphene, necomorphine, normethadone, normorphine, opium, oxycodone, oxymorphone, pholcodine, profadol remifentanil, sufentanil, tramadol, corresponding derivatives, physiologically acceptable compounds, salts and bases. In some embodiments, the medicament is fentanyl, *e.g.*, fentanyl citrate. In some embodiments, the medicament is buprenorphine.

[0052] The amount of medicament, *e.g.* fentanyl or buprenorphine, to be incorporated into the device of the present invention depends on the desired treatment dosage to be administered, *e.g.*, the fentanyl or fentanyl derivative can be present in

about 0.001% to about 50% by weight of the device of the present invention, and in some embodiments between about 0.005 and about 35% by weight or the buprenorphine can be present in about 0.001% to about 50% by weight of the device of the present invention, and in some embodiments between about 0.005 and about 35% by weight. In one embodiment, the device comprises about 3.5% to about 4.5% fentanyl or fentanyl derivative by weight. In one embodiment, the device comprises about 3.5% to about 4.5% buprenorphine by weight. In another embodiment, the device comprises about 800 μg of a fentanyl such as fentanyl citrate. In another embodiment the device comprises about 25, 50, 75, 100, 150, 200, 300, 400, 500, 600, 700, 900, 1000, 1200, 1500, 1600 or 2000 μg of a fentanyl such as fentanyl citrate or fentanyl derivative. It is to be understood that all values and ranges between these values and ranges are meant to be encompassed by the present invention. In another embodiment, the device comprises about 800 μg of buprenorphine. In another embodiment the device comprises about 100, 200, 300, 400, 500, 600, 700, 900, 1000, 1200, 1500, or 2000 μg of buprenorphine. In another embodiment the device comprises about 25, 50, 75, 100, 150, 200, 300, 400, 500, 600, 700, 900, 1000, 1200, 1500, 1600 or 2000 μg of any of the medicaments described herein.

[0053] One approach to reaching an effective dose is through titration with multiple dosage units such that patients start with a single 200 mcg unit and progressively increase the number of units applied until reaching an effective dose or 800 mcg (4 units) dose as the multiple discs once an effective dose has been identified. Accordingly, in some embodiments, the methods of the present invention also include a titration phase to identify a dose that relieves pain and produces minimal toxicity, because the dose of opioid, *e.g.*, fentanyl, required for control of breakthrough pain episodes is often not easily predicted. The linear relationship between surface area of the devices of the present invention and pharmacokinetic profile may be exploited in the dose titration process through the application of single or multiple discs to identify an appropriate dose, and then substitution of a single disc containing the same amount of medicament.

[0054] In one embodiment, the devices of the present invention are capable of delivering a greater amount of fentanyl systemically to the subject than conventional devices. According to the label for Actiq ® Oral Transmucosal Fentanyl Citrate, approximately 25% of the fentanyl in the ACTIQ product is absorbed via the buccal

mucosa, and of the remaining 75% that is swallowed, another 25% of the total fentanyl becomes available via absorption in the GI tract for a total of 50% total bioavailability. According to Fentora Fentanyl Buccal tablet literature, approximately 48% of the fentanyl in FENTORA product is absorbed via the buccal mucosa, and of the remainig 52%, another 17% of the total fentanyl becomes available via absorption in the GI tract for a total of 65% total bioavailability. Accordingly, in some embodiments, more than about 30% of the fentanyl disposed in the devices of the present invention becomes systemically available or bioavailable via absorption by the mucosa. In some embodiments, more than about 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75% or 80% becomes systemically available via mucosal absorption. In some embodiments, more than about 55%, 60%, 65% or 70% of the fentanyl disposed in the devices of the present invention becomes systemically available or bioavailable by any route, mucosal and/or GI tract. In some embodiments, more than about 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95% becomes systemically available.

[0055] Accordingly, another advantage of the devices and methods of the present invention is that because the devices of the present invention more efficiently deliver the medicament, *e.g.*, fentanyl or buprenorphine, than do conventional devices, less medicament can be included than must be included in conventional devices to deliver the same amount of medicament. Accordingly, in some embodiments, the devices of the present invention are not irritating to the mucosal surface on which it attaches. In some embodiments, the devices of the present invention cause little or no constipation, even when the devices include an opioid antagonist such as naloxone. In yet another embodiment, the present invention is directed to transmucosal delivery devices which include a fentanyl or fentanyl derivative that delivers the fentanyl or fentanyl derivative in an amount effective to treat pain, wherein oral irritation, oral ulceration and/or constipation associated with the delivery of the fentanyl or fentanyl derivative is not significant or eliminated.

[0056] Another advantage is the devices of the present invention are less subject to abuse than conventional devices because less medicament, *e.g.*, fentanyl or buprenorphine, is required in the device, *i.e.*, there is less medicament to be extracted by an abuser for injection into the bloodstream.

[0057] In some embodiments, the devices of the present invention have a dose response that is substantially directly proportional to the amount of medicament present

in the device. For example, if the C_{max} is 10 ng/mL for a 500 dose, then it is expected in some embodiments that a 1000 μg dose will provide a C_{max} of approximately 20 ng/mL. Without wishing to be bound by any particular theory, it is believed that this is advantageous in determining a proper dose in a subject.

[0058] In some embodiments, the devices of the present invention further comprise an opioid antagonist in any of various forms, e.g., as salts, bases, derivatives, or other corresponding physiologically acceptable forms. Opioid antagonists for use with the present invention include, but are not limited to, naloxone, naltrexone, nalmefene, nalide, nalmexone, nalorphine, naluphine, cyclazocine, levallorphan and physiologically acceptable salts and solvates thereof, or combinations thereof. In one embodiment, the device further comprises naloxone.

[0059] In some embodiments, the properties of the polymeric diffusion environment are effected by its pH. In one embodiment, *e.g.*, when the medicament is fentanyl, the pH of the mucoadhesive polymeric diffusion environment in the devices of the present invention is between about 6.5 and about 8. In another embodiment, the pH of the mucoadhesive polymeric diffusion environment is about 7.25. In another embodiment, the pH is between about 7.0 and about 7.5, or between about 7.25 and 7.5. In other embodiments, the pH is about 6.5, 7.0, 7.5, 8.0 or 8.5, or any incremental value thereof. It is to be understood that all values and ranges between these values and ranges are meant to be encompassed by the present invention.

[0060] In one embodiment, *e.g.*, when the medicament is buprenorphine, the pH of the mucoadhesive polymeric diffusion environment in the devices of the present invention is between about 4.0 and about 7.5. In another embodiment, the pH of the mucoadhesive polymeric diffusion environment is about 6.0. In one embodiment, the pH of the mucoadhesive polymeric diffusion environment is about 5.5 to about 6.5, or between about 6.0 and 6.5. In yet another embodiment, the pH of the mucoadhesive polymeric diffusion environment is about 7.25. In another embodiment, the pH is between about 7.0 and 7.5, or between about 7.25 and 7.5. In other embodiments, the pH of the device may be about 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, or 7.5, or any incremental value thereof. It is to be understood that all values and ranges between these values and ranges are meant to be encompassed by the present invention.

[0061] The pH of the mucoadhesive polymeric diffusion environment can be adjusted and/or maintained by methods including, but not limited to, the use of buffering

agents, or by adjusting the composition of the device of the present invention. For example, adjustment of the components of the device of the present invention that influence pH, e.g., the amount of anti-oxidant, such as citric acid, contained in the device will adjust the pH of the device.

[0062] In some embodiments, the properties of the polymeric diffusion environment are effected by its buffering capacity. In some embodiments, buffering agents are included in the mucoadhesive mucoadhesive polymeric diffusion environment. Buffering agents suitable for use with the present invention include, for example, phosphates, such as sodium phosphate; phosphates monobasic, such as sodium dihydrogen phosphate and potassium dihydrogen phosphate; phosphates dibasic, such as disodium hydrogen phosphate and dipotassium hydrogen phosphate; citrates, such as sodium citrate (anhydrous or dehydrate); bicarbonates, such as sodium bicarbonate and potassium bicarbonate may be used. In one embodiment, a single buffering agent, *e.g.*, a dibasic buffering agent is used. In another embodiment, a combination of buffering agents is employed, *e.g.*, a combination of a tri-basic buffering agent and a monobasic buffering agent.

[0063] In one embodiment, the mucoadhesive polymeric diffusion environment of the device will have a buffered environment, *i.e.*, a stabilized pH, for the transmucosal administration of a medicament. The buffered environment of the device allows for the optimal administration of the medicament to a subject. For example, the buffered environment can provide a desired pH at the mucosa when in use, regardless of the circumstances of the mucosa prior to administration.

[0064] Accordingly, in various embodiments, the devices include a mucoadhesive polymeric diffusion environment having a buffered environment that reduces or eliminates pH variability at the site of administration due to, for example, medications, foods and/or beverages consumed by the subject prior to or during administration. Thus, pH variation encountered at the site of administration in a subject from one administration to the next may have minimal or no effect on the absorption of the medicament. Further, pH variation at the administration site between different patients will have little or no effect on the absorption of the medicament. Thus, the buffered environment allows for reduced inter- and intra- subject variability during transmucosal administration of the medicament. In another embodiment, the present invention is directed to methods for enhancing uptake of a medicament that include administering to

a subject a device including a medicament disposed in a mucoadhesive polymeric diffusion environment having a buffered environment for the transmucosal administration. In yet another embodiment, the present invention is directed to methods of delivering a therapeutically effective amount of a medicament to a subject that include administering a device including a medicament disposed in a mucoadhesive polymeric diffusion environment having a buffered environment for the transmucosal administration.

[0065] The devices of the present invention can include any combination or sub-combination of ingredients, layers and/or compositions of, *e.g.*, the devices described in US Patent No. 6,159,498, US Patent No. 5,800,832, US Patent No. 6,585,997, US Patent No. 6,200,604, US Patent No. 6,759,059 and/or PCT Publication No. WO 05/06321. The entire contents of these patent and publications are incorporated herein by reference in their entireties.

[0066] In some embodiments, the properties of the polymeric diffusion environment are effected by the ionic nature of the polymers employed in the environment. In one embodiment, the mucoadhesive polymeric diffusion environment is water-erodible and can be made from a bioadhesive polymer(s) and optionally, a first film-forming water-erodible polymer(s). In one embodiment, the polymeric diffusion environment comprises at least one ionic polymer system, *e.g.*, polyacrylic acid (optionally crosslinked), sodium carboxymethylcellulose and mixtures thereof.

[0067] In some embodiments, the mucoadhesive polymeric diffusion environment can include at least one pharmacologically acceptable polymer capable of bioadhesion (the "bioadhesive polymer") and can optionally include at least one first film-forming water-erodible polymer (the "film-forming polymer"). Alternatively, the mucoadhesive polymeric diffusion environment can be formed of a single polymer that acts as both the bioadhesive polymer and the first film-forming polymer. Additionally or alternatively, the water-erodible mucoadhesive polymeric diffusion environment can include other first film-forming water-erodible polymer(s) and water-erodible plasticizer(s), such as glycerin and/or polyethylene glycol (PEG).

[0068] In some embodiments, the bioadhesive polymer of the water-erodible mucoadhesive polymeric diffusion environment can include any water erodible substituted cellulosic polymer or substituted olefinic polymer wherein the substituents may be ionic or hydrogen bonding, such as carboxylic acid groups, hydroxyl alkyl

groups, amine groups and amide groups. For hydroxyl containing cellulosic polymers, a combination of alkyl and hydroxyalkyl groups will be preferred for provision of the bioadhesive character and the ratio of these two groups will have an effect upon water swellability and disperability. Examples include polyacrylic acid (PAA), which can optionally be partially crosslinked, sodium carboxymethyl cellulose (NaCMC), moderately to highly substituted hydroxypropylmethyl cellulose (HPMC), polyvinylpyrrolidone (PVP, which can optionally be partially crosslinked), moderately to highly substituted hydroxyethylmethyl cellulose (HEMC) or combinations thereof. In one embodiment, HEMC can be used as the bioadhesive polymer and the first film forming polymer as described above for a mucoadhesive polymeric diffusion environment formed of one polymer. These bioadhesive polymers are preferred because they have good and instantaneous mucoadhesive properties in a dry, system state.

[0069] The first film-forming water-erodible polymer(s) of the mucoadhesive polymeric diffusion environment can be hydroxyalkyl cellulose derivatives and hydroxyalkyl alkyl cellulose derivatives preferably having a ratio of hydroxyalkyl to alkyl groups that effectively promotes hydrogen bonding. Such first film-forming water-erodible polymer(s) can include hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), hydroxypropylmethyl cellulose (HPMC), hydroxyethylmethyl cellulose (HEMC), or a combination thereof. Preferably, the degree of substitution of these cellulosic polymers will range from low to slightly above moderate.

[0070] Similar film-forming water-erodible polymer(s) can also be used. The film-forming water-erodible polymer(s) can optionally be crosslinked and/or plasticized in order to alter its dissolution kinetics.

[0071] In some embodiments, the mucoadhesive polymeric diffusion environment, *e.g.*, a bioerodable mucoadhesive polymeric diffusion environment, is generally comprised of water-erodible polymers which include, but are not limited to, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, hydroxyethylmethyl cellulose, polyacrylic acid (PAA) which may or may not be partially crosslinked, sodium carboxymethyl cellulose (NaCMC), and polyvinylpyrrolidone (PVP), or combinations thereof. Other mucoadhesive water-erodible polymers may also be used in the present invention. The term "polyacrylic acid" includes both uncrosslinked and partially crosslinked forms, *e.g.*, polycarbophil.

[0072] In some embodiments, the mucoadhesive polymeric diffusion environment is a mucoadhesive layer, e.g, a bioerodable mucoadhesive layer. In some embodiments, the devices of the present invention include a bioerodable mucoadhesive layer which comprises a mucoadhesive polymeric diffusion environment.

[0073] In some embodiments, the properties of the polymeric diffusion environment are effected by the barrier environment. The barrier environment is disposed such that the flux of medicament is substantially unidirectional. For example, in an exemplary layered device of the present invention, having a layer comprising a medicament dispersed in a polymeric diffusion environment and a co-terminus barrier layer (see, *e.g.*, Figure 4B), upon application to the mucosa, some medicament may move to and even cross the boundary not limited by the mucosa or barrier layer. In another exemplary layered device of the present invention, a barrier layer does not completely circumscribe the portion of the mucoadhesive polymeric diffusion environment that will not be in direct contact with the mucosa upon application of the device (see, *e.g.*, Figure 4C). A majority of the medicament in both of these cases, however, flows towards the mucosa. In another exemplary layered device of the present invention, having a barrier layer which circumscribes the portion of the mucoadhesive polymeric diffusion environment that will not be in direct contact with the mucosa upon application of the device (see, *e.g.*, Figure 4A), upon application to the mucosa, substantially all of the medicament typically flows towards the mucosa.

[0074] The barrier environment can be, *e.g.*, a backing layer. A backing layer can be included as an additional layer disposed adjacent to the mucoadhesive polymeric diffusion environment. The layers can be coterminous, or, *e.g.*, the barrier layer may circumscribe the portion of the mucoadhesive polymeric diffusion environment that will not be in direct contact with the mucosa upon application of the device. In one embodiment, the device comprises a backing layer disposed adjacent to the mucoadhesive polymeric diffusion environment. The device of the present invention can also comprise a third layer or coating. A backing layer can be also included in the devices of the present invention as a layer disposed adjacent to a layer which is, in turn, disposed adjacent to the mucoadhesive polymeric diffusion environment (i.e., a three layer device).

[0075] In one embodiment, the device further comprises at least one additional layer that facilitates unidirectional delivery of the medicament to the mucosa. In one

embodiment, the device of the present invention further comprises at least one additional layer disposed adjacent to the mucoadhesive polymeric diffusion environment. Such layer can include additional medicament or different medicaments, and/or can be present to further reduce the amount of medicament (originally in the mucoadhesive polymeric diffusion environment) that is washed away in the saliva.

[0076] Specialty polymers and non-polymeric materials may also optionally be employed to impart lubrication, additional dissolution protection, drug delivery rate control, and other desired characteristics to the device. These third layer or coating materials can also include a component that acts to adjust the kinetics of the erodability of the device.

[0077] The backing layer is a non-adhesive water-erodible layer that may include at least one water-erodible, film-forming polymer. In some embodiments, the backing layer will at least partially or substantially erode or dissolve before the substantial erosion of the mucoadhesive polymeric diffusion environment.

[0078] The barrier environment and/or backing layer can be employed in various embodiments to promote unidirectional delivery of the medicament (*e.g.*, fentanyl) to the mucosa and/or to protect the mucoadhesive polymeric diffusion environment against significant erosion prior to delivery of the active to the mucosa. In some embodiments, dissolution or erosion of the water-erodible non-adhesive backing layer primarily controls the residence time of the device of the present invention after application to the mucosa. In some embodiments, dissolution or erosion of the barrier environment and/or backing layer primarily controls the directionality of medicament flow from the device of the present invention after application to the mucosa.

[0079] The barrier environment and/or backing layer (*e.g.*, a water-erodible non-adhesive backing layer) can further include at least one water erodible, film-forming polymer. The polymer or polymers can include polyethers and polyalcohols as well as hydrogen bonding cellulosic polymers having either hydroxyalkyl group substitution or hydroxyalkyl group and alkyl group substitution preferably with a moderate to high ratio of hydroxyalkyl to alkyl group. Examples include, but are not limited to, hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), hydroxypropylmethyl cellulose (HPMC), hydroxyethylmethyl cellulose (HEMC), polyvinyl alcohol (PVA), polyethylene glycol (PEG), polyethylene oxide (PEO), ethylene oxide-propylene oxide co polymers, and combinations thereof. The water-erodible non-adhesive backing layer

component can optionally be crosslinked. In one embodiment, the water erodible non-adhesive backing layer includes hydroxyethyl cellulose and hydroxypropyl cellulose. The water-erodible non-adhesive backing layer can function as a slippery surface, to avoid sticking to mucous membrane surfaces.

[0080] In some embodiments, the barrier environment and/or backing layer, *e.g.*, a bioerodible non-adhesive backing layer, is generally comprised of water-erodible, film-forming pharmaceutically acceptable polymers which include, but are not limited to, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, hydroxyethylmethyl cellulose, polyvinylalcohol, polyethylene glycol, polyethylene oxide, ethylene oxide-propylene oxide co-polymers, or combinations thereof. The backing layer may comprise other water-erodible, film-forming polymers.

[0081] The devices of the present invention can include ingredients that are employed to, at least in part, provide a desired residence time. In some embodiments, this is a result of the selection of the appropriate backing layer formulation, providing a slower rate of erosion of the backing layer. Thus, the non-adhesive backing layer is further modified to render controlled erodibility which can be accomplished by coating the backing layer film with a more hydrophobic polymer selected from a group of FDA approved Eudragit™ polymers, ethyl cellulose, cellulose acetate phthalate, and hydroxyl propyl methyl cellulose phthalate, that are approved for use in other pharmaceutical dosage forms. Other hydrophobic polymers may be used, alone or in combination with other hydrophobic or hydrophilic polymers, provided that the layer derived from these polymers or combination of polymers erodes in a moist environment. Dissolution characteristics may be adjusted to modify the residence time and the release profile of a drug when included in the backing layer.

[0082] In some embodiments, any of the layers in the devices of the present invention may also contain a plasticizing agent, such as propylene glycol, polyethylene glycol, or glycerin in a small amount, 0 to 15% by weight, in order to improve the "flexibility" of this layer in the mouth and to adjust the erosion rate of the device. In addition, humectants such as hyaluronic acid, glycolic acid, and other alpha hydroxyl acids can also be added to improve the "softness" and "feel" of the device. Finally, colors and opacifiers may be added to help distinguish the resulting non-adhesive backing layer from the mucoadhesive polymeric diffusion environment. Some opacifers include titanium dioxide, zinc oxide, zirconium silicate, etc.

[0083] Combinations of different polymers or similar polymers with definite molecular weight characteristics can be used in order to achieve preferred film forming capabilities, mechanical properties, and kinetics of dissolution. For example, polylactide, polyglycolide, lactide-glycolide copolymers, poly-e-caprolactone, polyorthoesters, polyanhydrides, ethyl cellulose, vinyl acetate, cellulose, acetate, polyisobutylene, or combinations thereof can be used.

[0084] The device can also optionally include a pharmaceutically acceptable dissolution-rate-modifying agent, a pharmaceutically acceptable disintegration aid (*e.g.*, polyethylene glycol, dextran, polycarbophil, carboxymethyl cellulose, or poloxamers), a pharmaceutically acceptable plasticizer, a pharmaceutically acceptable coloring agent (e.g., FD&C Blue #1), a pharmaceutically acceptable opacifier (e.g., titanium dioxide), pharmaceutically acceptable anti-oxidant (e.g., tocopherol acetate), a pharmaceutically acceptable system forming enhancer (*e.g.*, polyvinyl alcohol or polyvinyl pyrrolidone), a pharmaceutically acceptable preservative, flavorants (e.g., saccharin and peppermint), neutralizing agents (e.g., sodium hydroxide), buffering agents (*e.g.*, monobasic, or tribasic sodium phosphate), or combinations thereof. Preferably, these components are individually present at no more than about 1% of the final weight of the device, but the amount may vary depending on the other components of the device.

[0085] The device can optionally include one or more plasticizers, to soften, increase the toughness, increase the flexibility, improve the molding properties, and/or otherwise modify the properties of the device. Plasticizers for use in the present invention can include, *e.g.*, those plasticizers having a relatively low volatility such as glycerin, propylene glycol, sorbitol, ethylene glycol, diethylene glycol, triethylene glycol, propylene glycol, polypropylene glycol, dipropylene glycol, butylene glycol, diglycerol, polyethylene glycol (*e.g.*, low molecular weight PEG's), oleyl alcohol, cetyl alcohol, cetostearyl alcohol, and other pharmaceutical-grade alcohols and diols having boiling points above about 100°C at standard atmospheric pressure. Additional plasticizers include, *e.g.*, polysorbate 80, triethyl titrate, acetyl triethyl titrate, and tributyl titrate. Additional suitable plasticizers include, *e.g.*, diethyl phthalate, butyl phthalyl butyl glycolate, glycerin triacetin, and tributyrin. Additional suitable plasticizers include, *e.g.*, pharmaceutical agent grade hydrocarbons such as mineral oil (*e.g.*, light mineral oil) and petrolatum. Further suitable plasticizers include, e.g., triglycerides such as medium-chain triglyceride, soybean oil, safflower oil, peanut oil,

and other pharmaceutical agent grade triglycerides, PEGylated triglycerides such as Labrifil®, Labrasol® and PEG-4 beeswax, lanolin, polyethylene oxide (PEO) and other polyethylene glycols, hydrophobic esters such as ethyl oleate, isopropyl myristate, isopropyl palmitate, cetyl ester wax, glyceryl monolaurate, and glyceryl monostearate.

[0086] One or more disintegration aids can optionally be employed to increase the disintegration rate and shorten the residence time of the device of the present invention. Disintegration aids useful in the present invention include, *e.g.*, hydrophilic compounds such as water, methanol, ethanol, or low alkyl alcohols such as isopropyl alcohol, acetone, methyl ethyl acetone, alone or in combination. Specific disintegration aids include those having less volatility such as glycerin, propylene glycol, and polyethylene glycol.

[0087] One or more dissolution-rate-modifying agents can optionally be employed to decrease the disintegration rate and lengthen the residence time of the device of the present invention. Dissolution-rate modifying agents useful in the present invention include, *e.g.*, hydrophobic compounds such as heptane, and dichloroethane, polyalkyl esters of di and tricarboxylic acids such as succinic and citric acid esterified with C6 to C20 alcohols, aromatic esters such as benzyl benzoate, triacetin, propylene carbonate and other hydrophobic compounds that have similar properties. These compounds can be used alone or in combination in the device of the invention.

[0088] The devices of the present invention can include various forms. For example, the device can be a disc or film. In one embodiment, the device comprises a mucoadhesive disc. In one embodiment of the methods and devices of the present invention, the device is a layered, flexible device. The thickness of the device of the present invention, in its form as a solid film or disc, may vary, depending on the thickness of each of the layers. Typically, the bilayer thickness ranges from about 0.01 mm to about 1 mm, and more specifically, from about 0.05 mm to about 0.5 mm. The thickness of each layer can vary from about 10% to about 90% of the overall thickness of the device, and specifically can vary from about 30% to about 60% of the overall thickness of the device. Thus, the preferred thickness of each layer can vary from about 0.005 mm to about 1.0 mm, and more specifically from about 0.01 mm to about 0.5 mm.

[0089] In one embodiment, the mucoadhesive polymeric diffusion environment of the device of the present invention has a thickness of about 0.03 mm to about 0.07 mm. In one embodiment, the mucoadhesive polymeric diffusion environment of the

device of the present invention has a thickness of about 0.04 mm to about 0.06 mm. In yet another embodiment, the mucoadhesive polymeric diffusion environment of the present invention has a thickness of about 0.05mm. The thickness of the mucoadhesive polymeric diffusion environment is designed to be thick enough so that it can be easily manufactured, yet thin enough to allow for maximum permeability of the medicament through the layer, and maximum absorption of the medicament into the mucosal layer.

[0090] In one embodiment, the backing layer of the device of the present invention has a thickness of about 0.050 mm to about 0.350 mm. In one embodiment, the backing layer of the device of the present invention has a thickness of about 0.100 mm to about 0.300 mm. In yet another embodiment, the backing layer of the present invention has a thickness of about 0.200 mm. The thickness of the backing layer is designed to be thick enough so that it allows for substantially unidirectional delivery of the medicament (towards the mucosa), yet thin enough to dissolve so that it does not have to be manually removed by the subject.

[0091] In these embodiments, there is relatively minimal mouth feel and little discomfort because of the thinness and flexibility of the devices as compared to conventional tablet or lozenge devices. This is especially advantageous for patients who have inflammation of the mucosa and/or who may otherwise not be able to comfortably use conventional devices. The devices of the present invention are small and flexible enough so that they can adhere to a non-inflamed area of the mucosa and still be effective, *i.e.*, the mucosa does not need to be swabbed with the device of the present invention.

[0092] In various embodiments, the devices of the present invention can be in any form or shape such as a sheet or disc, circular or square in profile or cross-section, etc., provided the form allows for the delivery of the active to the subject. In some embodiments, the devices of the present invention can be scored, perforated or otherwise marked to delineate certain dosages. For example, a device may be a square sheet, perforated into quarters, where each quarter comprises a 200 μg dose. Accordingly, a subject can use the entire device for an 800 μg dose, or detach any portion thereof for a 200 μg, 400 μg or 600 μg dose.

[0093] The devices of the present invention can be adapted for any mucosal administration. In some embodiments of the methods and devices of the present

invention, the device is adapted for buccal administration and/or sublingual administration.

[0094] Yet another advantage of the devices of the present invention is the ease with which they are administered. With conventional devices, the user must hold the device in place, or rub the device over the mucosa for the duration of administration, which may last from twenty to thirty minutes or more. The devices of the present invention adhere to the mucosal surface in less than about five seconds, and naturally erode in about twenty to thirty minutes, without any need to hold the device in place.

[0095] Without wishing to be bound by any particular theory, it is also believed that the devices of the present invention are substantially easier to use than devices of the prior art. When devices of the prior art are used, they are often subject to much variability, *e.g.*, due to variation in mouth size, diligence of the subject in correctly administering the device and amount of saliva produced in the subject's mouth. Accordingly, in some embodiments, the present invention provides a variable-free method for treating pain in a subject. The term "variable-free" as used herein, refers to the fact that the devices of the present invention provide substantially similar pharmacokinetic profile in all subjects, regardless of mouth size and saliva production.

[0096] Without wishing to be bound by any particular theory, it is also believed that the presence of a backing layer also imparts a resistance to the devices of the present invention. Accordingly, in some embodiments, the devices of the present invention are resistant to the consumption of food or beverage. That is, the consumption of food or beverage while using the devices of the present invention does not substantially interfere with the effectiveness of the device. In some embodiments, the performance of the devices of the present invention, *e.g.*, peak fentanyl concentrations and/or overall exposure to the medicament is unaffected by the consumption of foods and/or hot beverages.

[0097] In various embodiments, the devices can have any combination of the layers, ingredients or compositions described herein including but not limited to those described above.

EXEMPLIFICATION

Example 1: Preparation of Devices in Accordance with the Present Invention

[0098] Transmucosal devices were configured in the form of a disc, rectangular in shape with round corners, pink on one side and white on the other side. The drug is

present in the pink layer, which is the mucoadhesive polymeric diffusion environment, and this side is to be placed in contact with the buccal mucosa (inside the cheek). The drug is delivered into the mucosa as the disc erodes in the mouth. The white side is the non-adhesive, backing layer which provides a controlled erosion of the disc, and minimizes the oral uptake of the drug induced by constant swallowing, thus minimizing or preventing first pass metabolism. The mucoadhesive polymeric diffusion environment and backing layer are bonded together and do not delaminate during or after application.

[0099] The backing layer was prepared by adding water (about 77% total formulation, by weight) to a mixing vessel followed by sequential addition of sodium benzoate(about 0.1% total formulation, by weight), methylparaben (about 0.1% total formulation, by weight) and propylparaben (about 0.03% total formulation, by weight), citric acid (about 0.1% total formulation, by weight) and vitamin E acetate (about 0.01% total formulation, by weight), and sodium saccharin(about 0.1% total formulation, by weight). Subsequently, a mixture of the polymers hydroxypropyl cellulose (Klucel EF, about 14% total formulation, by weight) and hydroxyethyl cellulose (Natrosol 250L, about 7% total formulation, by weight) was added and stirred at a temperature between about 120 and 130°F, until evenly dispersed. Upon cooling to room temperature, titanium dioxide (about 0.6% total formulation, by weight) and peppermint oil (about 0.2% total formulation, by weight) were then added to the vessel and stirred. The prepared mixture was stored in an air-sealed vessel until it was ready for use in the coating operation.

[0100] The mucoadhesive polymeric diffusion environment was prepared by adding water (about 89% total formulation, by weight) to a mixing vessel followed by sequential addition of propylene glycol (about 0.5% total formulation, by weight), sodium benzoate (about 0.06% total formulation, by weight), methylparaben (about 0.1% total formulation, by weight) and propylparaben (about 0.03% total formulation, by weight), vitamin E acetate (about 0.01% total formulation, by weight) and citric acid (about 0.06% total formulation, by weight), red iron oxide (about 0.01% total formulation, by weight), and monobasic sodium phosphate (about 0.04% total formulation, by weight). After the components were dissolved, 800 μg fentanyl citrate (about 0.9% total formulation, by weight) was added, and the vessel was heated to 120 to 130°F. After dissolution, the polymer mixture [hydroxypropyl cellulose (Klucel EF,

about 0.6% total formulation, by weight), hydroxyethyl cellulose (Natrosol 250L, about 1.9% total formulation, by weight), polycarbophil (Noveon AA1(about 0.6% total formulation, by weight), and carboxy methyl cellulose (Aqualon 7LF, about 5.124% total formulation, by weight)] was added to the vessel, and stirred until dispersed. Subsequently, heat was removed from the mixing vessel. As the last addition step, tribasic sodium phosphate and sodium hydroxide were added to adjust the blend to a desired pH. For example, about 0.6% total formulation, by weight of sodium hydroxide and about 0.4% total formulation, by weight of tribasic sodium phosphate can be added to the formulation. Batches were made having pHs of about 6, 7.25, and 8.5. The blend was mixed under vacuum for a few hours. Each prepared mixture was stored in an air-sealed vessel until its use in the coating operation.

[0101] The layers were cast in series onto a St. Gobain polyester liner. First, the backing layer was cast using a knife-on-a-blade coating method. The backing layer was then cured in a continuous oven at about 65 to 95°C and dried. After two coating and drying iterations, an approximately 8 mil (203 to 213 micrometers) thick backing layer is obtained. Subsequently, the mucoadhesive polymeric diffusion environment was cast onto the backing layer, cured in an oven at about 65 to 95 °C and dried. The devices were then die-cut by kiss-cut method and removed from the casting surface.

Example 2: Study of Fentanyl Citrate Uptake in Humans for Delivery Devices of the Present Invention and a Commercially Available Delivery Device

[0102] The effect of system pH on the uptake of fentanyl citrate in three exemplary delivery devices of the present invention was evaluated, and compared to that observed in Actiq® Oral Transmucosal Fentanyl Citrate product (Cephalon, Inc., Salt Lake City, UT), referred to herein as "OTFC". A randomized, open-label, single-dose, four-period, Latin-square crossover study was conducted in 12 healthy volunteers. An Ethical Review Board approved the study and all subjects gave informed consent before participating. Bioanalytical work using a validated liquid chromatography/mass spectrometry/mass spectrometry (LC/MS/MS) method was performed by CEDRA Clinical Research, LLC (Austin, TX).

[0103] Twelve (9 male, 3 female) healthy volunteers ranging in age from 21 to 44 years were recruited for the instant study. Subjects tested were free from any significant clinical abnormalities on the basis of medical history and physical examination, electrocardiogram, and screening laboratories. Subjects weighed between about 50 kg

and 100 kg and were within 15% of their ideal body weight based on Metropolitan Life tables for height and weight. Subjects were instructed to not consume alcohol, caffeine, xanthine, or foods/beverages containing grapefruit for 48 hours prior to the first dose of study medication and for the entire duration of the study. Subjects were also instructed not to use tobacco or nicotine containing products for at least 30 days prior to the first dose of medication. No subject had participated in any investigational drug study for at least 30 days prior to the instant study; had any significant medical condition either at the time of the study or in the past (including glaucoma and seizure disorders); had a positive drug screen; had used any concomitant medication other than oral contraceptives or acetaminophen for at least 72 hours prior to the first dose; or had a history of allergic reaction or intolerance to narcotics. Premenopausal women not using contraception or having a positive urine beta HCG test were excluded. Table 2, below, shows the demographics of the subjects included in this study.

Table 2. Subject Demographics (N=12)

Age, years	
Mean (standard deviation)	32 (7)
Median	31
Range	21-44
Gender, n (%)	
Female	3 (25)
Male	9 (75)
Race, n (%)	
Black	3 (25)
Caucasian	4 (33)
Hispanic	5 (42)
Height (cm)	
Mean (standard deviation)	171.6 (9.3)
Median	172.0
Range	155.0 – 183.5
Weight (kg)	
Mean (standard deviation)	70.5 (9.0)
Median	70.7
Range	52.0 – 86.5

[0104] The study consisted of a screening visit and a 9-day inpatient period during which each subject received single buccal transmucosal doses of each of the four study treatments with 48 hours separating the doses. The four study treatments, each including 800 μg of fentanyl citrate, were: the OTFC and devices prepared as described

in Example 1 and buffered at a pH of about 6 ("device at pH 6"), a pH of about 7.25 ("device at pH 7.25"), and a pH of about 8.5 ("device at pH 8.5").

[0105] Subject eligibility was determined at the screening visit, up to 21 days prior to entering the study facility. Subjects arrived at the study facility at 6:00 PM the day prior to dosing (day 0). Predose procedures (physical examination, clinical laboratory tests, electrocardiogram, and substance abuse screen) were performed. After an overnight fast of at least 8 hours, subjects received an oral dose of naltrexone at 6 AM. A standard light breakfast was served approximately 1 hour prior to study drug dosing. A venous catheter was placed in a large forearm or hand vein for blood sampling, and a pulse oximeter and noninvasive blood pressure cuff were attached. Subjects were placed in a semi-recumbent position, which they maintained for 8 hours after each dose.

[0106] Subjects received the first dose of drug at 8 AM on day 1 and subsequent doses at the same time on days 3, 5, and 7. Blood samples (7 mL) were collected in ethylenediaminetetraacetic acid (EDTA) for measurement of plasma fentanyl just prior to dose 1 and 5, 7.5, 10, 15, 20, 25, 30, 45, and 60 minutes, and 2, 3, 4, 8, 12, 16, 20, 24, and 48 hours after each dose. The 48-hour post dose sample was collected just prior to administration of the subsequent dose. A total of 511 mL of blood was collected over the study period for pharmacokinetic analysis. Samples were centrifuged and the plasma portion drawn off and frozen at -20°C or colder.

[0107] Finger pulse oximetry was monitored continuously for 8 hours after each dose and then hourly for an additional four hours. If the subject's oxyhemoglobin saturation persistently decreased to less than 90%, the subject was prompted to inhale deeply several times and was observed for signs of decreased oxyhemoglobin saturation. If the oxyhemoglobin saturation value immediately increased to 90% or above, no further action was taken. If the oxyhemoglobin saturation remained below 90% for more than 1 minute, oxygen was administered to the subject via a nasal cannula. Heart rate, respiratory rate, and blood pressure were measured just prior to the dose, and every 15 minutes for 120 minutes, and at 4, 6, 8, and 12 hours post dose. Throughout the study, subjects were instructed to inform the study personnel of any adverse events.

[0108] Each subject received a single buccal dose of each of the 4 study treatments in an open-label, randomized crossover design. The measured pH on the three devices during the manufacturing process in accordance with Example 1 were 5.95 for the device at pH 6.0, 7.44 for the device at pH 7.25, and 8.46 for the device at pH

8.5. After subjects rinsed their mouths with water, the delivery devices of the present invention were applied to the oral mucosa at a location approximately even with the lower teeth. The devices were held in place for 5 seconds until the device was moistened by saliva and adhered to the mucosa membrane. After application, subjects were instructed to avoid rubbing the device with their tongues, as this would accelerate the dissolution of the device.

[0109] OTFC doses were administered according to the package insert. After each mouth was rinsed with water, the OTFC unit was placed in the mouth between the cheek and lower gum. The OTFC unit was occasionally moved from one side of the mouth to the other. Subjects were instructed to suck, not chew, the OTFC unit over a 15-minute period. To block the respiratory depressive effects of fentanyl, a 50 mg oral dose of naltrexone was administered to each subject at approximately 12 hours and 0.5 hours prior to each dose of study drug and 12 hours after study drug. Naltrexone has been shown not to interfere with fentanyl pharmacokinetics in opioid naïve subjects. Lor M, et al., *Clin Pharmacol Ther*; 77: P76 (2005).

[0110] At the end of the study, EDTA plasma samples were analyzed for plasma fentanyl concentrations using a validated liquid chromatography with tandem mass spectrophotometry (LC/MS/MS) procedure. Samples were analyzed on a SCIEX API 3000 spectrophotometer using pentadeuterated fentanyl as an internal standard. The method was validated for a range of 0.0250 to 5.00 ng/mL based on the analysis of 0.500 mL of EDTA human plasma. Quantitation was performed using a weighted (1/X2) linear least squares regression analysis generated from calibration standards.

[0111] Pharmacokinetic data were analyzed by noncompartmental methods in WinNonlin (Pharsight Corporation). In the pharmacokinetic analysis, concentrations below the limit of quantitation (<0.0250 ng/mL) were treated as zero from time-zero up to the time at which the first quantifiable concentration (C_{first}) was observed. Subsequent to C_{first}, concentrations below this limit were treated as missing. Full precision concentration data were used for all pharmacokinetic and statistical analyses. C_{first} was defined as the first quantifiable concentration above the pre-dose concentration because quantifiable data were observed in the pre-dose samples in some subjects. λ_z was calculated using unweighted linear regression analysis on at least three log-transformed concentrations visually assessed to be on the linear portion of the terminal slope. The $t_{1/2}$ was calculated as the ratio of 0.693 to λ_z. Pharmacokinetic parameters

were summarized by treatment using descriptive statistics. Values of t_{first}, t_{max}, C_{max}, and AUC_{inf} of the three exemplary devices of the present invention were compared to OTFC using an analysis of variance (ANOVA) model and Tukey's multiple comparison test. Statistical analysis was performed using SAS (SAS Institute Inc.). Table 3, below, presents the fentanyl pharmacokinetics for all 4 treatments after a single dose.

Table 3. Pharmacokinetic Parameters of OTFC and Three Formulations of BEMA Fentanyl Citrate

Parameter	OTFC 800 μg (N=12)		Device at pH 6 Fentanyl 800 μg (N=12)		Device at pH 7.25 Fentanyl 800 μg (N=12)		Device at pH 8.5 Fentanyl 800 μg (N=12)	
	Mean (SD)	CV%	Mean (SD)	CV %	Mean (SD)	CV%	Mean (SD)	CV %
t_{first} (hr)	0.23 (0.18)	78.03	0.13 (0.04)	27.99	0.15 (0.08)	54.18	0.21 (0.11)	55.21
C_{first} (ng/mL)	0.07 (0.05)	64.95	0.05 (0.02)	35.25	0.06 (0.02)	41.59	0.06 (0.02)	30.08
t_{max} (hr)	2.28 (1.32)	58.04	2.15 (1.14)	53.23	1.61 (1.04)	64.49	2.21 (1.34)	60.64
C_{max} (ng/mL)[1]	1.03 (0.25)	24.19	1.40 (0.49)	35.12	1.67 (0.75)	45.07	1.39 (0.41)	29.44
AUC_{last} (hr•ng/mL)	9.04 (3.53)	39.01	12.17 (4.28)	35.19	12.98 (5.59)	43.04	11.82 (4.54)	38.37
AUC_{0-24} (hr•ng/mL)	7.75 (2.52)	32.48	10.43 (3.00)	28.74	11.38 (4.30)	37.78	10.18 (3.20)	31.44
AUC_{inf} (hr•ng/mL)	10.30 (3.84)	37.29	13.68 (4.55)	33.24	14.44 (5.39)	37.33	13.11 (4.77)	36.40
% AUC_{extrap}	12.15 (8.31)	68.40	11.53 (6.84)	59.33	11.72 (6.91)	58.96	10.31 (4.49)	43.49
λz (hr^{-1})	0.05 (0.02)	37.83	0.05 (0.02)	31.10	0.05 (0.01)	21.18	0.06 (0.02)	26.98
$t_{1/2}$ (hr)	15.33 (6.85)	44.67	15.12 (5.09)	33.66	14.28 (2.75)	19.23	13.33 (4.14)	31.04
MRT	15.92 (6.17)	38.73	15.73 (4.19)	26.63	14.45 (3.12)	21.61	14.31 (4.45)	31.09

1. Mean differences of BEMA fentanyl formulations and OTFC significantly different by ANOVA, p=0.0304.

[0112] Abbreviations used herein are as follows: C_{first} is the first quantifiable drug concentration in plasma determined directly from individual concentration-time data; t_{first} is the time to the first quantifiable concentration; C_{max} is the maximum drug concentration in plasma determined directly from individual concentration-time data; t_{max} is the time to reach maximum concentration; λ_z is the observed elimination rate constant; $t_{1/2}$ is the observed terminal elimination half-life calculated as $\ln(2)/\lambda_z$; AUC_{0-24} is the area under the concentration-time curve from time zero to 24 hours post-dose; calculated using the linear trapezoidal rule and extrapolated using the elimination rate

constant if quantifiable data were not observed through 24 hours; AUC_{last} is the area under the concentration-time curve from time zero to the time of the last quantifiable concentration; calculated using the linear trapezoidal rule; AUC_{inf} is the area under the concentration-time curve from time zero extrapolated to infinity, calculated as $AUC_{last} + C_{last} / \lambda_z$; AUC_{extrap} (%) is the percentage of AUC_{inf} based on extrapolation; MRT is the mean residence time, calculated as $AUMC_{inf}/AUC_{inf}$, where $AUMC_{inf}$ is the area under the first moment curve (concentration-time vs. time), calculated using the linear trapezoidal rule form time zero to T_{last} ($AUMC_{last}$) and extrapolated to infinity. It should be noted that, because quantifiable data were observed in the pre-dose samples for some subjects, C_{first} was redefined as the first quantifiable concentration above the pre-dose concentration, which was set to zero in calculating mean fentanyl concentrations.

[0113] Figure 1 illustrates the plasma fentanyl concentration from 0 to 48 hours post-dose for the OTFC dose and the doses provided by the three exemplary devices of the present invention. The device at pH 7.25 provided the highest peak concentrations of fentanyl of the three devices of the present invention used in this study. In general, OTFC provided lower fentanyl concentrations for most time points as compared with the devices of the present invention. The device at pH 6 and the device at pH 8.5 yielded very similar concentration-time profiles, with C_{max} values of 1.40 ng/mL and 1.39 ng/mL, respectively. These values are midway between the maximum plasma fentanyl values of 1.03 ng/mL for OTFC and 1.67 ng/mL for the device at pH 7.25. After approximately 6 hours post-dose, the fentanyl concentration-time profiles for the three devices of the present invention were similar. The differences in fentanyl C_{max} values were statistically significant when comparing all of the devices of the present invention to OTFC ($p=0.0304$), and for pairwise comparisons of the device at pH 7.25 to OTFC ($p<0.05$).

[0114] In general, quantifiable fentanyl concentrations were observed earlier after administration of one of the three exemplary devices of the present invention (mean t_{first} of 8 to 13 minutes) compared with OTFC (mean t_{first} of 14 minutes). The device at pH 7.25 yielded the earliest average t_{max} (1.61 hours) and highest C_{max} (mean 1.67 ng/mL). As shown in Figure 2, fentanyl absorption from a device at pH 7.25 was more rapid over the first hour post dose than from OTFC, with 30-minute mean plasma concentrations of 0.9 ng/mL for the device at pH 7.25 and 0.5 ng/mL for OTFC.

[0115] The delivery devices of the present invention provided overall greater exposure to fentanyl, based on $AUC_{0\,24}$ as compared to OTFC. Fentanyl exposure as measured by AUC_{0-24} values, were similar across groups treated with one of the devices of the present invention, suggesting that comparable amounts of fentanyl enter the systemic circulation from each of the devices. The device at pH 7.25, however, demonstrated approximately 19% greater maximum plasma fentanyl concentration.

[0116] Overall, fentanyl concentrations were observed earlier and increased more rapidly after administration of a device of the present invention compared with OTFC. Mean 30 and 60 minute plasma fentanyl concentrations observed with use of the device at pH 7.25 were 1.8 and 1.7 times higher than with OTFC, respectively. Similarly, the maximum plasma fentanyl concentration was 60% higher using a device of the present invention (mean 1.67 ng/mL) when compared to use of OTFC (mean 1.03 ng/mL). The C_{max} for OTFC identified in this study is nearly identical to the 1.1 ng/mL C_{max} value reported by Lee and co-workers with both a single 800 mcg lozenge as well as two 400 mcg lozenges. Lee, M., et al., *J Pain Symptom Manage* 2003; 26:743-747. Overall, fentanyl exposure for the fentanyl formulations of the present invention were greater than for OTFC. Mean estimates of AUC_{last} and AUC_{inf} were slightly larger, but the same general trends were observed. This indicates that the transmucosal uptake is significantly improved in the devices of the present invention as compared to OTFC.

[0117] Mean $t_{1/2}$ values and MRT values were similar for all treatment groups and the values in both cases followed the same trend. Additionally, because MRT after extravascular administration is dependent on the absorption and elimination rates, the MRT values suggest that fentanyl absorbs faster from a delivery device of the present invention, particularly with the device at pH 7.25 and the device at pH 8.5. This observation is consistent with the t_{max} for the delivery devices of the present invention relative to OTFC.

[0118] Adverse events were similar across treatment groups and confounded by the co-administration of naltrexone with each study treatment. The most frequent adverse events were sedation and dizziness. One subject experienced oral mucosal irritation with OTFC. No subject experienced mucosal irritation with any of the three exemplary devices of the present invention. All reported adverse events were mild or moderate in nature.

[0119] As demonstrated above, the delivery devices of the present invention provide significantly higher plasma fentanyl concentrations than OTFC. The delivery device at pH 7.25 appeared to provide enhanced uptake believed to be attributable to a favorable balance between drug solubility and ionization. Similar studies have shown that the delivery devices of the present invention provide an absolute bioavailability of about 70.5% and buccal absorption was about 51% (estimated by subtracting the AUC_{inf} following an oral dose of fentanyl from the AUC_{inf} following BEMA fentanyl applied to the buccal mucosa, dividing by the single disc BEMA Fentanyl AUC_{inf}, and multiplying by 100).

Example 3: Preparation of Devices in Accordance with the Present Invention

[0120] Devices containing buprenorphine were also produced using the same method as described in Example 1, except that buprenorphine was added to the mucoadhesive polymeric diffusion environment, rather than fentanyl citrate.

Example 4: Study of Buprenorphine Uptake in Humans for Delivery Devices of the Present Invention

[0121] A study similar to that described in Example 2 was also performed with buprenorphine in exemplary devices of the present invention (at pH 6 and 7.25), suboxone sublingual and buprenex intramuscular. Results from this study are summarized in the graph in Figure 3. As demonstrated in Table 4, the delivery devices of the present invention at pH 6 appeared to provide enhanced uptake believed to be attributable to a favorable balance between drug solubility and ionization.

Table 4: Pharmacokinetic data for buprenorphine

pH	6	7.25
t_{first} (hr)	0.75	0.75
C_{first} (ng/mL)	0.0521	0.0845
t_{max} (hr)	3	3
C_{max} (ng/mL)[1]	1.05	0.86

EQUIVALENTS

[0122] Numerous modifications and alternative embodiments of the present invention will be apparent to those skilled in the art in view of the foregoing description. Accordingly, this description is to be construed as illustrative only and is for the purpose

of teaching those skilled in the art the best mode for carrying out the present invention. Details of the structure may vary substantially without departing from the spirit of the invention, and exclusive use of all modifications that come within the scope of the appended claims is reserved. It is intended that the present invention be limited only to the extent required by the appended claims and the applicable rules of law.

[0123] All literature and similar material cited in this application, including, patents, patent applications, articles, books, treatises, dissertations and web pages, regardless of the format of such literature and similar materials, are expressly incorporated by reference in their entirety. In the event that one or more of the incorporated literature and similar materials differs from or contradicts this application, including defined terms, term usage, described techniques, or the like, this application controls.

[0124] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described in any way.

[0125] While the present inventions have been described in conjunction with various embodiments and examples, it is not intended that the present teachings be limited to such embodiments or examples. On the contrary, the present inventions encompass various alternatives, modifications, and equivalents, as will be appreciated by those of skill in the art.

[0126] The claims should not be read as limited to the described order or elements unless stated to that effect. It should be understood that various changes in form and detail may be made without departing from the scope of the appended claims. Therefore, all embodiments that come within the scope and spirit of the following claims and equivalents thereto are claimed.

Claims:

1. A method for enhancing direct transmucosal delivery of a fentanyl or fentanyl derivative to a subject, said method comprising:

administering a bioerodable drug delivery device to an oral mucosal surface of a subject, the device comprising: a fentanyl or fentanyl derivative disposed in a mucoadhesive polymeric diffusion environment; and a barrier environment disposed relative to the polymeric diffusion environment such that a unidirectional gradient is created upon application to the mucosal surface and the fentanyl or fentanyl derivative is delivered to the subject.

2. A method for treating pain in a subject comprising transmucosally administering to a subject a therapeutically effective amount of a fentanyl or fentanyl derivative disposed in a mucoadhesive polymeric diffusion environment such that the effective amount of the fentanyl or fentanyl derivative is delivered in less than about 30 minutes.

3. The method of any of the preceding claims wherein chronic pain is alleviated in the subject.

4. The method of any of the preceding claims wherein acute pain is alleviated in the subject.

5. The method or device of any of the preceding claims, wherein the pain is breakthrough cancer pain.

6. A mucoadhesive delivery device suitable for direct transmucosal administration of an effective amount of a fentanyl or fentanyl derivative to a subject, the mucoadhesive device comprising: a fentanyl or fentanyl derivative disposed in a polymeric diffusion environment; and a barrier environment disposed relative to the polymeric diffusion environment such that a unidirectional gradient is upon application to a mucosal surface.

7. A transmucosal delivery device that delivers a fentanyl or fentanyl derivative with at least 50% direct buccal absorption and an absolute bioavailability of at least about 70%.

8. A transmucosal delivery device that delivers a fentanyl or fentanyl derivative directly to the mucosa to achieve onset of pain relief (T_{first}) of about 0.20 hours or less and time to peak plasma concentration (T_{max}) of about 1.6 hours or more.

9. A device comprising about 800 μg of fentanyl, which exhibits upon transmucosal administration to a subject at least one *in vivo* plasma profile selected from the group consisting of:

a C_{max} of about 1.10 ng/mL or more;

a T_{first} of about 0.20 hours or less; and

an AUC_{0-24} of about 10.00 hr·ng/mL or more.

10. A transmucosal delivery device comprising a fentanyl or fentanyl derivative that delivers the fentanyl or fentanyl derivative in an amount effective to treat pain, wherein oral irritation, oral ulceration and/or constipation associated with the delivery of the fentanyl or fentanyl derivative is insignificant or eliminated.

11. The method or device of any of the preceding claims, wherein the pH of the mucoadhesive polymeric diffusion environment is between about 6.5 and about 8.

12. The method or device of any of the preceding claims, wherein the pH of the mucoadhesive polymeric diffusion environment is about 7.25.

13. The method or device of any of the preceding claims, wherein the device comprises about 800 μg of fentanyl.

14. The method or device of any of the preceding claims, wherein the device further comprises at least one additional layer that facilitates unidirectional delivery of the fentanyl or fentanyl derivative to the mucosa.

15. The method or device of any of the preceding claims, wherein the fentanyl is fentanyl citrate.

16. The method or device of any of the preceding claims, wherein more than 30% of the fentanyl in the device becomes systemically available via mucosal absorption.

17. The method or device of any of the preceding claims, wherein more than 55% of the fentanyl in the device becomes systemically available.

18. A method for enhancing direct transmucosal delivery of buprenorphine to a subject, said method comprising:

administering a bioerodable drug delivery device to an oral mucosal surface of the subject, the device comprising: buprenorphine disposed in a mucoadhesive polymeric diffusion environment; and a barrier environment disposed relative to the

polymeric diffusion environment such that a unidirectional gradient is created upon application to the mucosal surface, and the buprenorphine is delivered to the subject.

19. A method for treating pain in a subject comprising transmucosally administering to a subject a therapeutically effective amount of buprenorphine disposed in a mucoadhesive polymeric diffusion environment such that the effective amount of the buprenorphine is delivered in less than about 30 minutes.

20. The method of any of the preceding claims wherein chronic pain is alleviated in the subject.

21. The method of any of the preceding claims wherein acute pain is alleviated in the subject.

22. A mucoadhesive delivery device suitable for direct transmucosal administration of an effective amount of buprenorphine to a subject, the mucoadhesive device comprising: buprenorphine derivative disposed in a polymeric diffusion environment; and a barrier environment disposed relative to the polymeric diffusion environment such that a unidirectional gradient is created upon application to a mucosal surface.

23. The method or device of any of claims 18-22, wherein the pH is between about 4.0 and about 7.5.

24. The method or device of any of claims 18-23, wherein the pH is about 6.0.

25. The method or device of any of claims 18-24, wherein the pH is about 7.25.

26. The method or device of any of claims 18-25, wherein the device further comprises at least one additional layer that facilitates unidirectional delivery of the buprenorphine to the mucosa.

27. The method or device of any of the preceding claims, wherein the device comprises a pH buffering agent.

28. The method or device of any of the preceding claims, wherein the device is adapted for buccal administration.

29. The method or device of any of the preceding claims, wherein the device is adapted for sublingual administration.

30. The method or device of any of the preceding claims, wherein the device is a mucoadhesive disc.

31. The method or device of any of the preceding claims, wherein the medicament is formulated as a mucoadhesive film formed to delineate different dosages.

32. The method or device of any of the preceding claims, wherein the device comprises a backing layer disposed adjacent to the mucoadhesive polymeric diffusion environment.

33. The method or device of any of the preceding claims, wherein the device further comprises an opioid antagonist.

34. The method or device of any of the preceding claims, wherein the device further comprises naloxone.

35. The method or device of any of the preceding claims, wherein the device is a layered, flexible device.

36. The method or device of any of the preceding claims, wherein the mucoadhesive polymeric diffusion environment has a buffered environment for the transmucosal administration.

37. The method or device of any of the preceding claims, wherein there is substantially no irritation at the site of transmucosal administration.

38. The method or device of any of the preceding claims, wherein there is about a 50% decrease in pain over about 30 minutes.

39. The method or device of any of the preceding claims, wherein the polymeric diffusion environment comprises at least one ionic polymer system.

40. The method or device of claim 39, wherein the ionic polymer system is selected from the group consisting of POLYCARBOPHIL, sodium carboxymethylcellulose and mixtures thereof.

41. The method or device of any of the preceding claims, wherein the polymeric diffusion environment comprises a buffer system.

42. The method or device of claim 41, wherein the buffer system comprises citric acid, sodium benzoate or mixtures thereof.

43. The method or device of any of the preceding claims, wherein the device has a thickness such that it exhibits minimal mouth feel.

44. The method or device of any of the preceding claims, wherein the device has a thickness of about 0.25 mm.

45. A flexible, bioerodable mucoadhesive delivery device suitable for direct transmucosal administration of an effective amount of a fentanyl, fentanyl derivative, buprenorphine or buprenorphine derivative to a subject, the mucoadhesive device comprising:

a mucoadhesive layer comprising a fentanyl, fentanyl derivative, buprenorphine or buprenorphine derivative disposed in a polymeric diffusion environment, wherein the polymeric diffusion environment has a pH of about 7.25 for the fentanyl or fentanyl derivative or a pH of about 6 for the buprenorphine or buprenorphine derivative; and

a backing layer comprising a barrier environment which is disposed adjacent to and coterminous with the mucoadhesive layer,

wherein the device has no or minimal mouth feel and is able to transmucosally deliver the effective amount of the , fentanyl derivative, buprenorphine or buprenorphine derivative in less than about 30 minutes; and

wherein a unidirectional gradient is created upon application of the device to a mucosal surface.

Figure 1. Mean Fentanyl Concentration-Time Plots For Three Exemplary Devices of the Invention and OTFC

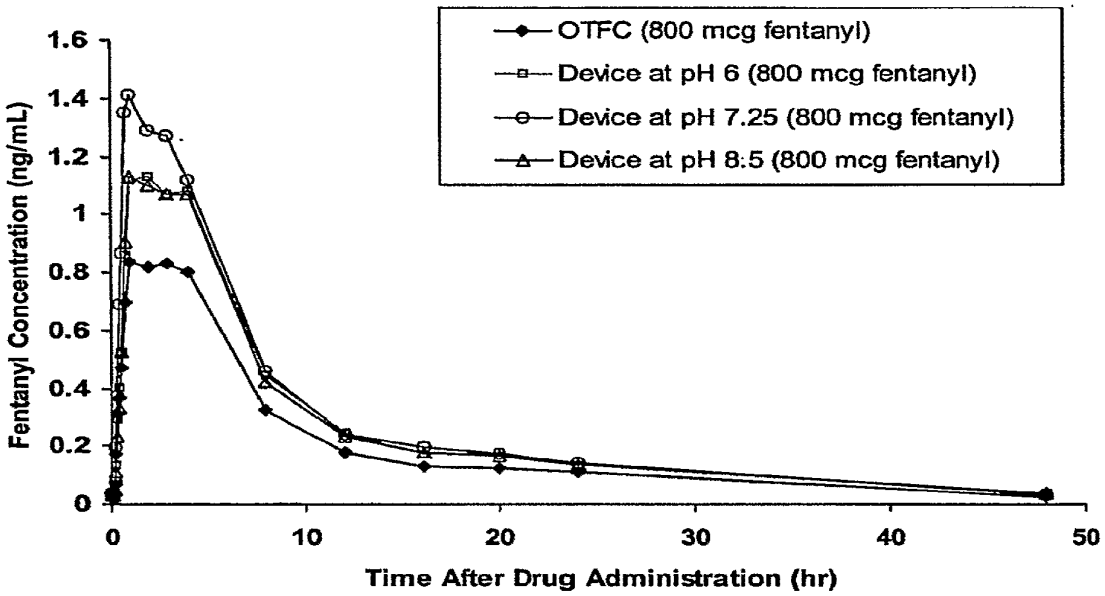


Figure 2. Mean (SD) Fentanyl Concentration Over Time Comparing an Exemplary Device According To The Present Invention and OTFC

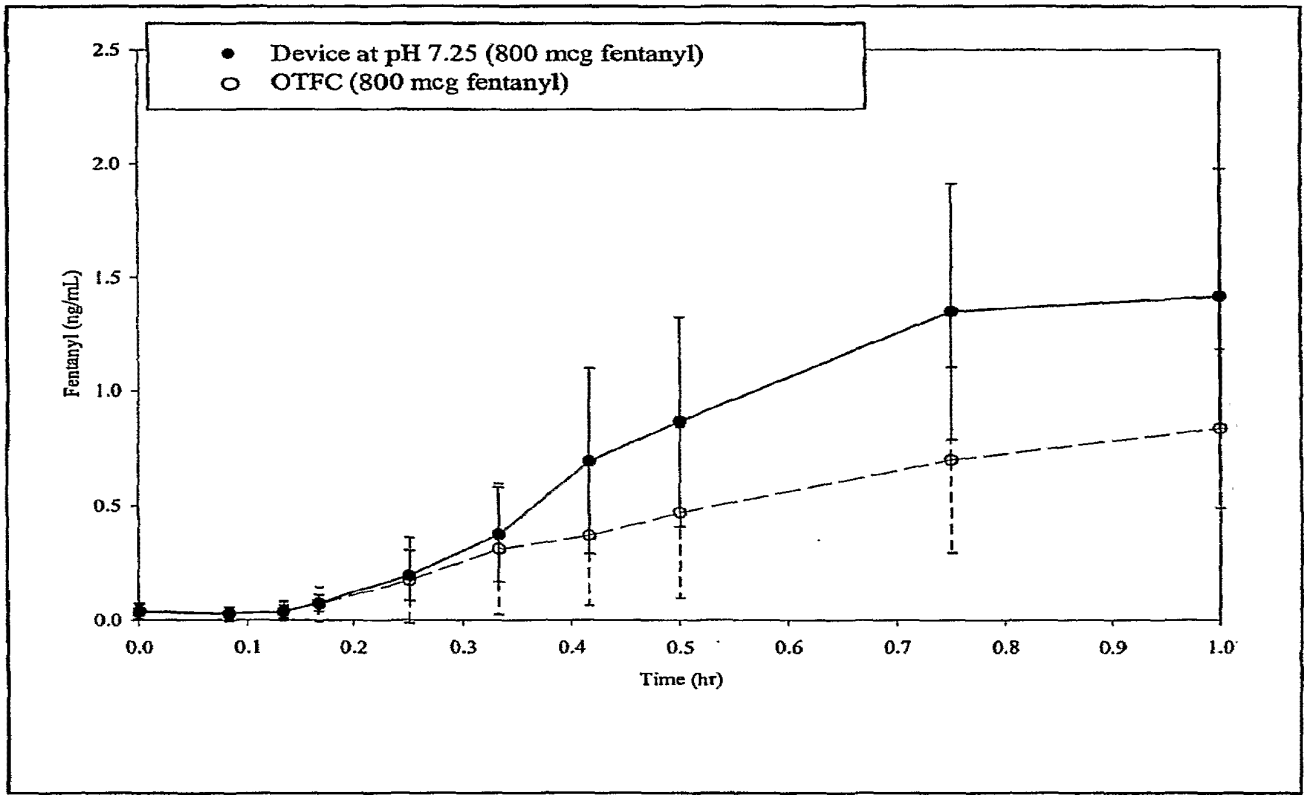


Figure 3. Mean (SD) Buprenorphine Concentration Over Time Comparing an Exemplary Device According To The Present Invention and Conventional Buprenorphine Delivery

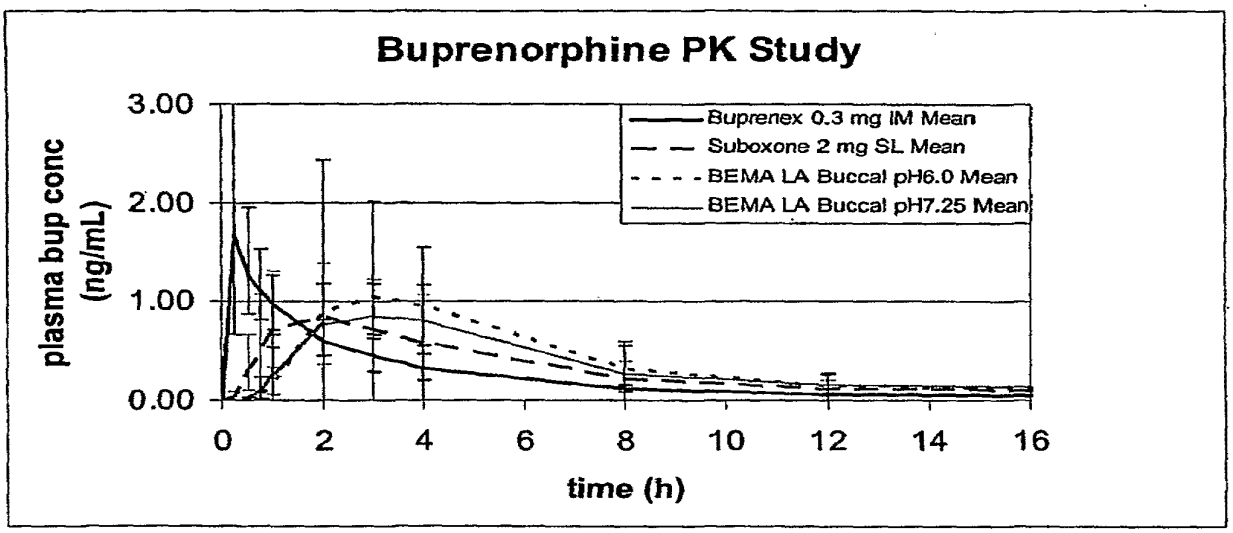


Figure 4: Exemplary Embodiments of the Present Invention

Figure 4A

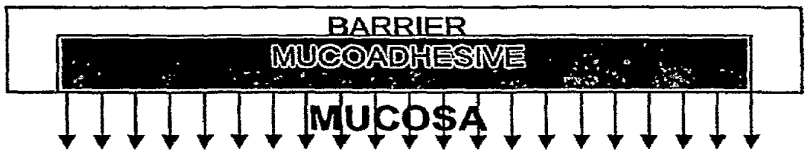


Figure 4B

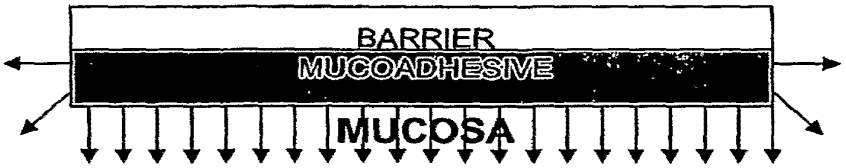
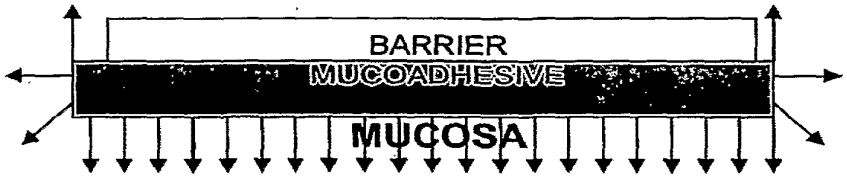


Figure 4C



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(74) Agents: **HANLEY, Elizabeth, A.** et al.; Lahive & Cockfield, Llp, One Post Office Square, Boston, MA 02109-2127 (US).

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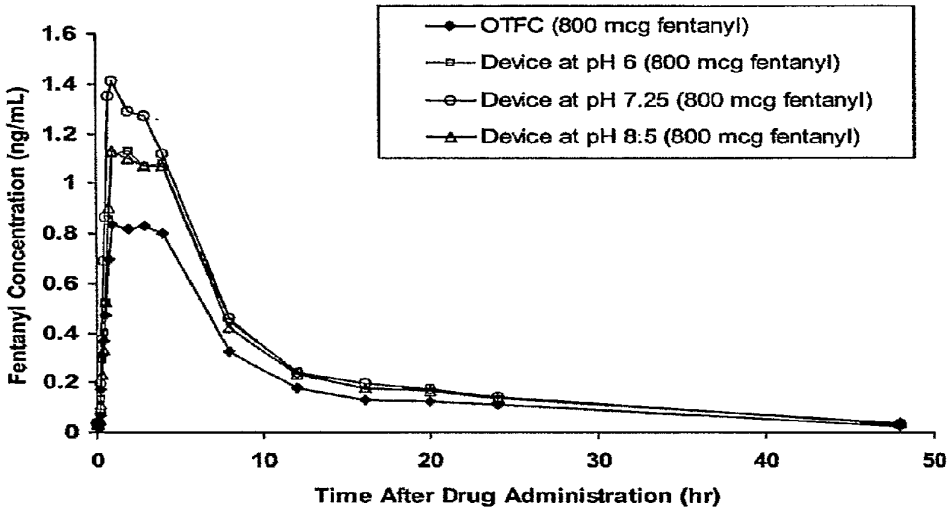
[Continued on next page]

(54) Title: TRANSMUCOSAL DELIVERY DEVICES WITH ENHANCED UPTAKE

Mean Fentanyl Concentration-Time Plots For Three Exemplary Devices of the Invention and OTFC



(57) Abstract: The present invention provides methods for enhancing transmucosal uptake of a medicament, e.g., fentanyl or buprenorphine, to a subject and related devices. The method includes administering to a subject a transmucosal drug delivery device comprising the medicament. Also provided are devices suitable for transmucosal administration of a medicament to a subject and methods of their administration and use. The devices include a medicament disposed in a mucoadhesive polymeric diffusion environment and a barrier environment.

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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[X] Further documents are listed in the continuation of Box C.

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/58447 A (EURO CELTIQUE SA [LU]; OSHLACK BENJAMIN [US]; CURTIS WRIGHT [US]) 16 August 2001 (2001-08-16) example 11	18-22, 30, 32-35, 37,43
Y	example 11	11,12, 23-25, 27,36, 41,42,45
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Y	claims 1,2,4,22; table 1	11,12, 23-25, 27,36, 41,42,45
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P,X	WO 2007/070632 A (BIODELIVERY SCIENCES INTERNATI [US]; FINN ANDREW [US]; VASISHT NIRAJ [ ) 21 June 2007 (2007-06-21) cited in the application claims; examples	1-4,6, 10,14, 18, 20-22, 26,28, 30,32, 35,37,43

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International application No
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First Named Inventor/Applicant Name:	Garry L. Myers
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HOFFMANN & BARON, LLP
6900 JERICHO TURNPIKE
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Assignment For Published Patent Application

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Early Publication Request: No
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Title

SUBLINGUAL AND BUCCAL FILM COMPOSITIONS

Preliminary Class

514

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Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

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PATENT APPLICATION SERIAL NO._____

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE
FEE RECORD SHEET

08/20/2009 VVAN11 00000028 082461 12537571

01 FC:2201 220.00 DA

PTO-1556
(5/87)

*U.S. Government Printing Office: 2002- 489-267/69033

PTO/SB/05 (08-08)
Approved for use through 06/30/2010. OMB 0651-0032
U.S. Patent and Trademark Office. U.S. DEPARTMENT OF COMMERCE

UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No.	1199-82
First Inventor	Garry L. Myers
Title	SUBLINGUAL AND BUCCAL FILM COMPO
Express Mail Label No.	

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

1. ☐ **Fee Transmittal Form** (e.g., PTO/SB/17)
2. ☑ **Applicant claims small entity status.** See 37 CFR 1.27.
3. ☑ **Specification** [*Total Pages* 37]
   Both the claims and abstract must start on a new page
   (For information on the preferred arrangement, see MPEP 608.01(a))
4. ☐ **Drawing(s)** (*35 U.S.C. 113*) [*Total Sheets* _____]
5. **Oath or Declaration** [*Total Sheets* _____]
   a. ☑ Newly executed (original or copy)
   b. ☐ A copy from a prior application (37 CFR 1.63(d))
   (for continuation/divisional with Box 18 completed)
   i. ☐ DELETION OF INVENTOR(S)
   Signed statement attached deleting inventor(s) name in the prior application, see 37 CFR 1.63(d)(2) and 1.33(b).
6. ☑ **Application Data Sheet.** See 37 CFR 1.76
7. ☐ **CD-ROM or CD-R** in duplicate, large table or Computer Program *(Appendix)*
   ☐ Landscape Table on CD
8. **Nucleotide and/or Amino Acid Sequence Submission**
   (if applicable, items a. – c. are required)
   a. ☐ Computer Readable Form (CRF)
   b. Specification Sequence Listing on:
      i. ☐ CD-ROM or CD-R (2 copies); or
      ii. ☐ Paper
   c. ☐ Statements verifying identity of above copies

ADDRESS TO: **Commissioner for Patents**
P.O. Box 1450
Alexandria VA 22313-1450

ACCOMPANYING APPLICATION PARTS

9. ☑ **Assignment Papers** (cover sheet & document(s))
   Name of Assignee MonoSol Rx, LLC
10. ☐ **37 CFR 3.73(b) Statement** *(when there is an assignee)* ☐ **Power of Attorney**
11. ☐ **English Translation Document** *(if applicable)*
12. ☐ **Information Disclosure Statement** (PTO/SB/08 or PTO-1449)
    ☐ Copies of citations attached
13. ☐ **Preliminary Amendment**
14. ☐ **Return Receipt Postcard** (MPEP 503)
    (*Should be specifically itemized)*
15. ☐ **Certified Copy of Priority Document(s)**
    (if foreign priority is claimed)
16. ☐ **Nonpublication Request** under 35 U.S.C. 122(b)(2)(B)(i). Applicant must attach form PTO/SB/35 or equivalent.
17. ☐ Other: _____

18. If a CONTINUING APPLICATION, *check appropriate box, and supply the requisite information below and in the first sentence of the specification following the title, or in an Application Data Sheet under 37 CFR 1.76:*

☐ Continuation ☐ Divisional ☐ Continuation-in-part (CIP) of prior application No.: .....

Prior application information: *Examiner* _____ *Art Unit:* _____

19. CORRESPONDENCE ADDRESS

☑ The address associated with Customer Number: 23869 ***OR*** ☐ Correspondence address below

Name					
Address					
City		State		Zip Code	
Country		Telephone		Email	

Signature	/Jon A. Chiodo, Reg. No. 52,739/	Date	August 7, 2009
Name (Print/Type)	Jon A. Chiodo	Registration No. (Attorney/Agent)	52739

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1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

PTO/SB/14 (07-07)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	1199-82
	Application Number	
Title of Invention	SUBLINGUAL AND BUCCAL FILM COMPOSITIONS	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Applicant Information:

Applicant 1 Remove

Applicant Authority ◉ Inventor ○ Legal Representative under 35 U.S.C. 117 ○ Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
	Garry	L.	Myers	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Kingsport	State/Province	TN	Country of Residence i	US

Citizenship under 37 CFR 1.41(b) i: US

Mailing Address of Applicant:

Address 1	908 Colfax Avenue		
Address 2			
City	Kingsport	State/Province	TN
Postal Code	37660	Country i	US

Applicant 2 Remove

Applicant Authority ◉ Inventor ○ Legal Representative under 35 U.S.C. 117 ○ Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
	Samuel	D.	Hilbert	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Jonesboro	State/Province	TN	Country of Residence i	US

Citizenship under 37 CFR 1.41(b) i: US

Mailing Address of Applicant:

Address 1	210 Mulberry Lane		
Address 2			
City	Jonesboro	State/Province	TN
Postal Code	37659	Country i	US

Applicant 3 Remove

Applicant Authority ◉ Inventor ○ Legal Representative under 35 U.S.C. 117 ○ Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
	Bill	J.	Boone	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Johnson City	State/Province	TN	Country of Residence i	US

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	1199-82
	Application Number	
Title of Invention	SUBLINGUAL AND BUCCAL FILM COMPOSITIONS	

Citizenship under 37 CFR 1.41(b) i					
Mailing Address of Applicant:					
Address 1	900 Carroll Creek Road				
Address 2					
City	Johnson City	**State/Province**	TN		
Postal Code	37601	**Country**i	US		

Applicant 4 Remove

Applicant Authority ◉ Inventor	○ Legal Representative under 35 U.S.C. 117	○ Party of Interest under 35 U.S.C. 118			
Prefix	**Given Name**	**Middle Name**	**Family Name**	**Suffix**	
	B.	Arlie	Bogue		
Residence Information (Select One) ◉ US Residency	○ Non US Residency	○ Active US Military Service			
City	New Carlisle	**State/Province**	IN	**Country of Residence** i	US
Citizenship under 37 CFR 1.41(b) i	US				
Mailing Address of Applicant:					
Address 1	5306 N. Fox Hollow				
Address 2					
City	New Carlisle	**State/Province**	IN		
Postal Code	46552	**Country**i	US		

Applicant 5 Remove

Applicant Authority ◉ Inventor	○ Legal Representative under 35 U.S.C. 117	○ Party of Interest under 35 U.S.C. 118			
Prefix	**Given Name**	**Middle Name**	**Family Name**	**Suffix**	
	Pradeep		Sanghvi		
Residence Information (Select One) ◉ US Residency	○ Non US Residency	○ Active US Military Service			
City	Schererville	**State/Province**	IN	**Country of Residence** i	US
Citizenship under 37 CFR 1.41(b) i	US				
Mailing Address of Applicant:					
Address 1	7409 Bell Street				
Address 2					
City	Schererville	**State/Province**	IN		
Postal Code	46375	**Country**i	US		

Applicant 6 Remove

Applicant Authority ◉ Inventor	○ Legal Representative under 35 U.S.C. 117	○ Party of Interest under 35 U.S.C. 118			
Prefix	**Given Name**	**Middle Name**	**Family Name**	**Suffix**	
	Madhusudan		Hariharan		
Residence Information (Select One) ◉ US Residency	○ Non US Residency	○ Active US Military Service			
City	Munster	**State/Province**	IN	**Country of Residence** i	IS
Citizenship under 37 CFR 1.41(b) i	US				

PTO/SB/14 (07-07)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	1199-82
	Application Number	
Title of Invention	SUBLINGUAL AND BUCCAL FILM COMPOSITIONS	

Mailing Address of Applicant:			
Address 1	1746 Redwood Court		
Address 2			
City	Munster	**State/Province**	IN
Postal Code	46321	**Country**[i]	US

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below. For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	23869		
Email Address		Add Email	Remove Email

Application Information:

Title of the Invention	SUBLINGUAL AND BUCCAL FILM COMPOSITIONS		
Attorney Docket Number	1199-82	**Small Entity Status Claimed**	☒
Application Type	Nonprovisional		
Subject Matter	Utility		
Suggested Class (if any)		**Sub Class (if any)**	
Suggested Technology Center (if any)			
Total Number of Drawing Sheets (if any)		**Suggested Figure for Publication (if any)**	

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S. C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Enter either Customer Number or complete the Representative Name section below. If both sections are completed the Customer Number will be used for the Representative Information during processing.

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	23869		

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	1199-82
	Application Number	
Title of Invention	SUBLINGUAL AND BUCCAL FILM COMPOSITIONS	

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, or 365(c) or indicate National Stage entry from a PCT application. Providing this information in the application data sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78(a)(2) or CFR 1.78(a)(4), and need not otherwise be made part of the specification.

Prior Application Status			Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button. Add

Foreign Priority Information:

This section allows for the applicant to claim benefit of foreign priority and to identify any prior foreign application for which priority is not claimed. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55(a).

Remove

Application Number	Country [i]	Parent Filing Date (YYYY-MM-DD)	Priority Claimed
			(•) Yes ( ) No

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button. Add

Assignee Information:

Providing this information in the application data sheet does not substitute for compliance with any requirement of part 3 of Title 37 of the CFR to have an assignment recorded in the Office.

Assignee 1 Remove

If the Assignee is an Organization check here.	[X]		
Organization Name	MonoSol Rx, LLC		
Mailing Address Information:			
Address 1	6560 Melton Road		
Address 2			
City	Portage	**State/Province**	IN
Country [i]	US	Postal Code	46368
Phone Number		Fax Number	
Email Address			

Additional Assignee Data may be generated within this form by selecting the **Add** button. Add

Signature:

A signature of the applicant or representative is required in accordance with 37 CFR 1.33 and 10.18. Please see 37 CFR 1.4(d) for the form of the signature.

Signature	/Jon A. CHIODO, Reg. No. 52,739/	Date (YYYY-MM-DD)	2009-08-07

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	1199-82
	Application Number	
Title of Invention	SUBLINGUAL AND BUCCAL FILM COMPOSITIONS	

First Name	Jon A.	Last Name	Chiodo	Registration Number	52739

This collection of information is required by 37 CFR 1.76. 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 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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The information provided by you in this form will be subject to the following routine uses:

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3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

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6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

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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.

SUBLINGUAL AND BUCCAL FILM COMPOSITIONS

FIELD OF THE INVENTION

[0001] The present invention relates to compositions, methods of manufacture, products and methods of use relating to films containing therapeutic actives. The invention more particularly relates to self-supporting film dosage forms which provide a therapeutically effective dosage, essentially matching that of currently-marketed tablets containing the same active. Such compositions are particularly useful for treating narcotic dependence while providing sufficient buccal adhesion of the dosage form.

BACKGROUND OF THE RELATED TECHNOLOGY

[0002] Oral administration of two therapeutic actives in a single dosage form can be complex if the intention is to have one active absorbed into the body and the other active remain substantially unabsorbed. For example, one active may be relatively soluble in the mouth at one pH, and the other active may be relatively insoluble at the same pH. Moreover, the absorption kinetics of each therapeutic agent may be substantially different due to differing absorption of the charged and uncharged species. These factors represent some of the challenges in appropriately co-administering therapeutic agents.

[0003] Co-administration of therapeutic agents has many applications. Among such areas of treatment include treating individuals who suffer from narcotic dependence. Such individuals have a tendency to suffer from serious physical dependence on the narcotic, resulting in potentially dangerous withdrawal effects when the narcotic is not administered to the individual. In order to help individuals addicted to narcotics, it is known to provide a reduced level of a drug, which provides an effect of satisfying the body's urge for the narcotic, but does not provide the "high" that is provided by the misuse of the narcotic. The drug provided may be an agonist or a partial agonist, which provides a reduced sensation and may help lower dependence on the drug. However, even though these drugs provide only a low level of euphoric effect, they are capable of being abused by the individuals parenterally. In such cases, it is desirable to provide a combination of the drug with a second drug, which may decrease the likelihood of diversion and abuse of the first drug. For example, it is known to provide a dosage of an antagonist in combination with the agonist or partial agonist. The narcotic antagonist

binds to a receptor in the brain to block the receptor, thus reducing the effect of the agonist.

[0004] One such combination of drugs has been marketed under the trade name Suboxone® as an orally ingestible tablet. However, such combinations in tablet form have the potential for abuse. In some instances, the patient who has been provided the drug may store the tablet in his mouth without swallowing the tablet, then later extract the agonist from the tablet and inject the drug into an individual's body. Although certain antagonists (such as highly water-soluble antagonists) may be used to help reduce the ability to separate the agonist, the potential for abuse still exists. It is desired to provide a dosage that cannot be easily removed from the mouth once it has been administered.

[0005] There is currently a need for an orally dissolvable film dosage form that provides the desired absorption levels of the agonist and antagonist, while providing an adhesive effect in the mouth, rendering it difficult to remove once placed in the mouth, thereby making abuse of the agonist difficult.

SUMMARY OF THE INVENTION

[0006] In one embodiment of the present invention, there is provided a film dosage composition including: a polymeric carrier matrix; a therapeutically effective amount of buprenorphine or a pharmaceutically acceptable salt thereof; a therapeutically effective amount of naloxone or a pharmaceutically acceptable salt thereof; and a buffer in an amount to provide a pH of the composition of a value sufficient to optimize absorption of the buprenorphine.

[0007] In another embodiment of the present invention, there is provided a film dosage composition including: a polymeric carrier matrix; a therapeutically effective amount of buprenorphine or a pharmaceutically acceptable salt thereof; a therapeutically effective amount of naloxone or a pharmaceutically acceptable salt thereof; and a buffer in an amount sufficient to inhibit the absorption of the naloxone when administered orally.

[0008] In still other embodiments, there may be provided a film dosage composition including: a polymeric carrier matrix; a therapeutically effective amount of buprenorphine or a pharmaceutically acceptable salt thereof; a therapeutically effective amount of naloxone or a pharmaceutically acceptable salt thereof; and a buffering system; where the buffering system includes a buffer capacity sufficient to maintain the

ionization of naloxone during the time which the composition is in the oral cavity of a user.

[0009] In another embodiment of the invention, there is provided a method of treating narcotic dependence of a user, including the steps of: providing a composition including: a polymeric carrier matrix; a therapeutically effective amount of buprenorphine or a pharmaceutically acceptable salt thereof; a therapeutically effective amount of naloxone or a pharmaceutically acceptable salt thereof; and a buffer in an amount to provide a pH of the composition of a value sufficient to optimize absorption of the buprenorphine; and administering the composition to the oral cavity of a user.

[0010] In still another embodiment of the invention, there is provided a process of forming a film dosage composition including the steps of: casting a film-forming composition, the film-forming composition including: a polymeric carrier matrix; a therapeutically effective amount of buprenorphine or a pharmaceutically acceptable salt thereof; a therapeutically effective amount of naloxone or a pharmaceutically acceptable salt thereof; and a buffer in an amount to provide a pH of the composition of a value sufficient to optimize absorption of the buprenorphine and drying the film-forming composition to form a self-supporting film dosage composition.

[0011] In another embodiment, there is provided a film dosage composition including a therapeutically sufficient amount of buprenorphine or a pharmaceutically acceptable salt thereof and a therapeutically sufficient amount of naloxone or a pharmaceutically acceptable salt thereof, the film dosage composition having a bioequivalent release profile as compared to a Suboxone® tablet containing about 2 times the amount of buprenorphine or a pharmaceutically acceptable salt thereof.

[0012] Still other embodiments of the present invention provide an orally dissolving film formulation including buprenorphine and naloxone, where the formulation provides an in-vivo plasma profile having a Cmax of between about 0.624 ng/ml and about 5.638 ng/ml for buprenorphine and an in-vivo plasma profile having a Cmax of between about 41.04 pg/ml to about 323.75 pg/ml for naloxone.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Definitions

[0013] As used herein, the term Cmax refers to the mean maximum plasma concentration after administration of the composition to a human subject. As also used herein, the term AUC refers to the mean area under the plasma concentration-time curve value after administration of the compositions formed herein. As will be set forth in more detail below, the term "optimizing the absorption" does not refer to reaching the maximum absorption of the composition, and rather refers to reaching the optimum level of absorption at a pH of about 2 to about 4. The "optimum" absorption may be, for example, a level that provides a bioequivalent absorption as administration of the currently available Suboxone® tablet. An "optimum" Cmax of buprenorphine is about 0.67 to about 5.36 mg/ml at dosages of from 2-16 mg buprenorphine at a given pH. Similarly, an "optimum" AUC of buprenorphine may be about 7.43 to about 59.46 hr*ng/ml at dosages of from 2-16 mg buprenorphine at a given pH. As will be described in more detail below, it has been surprisingly discovered that the absorption of one particular agonist, buprenorphine, can provide an optimum absorption at a pH of about 2-4 as well as about 5.5-6.5. Thus, one may "optimize" the absorption of buprenorphine by providing a pH of about 2-4 or about 5.5-6.5.

[0014] "Maximizing the absorption" refers to the maximum in vivo absorption values achieved at a pH of about 4 to about 9.

[0015] The term "local pH" refers to the pH of the region of the carrier matrix immediately surrounding the active agent as the matrix hydrates and/or dissolves, for example, in the mouth of the user.

[0016] By "inhibiting" the absorption of an active, it is meant achieving as complete an ionization state of the active as possible, such that little to none of the active is measurably absorbable. For example, at a pH of 3-3.5, the Cmax of an active such as naloxone for dosage of 0.5 mg to 4.0 mg ranges from 32.5 to 260 pg/ml, and an AUC of naloxone for dosage of 0.5 mg to 4.0 mg ranges from 90.55 to 724.4 hr*pg/ml. It is understood that at a pH lower than 3.0, further ionization would be expected and thus result in lower absorption.

[0017] The term "bioequivalent" means obtaining 80% to 125% of the Cmax and AUC values for a given active in a different product. For example, assuming Cmax and AUC values of buprenorphine for a commercially-available Suboxone® tablet (containing 2 mg buprenorphine and 0.5 mg naloxone) are 0.780 ng/ml and 6.789 hr*ng/ml, respectively, a bioequivalent product would have a Cmax of buprenorphine in the range of 0.624-0.975 ng/ml, and an AUC value of buprenorphine of 5.431-8.486 hr*ng/ml.

[0018] It will be understood that the term "film" includes thin films and sheets, in any shape, including rectangular, square, or other desired shape. The films described herein may be any desired thickness and size such that it may be placed into the oral cavity of the user. For example, the films may have a relatively thin thickness of from about 0.1 to about 10 mils, or they may have a somewhat thicker thickness of from about 10 to about 30 mils. For some films, the thickness may be even larger, i.e., greater than about 30 mils. Films may be in a single layer or they may be multi-layered, including laminated films.

[0019] Oral dissolving films generally fall into three main classes: fast dissolving, moderate dissolving and slow dissolving. Fast dissolving films generally dissolve in about 1 second to about 30 seconds in the mouth. Moderate dissolving films generally dissolve in about 1 to about 30 minutes in the mouth, and slow dissolving films generally dissolve in more than 30 minutes in the mouth. Fast dissolving films may consist of low molecular weight hydrophilic polymers (i.e., polymers having a molecular weight between about 1,000 to 9,000, or polymers having a molecular weight up to 200,000). In contrast, slow dissolving films generally have high molecular weight polymers (i.e., having a molecular weight in the millions).

[0020] Moderate dissolving films tend to fall in between the fast and slow dissolving films. Moderate dissolving films dissolve rather quickly, but also have a good level of mucoadhesion. Moderate dissolving films are also flexible, quickly wettable, and are typically non-irritating to the user. For the instant invention, it is preferable to use films that fall between the categories of fast dissolving and moderate dissolving. Such moderate dissolving films provide a quick enough dissolution rate, most desirably between about 1 minute and about 20 minutes, while providing an acceptable

mucoadhesion level such that the film is not easily removable once it is placed in the oral cavity of the user.

[0021] Inventive films described herein may include one or more agonists or partial agonists used for the treatment of drug addiction. As used herein, the term "agonist" refers to a chemical substance that is capable of providing a physiological response or activity in the body of the user. The films described herein may further include one or more antagonists. As used herein, the term "antagonist" refers to any chemical substance that acts within the body of the user to reduce the physiological activity of another chemical substance. In some embodiments, an antagonist used herein may act to reduce and/or block the physiological activity of the agonist. The actives may be water-soluble, or they may be water-insoluble. As used herein, the term "water-soluble" refers to substances that are at least partially dissolvable in a solvent, including but not limited to water. The term "water-soluble" does not necessarily mean that the substance is 100% dissolvable in the solvent. The term "water-insoluble" refers to substances that are not dissolvable in a solvent, including but not limited to water. Solvents may include water, or alternatively may include other polar solvents by themselves or in combination with water.

Inventive Films

[0022] The present invention relates to methods of treating narcotic dependence in an individual. More desirably, the invention relates to the treatment of opioid dependence in an individual, while using a formulation and delivery that hinders misuse of the narcotic. Currently, treatment of opioid dependence is aided by administration of Suboxone®, which is an orally dissolvable tablet. This tablet which provides a combination of buprenorphine (an opioid agonist) and naloxone (an opioid antagonist). Therefore, the present invention provides a method of treating narcotic dependence by providing an orally dissolvable film dosage, which provides a bioequivalent effect to Suboxone®. The film dosage preferably provides buccal adhesion while it is in the user's mouth, rendering it difficult to remove after placement.

[0023] The film dosage composition preferably includes a polymeric carrier matrix. Any desired polymeric carrier matrix may be used, provided that it is orally dissolvable. Desirably, the dosage should have enough bioadhesion to not be easily removed and it

should form a gel like structure when administered. The orally consumable films are preferably moderate-dissolving in the oral cavity and particularly suitable for delivery of actives, although both fast and sustained release compositions are also among the various embodiments contemplated.

[0024] The films used in the pharmaceutical products may be produced by a combination of at least one polymer and a solvent, optionally including other fillers known in the art. The solvent may be water, a polar organic solvent including, but not limited to, ethanol, isopropanol, acetone, or any combination thereof. In some embodiments, the solvent may be a non-polar organic solvent, such as methylene chloride. The film may be prepared by utilizing a selected casting or deposition method and a controlled drying process. For example, the film may be prepared through controlled drying processes, which include application of heat and/or radiation energy to the wet film matrix to form a visco-elastic structure, thereby controlling the uniformity of content of the film. Such processes are described in more detail in commonly assigned U.S. Application No. 10/074,272, filed on February 14, 2002, and published as U.S. Patent Publication No. 2003/0107149 A1, the contents of which are incorporated herein by reference in their entirety. Alternatively, the films may be extruded as described in commonly assigned U.S. Application No. 10/856,176, filed on May 28, 2004, and published as U.S. Patent Publication No. 2005/0037055 A1, the contents of which are incorporated herein by reference in their entirety.

[0025] The polymer included in the films may be water-soluble, water-swellable, water-insoluble, or a combination of one or more either water-soluble, water-swellable or water-insoluble polymers. The polymer may include cellulose or a cellulose derivative. Specific examples of useful water-soluble polymers include, but are not limited to, polyethylene oxide, pullulan, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, polyvinyl pyrrolidone, carboxymethyl cellulose, polyvinyl alcohol, sodium alginate, 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. For higher dosages, it may be desirable to incorporate a polymer that provides a high level of viscosity as compared to lower dosages.

[0026] 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. In some embodiments, films formed from such water-soluble polymers may be sufficiently water-soluble to be dissolvable upon contact with bodily fluids.

[0027] Other polymers useful for incorporation into the films include biodegradable polymers, copolymers, block polymers and combinations thereof. It is understood that the term "biodegradable" is intended to include materials that chemically degrade, as opposed to materials that physically break apart (i.e., bioerodable materials). Among the known useful polymers or polymer classes which meet the above criteria are: poly(glycolic acid) (PGA), poly(lactic acid) (PLA), polydioxanes, 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.

[0028] 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).

[0029] The Biodel materials represent a family of various polyanhydrides which differ chemically.

[0030] Although a variety of different polymers may be used, it is desired to select polymers that provide mucoadhesive properties to the film, as well as a desired dissolution and/or disintegration rate. In particular, the time period for which it is desired to maintain the film in contact with the mucosal tissue depends on the type of active contained in the composition. Some actives may only require a few minutes for delivery through the mucosal tissue, whereas other actives may require up to several hours or even longer. Accordingly, in some embodiments, one or more water-soluble polymers, as described above, may be used to form the film. In other embodiments, however, it may be desirable to use combinations of water-soluble polymers and polymers that are water-swellable, water-insoluble and/or biodegradable, as provided above. The inclusion of one or more polymers that are water-swellable, water-insoluble and/or biodegradable may provide films with slower dissolution or disintegration rates than films formed from water-soluble polymers alone. As such, the film may adhere to the mucosal tissue for longer periods or time, such as up to several hours, which may be desirable for delivery of certain active components.

[0031] Desirably, the individual film dosage has a small size, which is between about 0.5-1 inch by about 0.5-1 inch. Most preferably, the film dosage is about 0.75 inches x 0.5 inches. The film dosage should have good adhesion when placed in the buccal cavity

or in the sublingual region of the user. Further, the film dosage should disperse and dissolve at a moderate rate, most desirably dispersing within about 1 minute and dissolving within about 3 minutes. In some embodiments the film dosage may be capable of dispersing and dissolving at a rate of between about 1 to about 1.5 minutes.

[0032] For instance, in some embodiments, the films may include polyethylene oxide alone or in combination with a second polymer component. The second polymer may be another water-soluble polymer, a water-swellable polymer, a water-insoluble polymer, a biodegradable polymer or any combination thereof. Suitable water-soluble polymers include, without limitation, any of those provided above. In some embodiments, the water-soluble polymer may include hydrophilic cellulosic polymers, such as hydroxypropyl cellulose and/or hydroxypropylmethyl cellulose. In accordance with some embodiments, polyethylene oxide may range from about 20% to 100% by weight in the polymer component, more specifically about 30% to about 70% by weight, and even more specifically about 40% to about 60% by weight. In some embodiments, one or more water-swellable, water-insoluble and/or biodegradable polymers also may be included in the polyethylene oxide-based film. Any of the water-swellable, water-insoluble or biodegradable polymers provided above may be employed. The second polymer component may be employed in amounts of about 0% to about 80% by weight in the polymer component, more specifically about 30% to about 70% by weight, and even more specifically about 40% to about 60% by weight.

[0033] The molecular weight of the polyethylene oxide also may be varied. In some embodiments, high molecular weight polyethylene oxide, such as about 4 million, may be desired to increase mucoadhesivity of the film. In some other embodiments, the molecular weight may range from about 100,000 to 900,000, more specifically from about 100,000 to 600,000, and even more specifically from about 100,000 to 300,000. In some embodiments, it may be desirable to combine high molecular weight (600,000 to 900,000) with low molecular weight (100,000 to 300,000) polyethylene oxide in the polymer component.

[0034] A variety of optional components and fillers also may be added to the films. These may include, without limitation: surfactants; plasticizers; polyalcohols; anti-foaming agents, such as silicone-containing compounds, which promote a smoother film

surface by releasing oxygen from the film; thermo-setting gels such as pectin, carageenan, and gelatin, which help in maintaining the dispersion of components; inclusion compounds, such as cyclodextrins and caged molecules; coloring agents; and flavors. In some embodiments, more than one active components may be included in the film.

[0035] Additives may be included in the films. 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).

[0036] 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.

[0037] 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 film components.

[0038] Further additives may flow agents and opacifiers, 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 film components.

[0039] 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.

[0040] There may further be added compounds to improve the texture 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.

[0041] 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 film composition.

[0042] It further may be 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 flow agents and opacifiers.

[0043] Lecithin is one surface active agent for use in the films described herein. Lecithin may 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.

[0044] 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.

[0045] Further potential additives include solubility enhancing agents, such as substances that form inclusion compounds with active components. Such agents may be useful in improving the properties of very insoluble and/or unstable actives. In general, these substances are doughnut-shaped molecules with hydrophobic internal cavities and hydrophilic exteriors. Insoluble and/or instable actives may fit within the hydrophobic cavity, thereby producing an inclusion complex, which is soluble in water. Accordingly, the formation of the inclusion complex permits very insoluble and/or instable actives to be dissolved in water. A particularly desirable example of such agents are cyclodextrins, which are cyclic carbohydrates derived from starch. Other similar substances, however, are considered well within the scope of the present invention.

[0046] Suitable coloring agents 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.

[0047] 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.

[0048] 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.

[0049] 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.

[0050] 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.

[0051] Anti-foaming and/or de-foaming components may also be used with the films. These components aid in the removal of air, such as entrapped air, from the film-forming compositions. 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.

[0052] As a related matter, simethicone and related agents may be employed for densification purposes. More specifically, such agents may facilitate the removal of voids, air, moisture, and similar undesired components, thereby providing denser, and thus more uniform films. Agents or components which perform this function can be referred to as densification or densifying agents. As described above, entrapped air or undesired components may lead to non-uniform films.

[0053] 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.

[0054] 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.

[0055] In order to prevent the formation of air bubbles in the films, 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.

[0056] 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.

[0057] Any other optional components described in commonly assigned U.S. Patent No. 7,425,292 and U.S. Application No. 10/856,176, referred to above, also may be included in the films described herein.

[0058] When the dosage form includes at least one antagonist, it may be desired to control the release of the antagonist, so as to delay or wholly prevent the release of the antagonist from the dosage when taken orally. Desirably, the dosage form is a self-supporting film composition, which is placed into the oral cavity of the user. In a dosage form that is to be placed in the oral cavity, it is desired to absorb the agonist buccally, so as to provide rapid integration of the agonist into the body of the user. At the same time, it may be desired to prevent or reduce absorption of any antagonist buccally, thereby allowing the antagonist to be swallowed and destroyed in the stomach. Reducing the absorption of an antagonist may be achieved via physical means, such as by encapsulating the antagonist in a material that blocks absorption. It is desired, however, to reduce the absorption of the antagonist by chemical means, such as by controlling the local pH of the dosage.

[0059] It has been found that by controlling the local pH of the dosage form, the release and/or absorption of the actives therein may be controlled. For example, in a dosage that includes an amount of an agonist, the local pH may be controlled to a level that

maximizes its release and/or absorption into the oral cavity of the user. In dosages incorporating an amount of an agonist and an amount of an antagonist, the local pH may be controlled to a level that maximizes the release and/or absorption of the agonist while simultaneously minimizing the release and/or absorption of the antagonist.

[0060] The dosage form preferably includes a combination of a partial agonist and an antagonist, while the dosage has a controlled pH. In one embodiment, the partial agonist may include buprenorphine or a pharmaceutically acceptable salt thereof, while the antagonist includes naloxone or a therapeutically acceptable salt thereof. It should be understood that the present invention is not limited to the use of buprenorphine and naloxone, and any agonist (or partial agonist) and any antagonist may be incorporated into the present invention for use in treatment of drug addiction. The agonist and optional antagonist should be selected from those agonists and antagonists that are useful in treating the particular narcotic dependence being treated.

[0061] As discussed above, the local pH of the dosage is preferably controlled to provide the desired release and/or absorption of the agonist and antagonist. Buprenorphine is known to have a pKa of about 8.42, while naloxone has a pKa of about 7.94. According to pH partition theory, one would expect that saliva (which has a pH of about 6.5) would maximize the absorption of both actives. However, it has been surprisingly discovered by the Applicants that by buffering the dosage to a particular pH level, the optimum levels of absorption of the agonist and antagonist may be achieved. Desirably, the local pH of a composition including an agonist and an antagonist is between about 2 to about 4, and most desirably is from 3 to 4. At this local pH level, the optimum absorption of the agonist and the antagonist is achieved. As will be described in more detail in the Examples below, controlling the local pH of the film compositions of the present invention provides a system in which the desired release and/or absorption of the components is bioequivalent to that of a similar Suboxone® tablet.

[0062] In one embodiment, the dosage form is a self-supporting film. In this embodiment, the film dosage includes a polymer carrier matrix, a therapeutically effective amount of buprenorphine, an agonist. The buffer is preferably capable of providing a local pH of the composition within a range that provides the desired level of absorption of the buprenorphine. The resulting dosage is a film composition that allows

for a rapid and effective release of buprenorphine into the oral cavity of the user. At the same time, the film composition preferably has a sufficient adhesion profile, such that the film cannot easily be removed from the oral cavity of the user once it has been placed into the cavity. Full release of the buprenorphine preferably takes place within less than about thirty minutes, and preferably remains in the oral cavity for at least 1 minute.

[0063] As explained above, while providing a pharmaceutically acceptable level of an agonist is helpful in treating those with narcotic addiction, it may be desirable to provide the buprenorphine in combination with naloxone (an antagonist) so as to reduce the effect of the agonist and therefore aid in reducing dependency of the narcotic. Therefore, it may be desirable to combine the opioid agonist (or partial agonist) in the film composition with an opioid antagonist or a pharmaceutically acceptable salt thereof. The actives may be dispersed throughout the dosage separately or they may be combined together and dispersed into the dosage. Most desirably the antagonist includes naloxone, but any suitable basic antagonist may be selected as desired. The antagonist may optionally be water-soluble, so as to render separation of the antagonist and agonist difficult, thereby lessening the potential for abuse of the agonist.

[0064] As with a film including an agonist, the film including an agonist and an antagonist is desirably pH-controlled through the inclusion of a buffer. In such combination films, it has been discovered that the local pH of the film composition should preferably be in the range of about 2 to about 4, and more preferably about 3 to about 4 so as to provide a bioequivalent product as the commercially-available Suboxone® tablet. Most preferably the local pH of the film composition is about 3.5. At this local pH level, absorption of the buprenorphine is optimized while the absorption of the naloxone is inhibited.

[0065] The film may contain any desired level of self-supporting film forming polymer, such that a self-supporting film composition is provided. In one embodiment, the film composition contains a film forming polymer in an amount of at least 25% by weight of the composition. The film forming polymer may alternatively be present in an amount of at least 50% by weight of the composition. As explained above, any film forming polymers that impart the desired mucoadhesion and rate of film dissolution may be used as desired.

[0066] Any desired level of agonist and optional antagonist may be included in the dosage, so as to provide the desired effect. In one particular embodiment, the film composition includes about 2 mg to about 16 mg of agonist per dosage. More desirably, the film composition includes about 4 mg to about 12 mg of agonist per dosage. If desired, the film composition may include about 0.5 mg to about 5 mg of antagonist per dosage. More desirably, the film composition includes about 1 mg to about 3 mg of antagonist per dosage. If an antagonist is incorporated into the film, the film composition may include the antagonist in a ratio of about 6:1 – 2:1 agonist to antagonist. Most desirably, the film composition contains about 4:1 agonist to antagonist per dosage. For example, in one embodiment, the dosage includes an agonist in an amount of about 12 mg, and includes an antagonist in an amount of about 3 mg.

[0067] The film compositions further desirably contains a buffer so as to control the local pH of the film composition. Any desired level of buffer may be incorporated into the film composition so as to provide the desired local pH level. The buffer is preferably provided in an amount sufficient to control the release from the film and/or the absorption into the body of the agonist and the optional antagonist. In a desired embodiment, the film composition includes buffer in a ratio of buffer to agonist in an amount of from about 2:1 to about 1:5 (buffer:agonist). The buffer may alternatively be provided in a 1:1 ratio of buffer to agonist. As stated above, the film composition preferably has a local pH of about 2 to about 4, and most preferably has a local pH of about 3.5. Any buffer system may be used as desired. In some embodiments, the buffer may include sodium citrate, citric acid, and combinations thereof.

[0068] In this embodiment, the resulting film composition includes a polymer matrix, an agonist, and an optional antagonist, while the film composition has a controlled local pH to the level desired. The buffer is preferably present in an amount to provide a therapeutically adequate absorption of the agonist, while simultaneously limiting the absorption of the antagonist. Controlling of the local pH allows for the desired release and/or absorption of the components, and thus provides a more useful and effective dosage.

[0069] The film dosage composition may include a polymer carrier matrix, a therapeutically effective amount of agonist, a therapeutically effective amount of

antagonist, and a buffering system. The buffering system may include a buffer in addition to a solvent. The buffering system desirably includes a sufficient level of buffer so as to provide a desired local pH level of the film dosage composition.

[0070] In addition to a desired local pH level, the buffer preferably has a buffer capacity sufficient to maintain the ionization of the optional antagonist during the time that the composition is in the oral cavity of a user. Maintaining the ionization of the antagonist serves to limit the absorption of the antagonist, and thus provide the desired control of the antagonist. While the ionization of the antagonist is limited, the ionization of the agonist may not be so limited. As such, the resulting dosage form provides absorption of the agonist to the user, while sufficiently reducing and/or preventing absorption of the antagonist. By keeping the antagonist ionized and the local pH at the optimum pH, the antagonist has limited if any absorption, but is still present should the product be abused or taken via a different route of administration. However, when taken as administered, the antagonist has little to no effect in blocking the agonist.

[0071] The film dosage composition including an agonist may be configured to provide an in vivo plasma profile having a mean maximum plasma concentration (Cmax) in a desired range. It has been discovered by the Applicants that controlling the Cmax of the film composition allows one to control the absorption of the active (such as an agonist) into the user. The resulting film composition is more effective and suitable for delivery to a user.

[0072] As explained, the film dosage composition provides a bioequivalent result to a commercially available Suboxone® product. As will be explained more in the Examples below, commercially available Suboxone® provides different absorption levels depending on the amount of buprenorphine and naloxone administered. The present invention desirably provides a film product providing bioequivalent release as that of the Suboxone® product. As with the Suboxone® product, the buprenorphine may be present in an amount of from about 2 mg to about 16 mg per dosage, or, if desired about 4 mg to about 12 mg per dosage. Additionally, the naloxone may be present in any desired amount, preferably at about 25% the level of buprenorphine. For example, an inventive film product may have 2 mg buprenorphine and 0.5 mg naloxone, 4 mg buprenorphine

and 1 mg naloxone, 8 mg buprenorphine and 2 mg naloxone, 12 mg buprenorphine and 3 mg naloxone, 16 mg buprenorphine and 4 mg naloxone, or any similar amounts.

[0073] It has further been discovered that, by controlling the mean area under the curve (AUC) value of the film composition, a more effective dosage form may be provided. As is described in more detail in the Examples below, the inventive film composition preferably provides an AUC value so as to provide a bioequivalent result as that provided by the commercially available Suboxone® tablet. In one embodiment, the film composition may include a mean AUCinf value of about 6.8 hr.ng/ml or greater. Alternatively, the film composition may include a mean AUCinf value of from about 6.8 hr.ng/ml to about 66 hr.ng/ml.

[0074] As explained above, the film compositions may include naloxone, an antagonist. When the film composition includes a combination of agonist and antagonist, the film composition may be configured to provide a particular Cmax and/or AUCinf for the antagonist. For example, when a buprenorphine agonist and a naloxone antagonist are incorporated into the film composition, the naloxone may be configured to provide a Cmax of less than about 400 pg/ml, less than about 318 pg/ml, less than about 235 pg/ml, less than about 92 pg/ml or less than about 64 pg/ml. In such films, the naloxone may provide a mean AUCinf value of less than about 1030 hr.ng/ml.

[0075] In formulations which include an agonist in combination with an antagonist, the film composition may be prepared to provide a desired Cmax and/or AUCinf value for each of the agonist and antagonist. In one embodiment, the film composition provides an in vivo plasma profile having a Cmax of less than about 6.4 ng/ml for the agonist and an in vivo plasma profile having a Cmax of less than about 400 pg/ml for the antagonist. In such embodiments, the formulation may provide an AUCinf value of more than about 6.8 hr.ng/ml for the agonist. If desired, the formulation may provide an AUCinf value of less than about 1030 hr.pg/ml for the antagonist. Such compositions may include the agonist and the antagonist in any desired amount, and in a preferred embodiment, the composition includes about 2 mg to about 16 mg of the agonist per dosage and about 0.5 mg to about 4 mg of the antagonist per dosage.

[0076] The present invention provides a method of treating narcotic dependence in a patient. In one embodiment, the patient is dependent on opioid narcotics, but the patient

may have a dependence on non-opioid narcotics. Desirably, the patient is treated by providing a dosage to the patient, which provides an effective release of actives but simultaneously provides a suitable adhesion so that the dosage cannot be easily removed. In one method of treatment, an orally dissolvable film composition is provided to a patient.

[0077] Depending on the particular narcotic that the patient experiences dependence upon, the film composition may include one or more particular active components. In one embodiment, the film composition includes a polymer carrier matrix and a therapeutically effective amount of an agonist. Desirably the agonist is a partial agonist. For opioid dependency, the agonist may be an opioid agonist, such as buprenorphine or a pharmaceutically acceptable salt thereof. The film composition preferably includes a buffer in an amount sufficient to control the local pH of the film composition. Any buffer system may be used, including sodium citrate, citric acid, and combinations thereof. In compositions solely including an agonist, the local pH of the film composition is desirably about 5 to about 6.5, and most desirably the local pH is about 5.5. At this level, the absorption of the agonist is most effective. To treat the dependency, the film composition is administered to the patient, most desirably into the oral cavity of the patient.

[0078] If desired, the composition may include a therapeutically effective amount of an antagonist, to prevent abuse of the agonist. A "therapeutically effective amount" of an antagonist is intended to refer to an amount of the antagonist that may be useful in diverting abuse of the agonist by a user. The antagonist may be any desired antagonist, and in one embodiment includes naloxone or a pharmaceutically acceptable salt thereof. The film composition is preferably administered to a patient through the oral cavity of the patient, but may be administered in any desired means. The orally dissolvable film composition is then allowed to dissolve in the oral cavity of the patient for a sufficient time so as to release the active(s) therein. In some embodiments, the film composition may remain in the oral cavity for at least 30 seconds, and in some embodiments may remain in the oral cavity for at least 1 minute. After the film composition is placed into the oral cavity of the patient, the film preferably becomes sufficiently adhered so as to render its removal difficult. After the film composition has been administered to the

patient, the active(s) are sufficiently released from the composition and allowed to take effect on the patient.

[0079] The film compositions of the present invention may be formed via any desired process. Suitable processes are set forth in U.S. Patent Nos. 7,425,292 and 7,357,891, the entire contents of which are incorporated by reference herein. In one embodiment, the film dosage composition is formed by first preparing a wet composition, the wet composition including a polymeric carrier matrix, a therapeutically effective amount of an agonist, and a buffer in an amount sufficient to control the local pH of the composition to a desired level. The wet composition is cast into a film and then sufficiently dried to form a self-supporting film composition. The wet composition may be cast into individual dosages, or it may be cast into a sheet, where the sheet is then cut into individual dosages. The agonist may be a partial agonist. If desired, the wet composition may include a therapeutically effective amount of an antagonist.

[0080] The agonist and the optional antagonist are preferably selected to treat a particular narcotic dependency. For opioid dependency, for example, the agonist may include buprenorphine or a pharmaceutically acceptable salt thereof, while the antagonist may include naloxone or a pharmaceutically acceptable salt thereof. The local pH of the film composition is desirably maintained at about 2 to about 4.

EXAMPLES

Example 1 – Composition of Buprenorphine/Naloxone Films at Various Strengths

[0081] Film strips including a combination of buprenorphine and naloxone were prepared. Four different strength film compositions were prepared, which include a ratio of buprenorphine to naloxone of 16/4, 12/3, 8/2, and 2/0.5. The compositions are summarized in Table 1 below.

Table 1 – Various Compositions of Film Dosages

Components	**Buprenorphine/Naloxone Films Unit Formula (mg per film strip)**			
Buprenorphine/Naloxone Ratios	**16/4**	**12/3**	**8/2**	**2/0.5**
Active Components				
Buprenorphine HCl	17.28	12.96	8.64	2.16
Naloxone HCl Dihydrate	4.88	3.66	2.44	0.61

Inactive Components				
Polyethylene Oxide, NF (MW 200,000)	27.09	20.32	13.55	--
Polyethylene Oxide, NF (MW 100,000)	12.04	9.03	6.02	19.06
Polyethylene Oxide, NF (MW 900,000)	4.82	3.62	2.41	2.05
Maltitol, NF	12.04	9.03	6.02	5.87
Flavor	6.0	4.5	3.0	2.4
Citric Acid, USP	5.92	4.44	2.96	2.96
HPMC	4.22	3.16	2.11	2.34
Ace-K	3.0	2.25	1.5	1.2
Sodium Citrate, anhydrous	2.68	2.01	1.34	1.34
Colorant	0.03	0.02	0.01	0.01
Total (mg)	100	75	50	40

Example 2 – Absorption studies for Suboxone® products

[0082] Various film and tablet products were prepared and tested for absorption data, including Cmax and AUC absorption levels. The products tested included Suboxone® tablets made with either 2 mg or 16 mg buprenorphine as well as either 0.5 mg or 4.0 mg naloxone. For 16 mg buprenorphine tablets, two 8 mg buprenorphine tablets were combined together to provide the level of components of a 16 mg buprenorphine tablet. In instances where a 12 mg buprenorphine tablet was evaluated, this dosage was obtained by combining one 8 mg buprenorphine tablet and two 2 mg buprenorphine tablets. These products were tested for absorption levels, with the amounts listed in Table 2 below.

Table 2 - Absorption Data for Suboxone® products

Sample	**C max**	**AUC**
Buprenorphine (2 mg) Suboxone® Tablet	0.780 ng/ml	6.789 hr*ng/ml
Naloxone (0.5 mg) Suboxone® Tablet	51.30 pg/ml	128.60 hr*pg/ml
Buprenorphine (16 mg) Suboxone®	4.51 ng/ml	44.99 hr*ng/ml

Tablet		
Naloxone (4 mg) Suboxone® Tablet	259.00 pg/ml	649.60 hr*pg/ml

[0083] Using the data from Table 2, absorption data for the Suboxone® tablets for other levels of buprenorphine and naloxone are set forth in Table 2A below.

Table 2A – Extrapolated Absorption Data for Suboxone® products

Sample	**C max**	**AUC**
Buprenorphine (4 mg) Suboxone® Tablet	1.35 ng/ml	12.25 hr*ng/ml
Naloxone (1 mg) Suboxone® Tablet	80.97 pg/ml	203 hr*pg/ml
Buprenorphine (8 mg) Suboxone® Tablet	2.29 ng/ml	23.17 hr*ng/ml
Naloxone (2 mg) Suboxone® Tablet	140.31 pg/ml	351.8 hr*pg/ml
Buprenorphine (12 mg) Suboxone® Tablet	3.23 ng/ml	34.08 hr*ng/ml
Naloxone (3 mg) Suboxone® Tablet	199.7 pg/ml	500.6 hr*pg/ml

Example 3 – Evaluation of Bioequivalence of Suboxone® Tablets

[0084] Using the data generated for Suboxone® tablets in Table 2 above, acceptable bioequivalence ranges are generated to provide an equivalent treatment level as the Suboxone® tablet. As currently understood, a product provides a bioequivalent effect if it provides absorption levels between about 80% to about 125% of the Suboxone® tablet. Absorption in this range is considered to be bioequivalent.

Table 3 - Acceptable Bioequivalence Ranges for Suboxone® Tablets (80 to 125%)

Description of Sample	**C max**	**AUC**
Buprenorphine 2 mg	0.624 to 0.975 ng/ml	5.431 to 8.486 hr*ng/ml
Naloxone 0.5 mg	41.04 to 64.13 pg/ml	102.88 to 160.75 hr*pg/ml
Buprenorphine 16 mg	3.608 to 5.638 ng/ml	35.992 to 56.238 hr*ng/ml
Naloxone 4 mg	207.20 to 323.75 pg/ml	519.68 to 812.00 hr*pg/ml

[0085] Thus, to be considered bioequivalent to the Suboxone® tablet, the Cmax of buprenorphine is between about 0.624 and 5.638, and the AUC of buprenorphine is between about 5.431 to about 56.238. Similarly, to be considered bioequivalent to the

Suboxone® tablet, the Cmax of naloxone is between about 41.04 to about 323.75, and the AUC of naloxone is between about 102.88 to about 812.00.

Example 4 – Absorption studies for film products at pH 3.5

[0086] Various film products were prepared and tested for absorption data, including Cmax and AUC absorption levels. The products tested included inventive film strips, the film strips having either 2 mg or 16 mg buprenorphine as well as either 0.5 mg or 4.0 mg naloxone. These products were tested for absorption levels, with the amounts listed in Table 4 below.

Table 4 - Absorption Data for inventive film products at pH 3.5

Sample	**C max**	**AUC**
Buprenorphine (2 mg) Sublingual Film	0.947 ng/ml	7.82 hr*ng/ml
Naloxone (0.5 mg) Sublingual Film	51.10 pg/ml	128.60 hr*pg/ml
Buprenorphine (16 mg) Sublingual Film	5.47 ng/ml	55.30 hr*ng/ml
Naloxone (4 mg) Sublingual Film	324.00 pg/ml	873.60 hr*pg/ml

[0087] As can be seen, in this experiment, the values for buprenorphine absorbance were squarely in the bioequivalence range evaluated above. The inventive films were therefore determined to have provided a bioequivalent absorption of buprenorphine at a local pH of 3.5 as the commercially available Suboxone® tablet. The values for absorption of naloxone were very close to the bioequivalent range of Suboxone®. The slightly higher absorption of Naloxone was not due to the local pH but rather to the amount of buffer (buffer capacity as discussed in the application). This is confirmed by the fact that the lower 2/0.5 mg dose is in range for the Naloxone and this is due to the higher buffer capacity for the 2/0.5 dose as pointed out in the buffer capacity chart.

Example 5 – Preparation of Films For In Vivo Study

[0088] Film dosages were prepared for use in an *in vivo* study to determine the bioavailability of buprenorphine/naloxone tablets and film formulations. Specifically, the films were tested to determine whether the film provides a bioequivalent effect to that of a tablet formulation.

[0089] Three film formulations including 8 mg buprenorphine and 2 mg naloxone were prepared, each being buffered to a different pH. The first film did not include any buffer, providing a local pH of about 6.5. The second was buffered to a local pH level of about 3-3.5. The third was buffered to a local pH value of about 5-5.5. The formulations are set forth in Table 5 below.

Table 5 – Formulations of Test Films at Various pH Levels

Component	**Test formulation 1 8 mg/2 mg pH = 6.5**		**Test formulation 2 8 mg/2 mg pH = 3-3.5**		**Test formulation 3 8 mg/2 mg pH = 5-5.5**	
	%w/w	Mg/film	%w/w	Mg/film	%w/w	Mg/film
Buprenorphine HCl	21.61	8.64	17.28	8.64	17.28	8.64
Naloxone HCl Dihydrate	6.10	2.44	4.88	2.44	4.88	2.44
Polymer	5.05	2.02	4.82	2.41	4.82	2.41
Polymer	28.48	11.39	27.09	13.55	27.09	13.55
Polymer	12.65	5.06	12.04	6.02	12.04	6.02
Polymer	4.43	1.77	4.22	2.11	4.22	2.11
Sweetener	12.65	5.06	12.04	6.02	12.04	6.02
Sweetener	3	1.2	3	1.5	3	1.5
Flavor	6	2.4	6	3	6	3
Citric acid	0	0	5.92	2.96	2.51	1.26
Sodium citrate	0	0	2.68	1.34	6.08	3.04
FD&C yellow #6	0.025	0.01	0.03	0.02	0.03	0.02
Total	**100**	**40**	**100**	**50**	**100**	**50**

Example 6 – Analysis of *In Vivo* Absorption of Film Having a pH of 6.5

[0090] The film dosage composition of film having a local pH of 6.5 was analyzed. Specifically, Test Formulation 1, as prepared in Example 5 was analyzed in vivo to determine the absorption of buprenorphine and of naloxone. The comparative film was compared to the absorption of buprenorphine and of naloxone provided by a one dose tablet (Suboxone®). The test film was compared to determine whether it provided a bioequivalent effect as the tablet product.

[0091] The results for Test Formulation 1, which had a local pH of about 6.5, as compared to the one dose tablet, are set forth in Tables 6 and 7 below.

Table 6 – Buprenorphine In Vivo Absorption Data for Test Formulation 1

	Suboxone® sublingual				Test Formulation 1 (pH = 6.5)			
Parameter	**n**	**Mean**	**SD**	**CV%**	**n**	**Mean**	**SD**	**CV%**
T_{max} (hr)	15	1.60	0.47	29.41	15	1.50	0.62	41.23
C_{max} (ng/mL)	15	2.27	0.562	24.77	15	2.60	0.872	33.53
AUC_{last} (hr*ng/mL)	15	27.08	10.40	38.41	15	31.00	12.93	41.72
AUC_{inf} (hr*ng/mL)	15	29.58	11.15	37.68	15	33.37	13.88	41.61
$T_{1/2}$ (hr)	15	44.76	20.86	46.60	15	40.73	14.93	36.66

Table 7 – Naloxone In Vivo Absorption Data for Test Formulation 1

	Suboxone® sublingual				Test Formulation 1 (pH = 6.5)			
Parameter	**n**	**Mean**	**SD**	**CV%**	**n**	**Mean**	**SD**	**CV%**
T_{max} (hr)	15	0.90	0.23	25.32	15	0.68	0.18	25.75
C_{max} (pg/mL)	15	94.6	39.1	41.33	15	410	122	29.75
AUC_{last} (hr*pg/mL)	15	297.1	120.7	40.62	15	914.8	158.1	17.29
AUC_{inf} (hr*pg/mL)	15	306.1	122.6	40.06	15	924.2	158.8	17.18
$T_{1/2}$ (hr)	15	6.62	2.60	39.26	15	6.86	2.08	30.27

[0092] As can be seen, the in vivo data indicates that buprenorphine is absorbed very well from the film formulation at a local pH of 6.5, and matched closely the absorption seen in the Suboxone® one dose tablet. However, the absorption was also maximized for the naloxone, which was undesirable. It was determined that a film having a combination of buprenorphine and naloxone and a local pH of 6.5 did not provide a bioequivalent effect as the Suboxone® tablet for both buprenorphine and naloxone.

Example 7 – Analysis of In Vivo Absorption of Film Having a pH of 5-5.5

[0093] Having determined the absorption of buprenorphine and naloxone in film having a local pH of 6.5, a film dosage composition of film having a local pH of 5-5.5 was analyzed. Specifically, Test Formulation 3, as prepared in Example 5 was analyzed in vivo to determine the absorption of buprenorphine and of naloxone. The comparative films were compared to the absorption of buprenorphine and of naloxone provided by the

Suboxone® one dose tablet. The test film was compared to determine whether it provided a bioequivalent effect as the Suboxone® tablet.

[0094] The results for Test Formulation 3, which had a local pH of about 5-5.5, as compared to the Suboxone® tablet, are set forth in Tables 8 and 9 below.

Table 8 – Buprenorphine In Vivo Absorption Data for Test Formulation 3

	Suboxone® sublingual				**Test Formulation 3 (pH = 5-5.5)**			
Parameter	**n**	**Mean**	**SD**	**CV%**	**n**	**Mean**	**SD**	**CV%**
T_{max} (hr)	15	1.60	0.47	29.41	14	1.50	0.43	28.50
C_{max} (ng/mL)	15	2.27	0.562	24.77	14	3.47	1.57	45.40
AUC_{last} (hr*ng/mL)	15	27.08	10.40	38.41	14	33.25	16.01	48.16
AUC_{inf} (hr*ng/mL)	15	29.58	11.15	37.68	13	38.34	15.38	40.13
$T_{1/2}$ (hr)	15	44.76	20.86	46.60	13	41.71	17.70	42.42

Table 9 – Naloxone In Vivo Absorption Data for Test Formulation 3

	Suboxone® sublingual				**Test Formulation 3 (pH = 5-5.5)**			
Parameter	**n**	**Mean**	**SD**	**CV%**	**n**	**Mean**	**SD**	**CV%**
T_{max} (hr)	15	0.90	0.23	25.32	14	0.98	0.62	63.51
C_{max} (pg/mL)	15	94.6	39.1	41.33	14	173	84.5	48.79
AUC_{last} (hr*pg/mL)	15	297.1	120.7	40.62	14	455.2	195.5	42.94
AUC_{inf} (hr*pg/mL)	15	306.1	122.6	40.06	13	474.4	203.1	42.81
$T_{1/2}$ (hr)	15	6.62	2.60	39.26	13	9.45	6.90	73.00

[0095] As can be seen, the in vivo data indicated that the absorption of buprenorphine increased as the local pH level decreased. It appeared that by decreasing the local pH from 6.5 to 5.5, the absorption of buprenorphine was being moved to a level further away from that of the one dose tablet. In addition, the naloxone values did not provide a bioequivalent result as the one dose tablet. Thus, it was determined that the film having a local pH of 5.5 did not provide a bioequivalent result as that of the Suboxone® tablet for both buprenorphine and naloxone.

[0096] It was noted that by reducing the local pH of the film to a level of 5.5, there would be provided an increased level of absorption of buprenorphine. Thus, it may be desirable

to buffer a film composition incorporating buprenorphine itself to a level of about 5.5 to provide an increased absorption.

Example 8 – Analysis of In Vivo Absorption of Film Having a pH of 3-3.5

[0097] Having determined the absorption of buprenorphine and naloxone in films having a local pH of 6.5 and 5.5, a film dosage composition of film having a local pH of about 3-3.5 was analyzed. It was assumed that the absorption of buprenorphine would continue to be increased as it had demonstrated at a local pH of 5.5. Thus, it was assumed that at a local pH of 3.5, the film would not be bioequivalent to that of the tablet.

[0098] Specifically, Test Formulation 2, as prepared in Example 5, was analyzed in vivo to determine the absorption of buprenorphine and of naloxone. The comparative films were compared to the absorption of buprenorphine and of naloxone provided by the Suboxone® one dose tablet. The test film was compared to determine whether it provided a bioequivalent effect as the tablet product.

[0099] The results for Test Formulation 2, which had a local pH of about 3-3.5, as compared to the Suboxone® tablet, are set forth in Tables 10 and 11 below.

Table 10 – Buprenorphine In Vivo Absorption Data for Test Formulation 2

	Suboxone® sublingual				**Test Formulation 2 (pH = 3-3.5)**			
Parameter	**n**	**Mean**	**SD**	**CV%**	**n**	**Mean**	**SD**	**CV%**
T_{max} (hr)	15	1.60	0.47	29.41	14	1.68	0.58	34.68
C_{max} (ng/mL)	15	2.27	0.562	24.77	14	2.68	0.910	33.99
AUC_{last} (hr*ng/mL)	15	27.08	10.40	38.41	14	29.73	12.05	40.54
AUC_{inf} (hr*ng/mL)	15	29.58	11.15	37.68	14	31.45	12.98	41.26
$T_{1/2}$ (hr)	15	44.76	20.86	46.60	14	30.03	13.95	46.46

Table 11 – Naloxone In Vivo Absorption Data for Test Formulation 2

	Suboxone® sublingual				**Test Formulation 2 (pH = 3-3.5)**			
Parameter	**n**	**Mean**	**SD**	**CV%**	**n**	**Mean**	**SD**	**CV%**
T_{max} (hr)	15	0.90	0.23	25.32	14	0.84	0.19	22.19
C_{max} (pg/mL)	15	94.6	39.1	41.33	14	130	72.9	56.04
AUC_{last}	15	297.1	120.7	40.62	14	362.2	155.9	43.03

(hr*pg/mL)								
AUC_{inf} (hr*pg/mL)	15	306.1	122.6	40.06	12	350.4	142.3	40.61
$T_{1/2}$ (hr)	15	6.62	2.60	39.26	12	8.07	4.75	58.84

[00100] As can be seen, the in vivo data indicated that the absorption of buprenorphine was substantially bioequivalent to that of the one dose tablet when the film composition local pH was lowered to about 3-3.5. This result was surprising as it did not appear to follow the pH partition theory. Further, at a local pH of about 3-3.5, it was seen that the absorption of naloxone was substantially bioequivalent to that of the one dose tablet.

[00101] Thus, it was determined that the film product including buprenorphine and naloxone at a local pH of 3-3.5 was substantially bioequivalent to that of the Suboxone® one dose tablet.

Example 9 – Normalized Values for Naloxone in Films and Tablets

[00102] Various film compositions including buprenorphine and naloxone in 8/2 mg and 2/0.5 mg dosages, and having different local pH values from 6.5 to 3.5, were prepared and analyzed. The data was normalized and compared to the one dose tablet. The results are set forth in Table 12 below.

Table 12 – Normalized Values for Naloxone Film Compared to Tablet

pH	Dose (mg) Buprenorphine/ Naloxone	AUC (Normalized)	Cmax	Mg Citric Acid	Ratio Citric Acid (mg)/Naloxone (mg)
6.5	8/2	3.02	4.33	1.34	0.67
5.5	8/2	1.55	1.83	1.34	0.67
3.5	8/2	1.14	1.37	1.34	0.67
3.5	2/0.5	0.98	0.90	1.34	2.68
5.5	2/0.5	1.41	1.41	1.34	2.68

[00103] The data indicates that not only is the local pH of significant importance, but the amount of buffer present in the formula is also important. The improvement from the 8/2 dose to the 2/0.5 dose (at a local pH of 3.5) demonstrates this importance. The

8/2 dose has a ratio of buffer/naloxone of 0.67, and this dose provided borderline acceptable bioequivalent results. In contrast, the 2/0.5 dose has a ratio of buffer/naloxone of 2.68, and provides a more bioequivalent absorption value than the 8/2 dose.

[00104] In fact, the data shows that the 2/0.5 dose at a local pH of 3.5 had an even lower buccal absorption than the one dose tablet, as seen from the normalized values for the AUC and Cmax. This demonstrates that even less absorption of the naloxone occurs for the film formulation at a local pH of 3.5 than the tablet formulation. Given the goal of reducing the absorption of naloxone, it appears that the film product buffered at a local pH of 3.5 with a buffer ratio of buffer/Naloxone of 2.68 provides even better results than the Suboxone® tablet formulation.

What is claimed is:

1. A film dosage composition comprising:
    a. A polymeric carrier matrix;
    b. A therapeutically effective amount of buprenorphine or a pharmaceutically acceptable salt thereof;
    c. A therapeutically effective amount of naloxone or a pharmaceutically acceptable salt thereof; and
    d. A buffer in an amount to provide a local pH of said composition of a value sufficient to optimize absorption of said buprenorphine.
2. The composition of claim 1, wherein said local pH is about 2 to about 4.
3. The composition of claim 2, wherein the local pH of said composition is from about 3 to about 4.
4. The composition of claim 1, wherein said film dosage composition provides a bioequivalent absorption of buprenorphine to that of a tablet having an equivalent amount of buprenorphine or a pharmaceutically acceptable salt thereof.
5. The composition of claim 1, wherein said polymeric carrier matrix comprises at least one polymer in an amount of at least 25% by weight of said composition.
6. The composition of claim 1, wherein said buffer is present in an amount of from about 2:1 to about 1:5 by weight of buffer to buprenorphine.
7. The composition of claim 1, wherein said polymeric carrier matrix comprises at least one self-supporting film forming polymer.
8. The film dosage composition of claim 1, wherein said buprenorphine is present in an amount of from about 2 mg to about 16 mg per dosage.
9. The film dosage composition of claim 1, wherein said buffer comprises sodium citrate, citric acid, and combinations thereof.
10. The film dosage composition of claim 1, wherein said buffer comprises acetic acid, sodium acetate, and combinations thereof.
11. A film dosage composition comprising:
    a. A polymeric carrier matrix;
    b. A therapeutically effective amount of buprenorphine or a pharmaceutically acceptable salt thereof;

c. A therapeutically effective amount of naloxone or a pharmaceutically acceptable salt thereof; and

d. A buffer in an amount sufficient to inhibit the absorption of said naloxone when administered orally.

12. The composition of claim 11, wherein said composition has a local pH of about 2 to about 4.

13. The composition of claim 11, wherein said buffer is present in an amount sufficient to provide a therapeutically adequate absorption of buprenorphine.

14. The composition of claim 13, wherein a therapeutically adequate absorption of buprenorphine comprises a bioequivalent level of absorption of buprenorphine as a tablet having an equivalent amount of buprenorphine or a pharmaceutically acceptable salt thereof.

15. A film dosage composition comprising:

a. A polymeric carrier matrix;

b. A therapeutically effective amount of buprenorphine or a pharmaceutically acceptable salt thereof;

c. A therapeutically effective amount of naloxone or a pharmaceutically acceptable salt thereof; and

d. A buffering system;

wherein said buffering system comprises a buffer capacity sufficient to maintain the ionization of naloxone during the time which said composition is in the oral cavity of a user.

16. The composition of claim 15, wherein said composition has a local pH of about 2 to about 4.

17. A method of treating narcotic dependence of a user, comprising the steps of:

a. providing a composition comprising:

i. A polymeric carrier matrix;

ii. A therapeutically effective amount of buprenorphine or a pharmaceutically acceptable salt thereof;

iii. A therapeutically effective amount of naloxone or a pharmaceutically acceptable salt thereof; and

iv. A buffer in an amount to provide a local pH of said composition of a value sufficient to optimize absorption of said buprenorphine; and

b. administering said composition to the oral cavity of a user.

18. The composition of claim 17, wherein said method provides a bioequivalent absorption of buprenorphine to that of a tablet having an equivalent amount of buprenorphine or a pharmaceutically acceptable salt thereof.

19. The method of claim 17, wherein said composition has a local pH of about 2 to about 4.

20. The method of claim 17, wherein said film dosage composition is administered to the user through buccal administration, sublingual administration, and combinations thereof.

21. The method of claim 17, wherein said film dosage composition remains in the oral cavity of the user for a period of at least 1 minute.

22. The method of claim 17, wherein said film dosage composition remains in the oral cavity of the user for a period of between about 1 and 1.5 minutes.

23. The method of claim 17, wherein said film dosage composition remains in the oral cavity of the user for a period of up to 3 minutes.

24. A process of forming a film dosage composition comprising the steps of:

a. casting a film-forming composition, said film-forming composition comprising:

i. A polymeric carrier matrix;

ii. A therapeutically effective amount of buprenorphine or a pharmaceutically acceptable salt thereof;

iii. A therapeutically effective amount of naloxone or a pharmaceutically acceptable salt thereof; and

iv. A buffer in an amount to provide a local pH of said composition of a value sufficient to optimize absorption of said buprenorphine; and

b. drying said film-forming composition to form a self-supporting film dosage composition.

25. The process of claim 24, wherein said composition has a local pH of about 2 to about 4.
26. A film dosage composition comprising a therapeutically sufficient amount of buprenorphine or a pharmaceutically acceptable salt thereof and a therapeutically sufficient amount of naloxone or a pharmaceutically acceptable salt thereof, said film dosage composition having a bioequivalent release profile as a tablet containing about 2 times the amount of buprenorphine or a pharmaceutically acceptable salt thereof.
27. An orally dissolving film formulation comprising buprenorphine and naloxone, wherein said formulation provides an in vivo plasma profile having a Cmax of between about 0.624 ng/ml and about 5.638 ng/ml for buprenorphine and an in vivo plasma profile having a Cmax of between about 41.04 pg/ml to about 323.75 pg/ml for naloxone.
28. The formulation of claim 27, wherein said formulation provides a mean AUC of between about 5.431 hr.ng/ml to about 56.238 hr.ng/ml for buprenorphine.
29. The formulation of claim 27, wherein said formulation provides a mean AUC of between about 102.88 hr.pg/ml to about 812.00 hr.pg/ml for naloxone.
30. The formulation of claim 27, wherein said formulation comprises about 2 to about 16 mg of buprenorphine or a salt thereof.
31. The formulation of claim 27, wherein said formulation comprises about 0.5 to about 4 mg of naloxone or a salt thereof.

ABSTRACT

The present invention relates to products and methods for treatment of narcotic dependence in a user. The invention more particularly relates to self-supporting dosage forms which provide an active agent for treating narcotic dependence while providing sufficient buccal adhesion of the dosage form.

PATENT

Attorney's Docket No. **1199-82**

COMBINED DECLARATION AND POWER OF ATTORNEY

(ORIGINAL, DESIGN, NATIONAL STAGE OF PCT, SUPPLEMENTAL, DIVISIONAL, CONTINUATION OR CIP)

As a below named inventor, I hereby declare that:

TYPE OF DECLARATION

This declaration is of the following type: *(check one)*

- ☒ Original
- ☐ Supplemental
- ☐ Design
- ☐ National Stage PCT
- ☐ Divisional
- ☐ Continuation
- ☐ Continuation-in-Part (CIP)

INVENTORSHIP IDENTIFICATION

NOTE: If the inventors are each not the inventors of all the claims an explanation of the facts, including the ownership of all the claims at the time the last claimed invention was made, should be submitted.

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

SUBLINGUAL AND BUCCAL FILM COMPOSITIONS

the specification of which: *(complete (a), (b) or (c))*

(a) ☒ is attached hereto.
- ☒ To comply with 37 C.F.R. §1.63 for identifying the application, I, an Inventor signing below, hereby authorize and request my attorney to insert below the filing date and application number when they become known:
  U.S. Application No. _____, filed _____.

(b) ☐ was filed on _____ as
- ☐ Serial No._____ or
- ☐ Express Mail No. _____, as Serial No. not yet known and was amended on _____. *(If applicable)*

(c) ☐ was described and claimed in PCT International Application No. **PCT/**_____ filed on _____ and as amended under PCT Article 19 on _____. *(If any)*

ACKNOWLEDGMENT OF REVIEW OF PAPERS AND DUTY OF CANDOR

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above, and that the filing of said specification, if heretofore filed, was authorized by me.

I acknowledge the duty to disclose information which is material to patentability of this application in accordance with Title 37, Code of Federal Regulations, §1.56.

CLAIM OF PRIORITY OF EARLIER FOREIGN APPLICATION(S) UNDER 35 U.S.C. §119(a)-(d)

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

(List prior foreign/PCT application(s) filed within 12 months (6 months for design) prior to this U.S. application.)

NOTE: Where item (c) is entered above and the International Application which designated the U.S. claimed priority check item (e), enter the details below and make the priority claim.

COUNTRY (orPCT)	APPLICATION NO.	DATE OF FILING *(Day/Month/Year)*	PRIORITY CLAIMED UNDER 35 USC §119
			☐ YES ☐ NO
			☐ YES ☐ NO

CLAIM FOR BENEFIT OF PRIOR U.S. PROVISIONAL APPLICATION(S) UNDER 35 U.S.C. §119(e)

I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below:

(List prior U.S. provisional applications.)

PROVISIONAL APPLICATION NO.	FILING DATE *(Day/Month/Year)*

CLAIM FOR BENEFIT OF EARLIER U.S./PCT APPLICATION(S) UNDER 35 U.S.C. 120

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) or PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in such prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56 which occurred between the filing date of the prior application(s) and the national or PCT international filing date of this application:

(List prior U.S. applications or PCT international applications designating the U.S. for benefit under 35 U.S.C. §120.)

U.S. APPLICATIONS		**STATUS** *(Check One)*		
U.S. SERIAL NO.	U.S. FILING DATE *(Day/Month/Year)*	Patented	Pending	Abandoned
0 /		☐	☐	☐
0 /		☐	☐	☐

PCT APPLICATIONS DESIGNATING THE U.S.			**STATUS** *(Check One)*		
PCT APPLN. NO.	PCT FILING DATE *(Day/Month/Year)*	U.S. SERIAL NOS ASSIGNED (If any)	Patented	Pending	Abandoned
PCT/			☐	☐	☐
PCT/			☐	☐	☐

35 USC 119 PRIORITY CLAIM, IF ANY, FOR ABOVE LISTED U.S./PCT APPLICATIONS

PRIORITY APPLICATION NO.	PRIORITY COUNTRY	FILING DATE *(Day/Month/Year)*	ISSUE DATE *(Day/Month/Year)*

POWER OF ATTORNEY

As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) at Customer Number **23869** to prosecute this application and transact all business in the Patent and Trademark Office in connection therewith.

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Date: April 13, 2009	Inventor's signature PP Sanghvi
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Date: _____	Inventor's signature _____

NOTE: All above spaces identifying inventors must be completed or deleted before any inventor executes this application

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DECLARATION

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

SIGNATURE(S)

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Post Office Address:	**Same as above**
Date: AUG 6, 2009	Inventor's signature

NOTE: All above spaces identifying inventors must be completed or deleted before any inventor executes this application

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	SUBLINGUAL AND BUCCAL FILM COMPOSITIONS
First Named Inventor/Applicant Name:	Garry L. Myers
Filer:	Jon Anthony Chiodo/Kathleen Goodhand
Attorney Docket Number:	1199-82

Filed as Small Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Utility filing Fee (Electronic filing)	4011	1	82	82
Utility Search Fee	2111	1	270	270
Utility Examination Fee	2311	1	110	110
Pages:				
Claims:				
Claims in excess of 20	2202	11	26	286
Independent claims in excess of 3	2201	2	110	220
Miscellaneous-Filing:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**968**

Electronic Acknowledgement Receipt

EFS ID:	5849679
Application Number:	12537571
International Application Number:	
Confirmation Number:	5630
Title of Invention:	SUBLINGUAL AND BUCCAL FILM COMPOSITIONS
First Named Inventor/Applicant Name:	Garry L. Myers
Customer Number:	23869
Filer:	Jon Anthony Chiodo/Kathleen Goodhand
Filer Authorized By:	Jon Anthony Chiodo
Attorney Docket Number:	1199-82
Receipt Date:	07-AUG-2009
Filing Date:	
Time Stamp:	14:50:34
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$968
RAM confirmation Number	909
Deposit Account	082461
Authorized User	

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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal of New Application	Utiltiy_Patent_Application_Transmittal.pdf	277351 2f59b0513b90f193635995bd55fd6ab44217ea5e	no	2
Warnings:					
Information:					
2	Application Data Sheet	Application_Data_Sheet.pdf	1346186 4e2f25c628b5fd4fdac2dfcbd414231e12c7c7af	no	6
Warnings:					
Information:					
3		application.pdf	231122 aa12b9e8b339eab3bb2c19e8f9b8481a4929cbca	yes	37

Multipart Description/PDF files in .zip description

Document Description	Start	End
Specification	1	32
Claims	33	36
Abstract	37	37

Warnings:					
Information:					
4	Oath or Declaration filed	declaration.pdf	554757 0dec40b1c7c065c9cc5fc97307556e343556f9a5	no	6
Warnings:					
Information:					
5	Fee Worksheet (PTO-875)	fee-info.pdf	38104 581acc199961ec0800cf665739a49b5604d6b32d	no	2
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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.

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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.

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Electronic Acknowledgement Receipt

EFS ID:	5849679
Application Number:	12537571
International Application Number:	
Confirmation Number:	5630
Title of Invention:	SUBLINGUAL AND BUCCAL FILM COMPOSITIONS
First Named Inventor/Applicant Name:	Garry L. Myers
Customer Number:	23869
Filer:	Jon Anthony Chiodo/Kathleen Goodhand
Filer Authorized By:	Jon Anthony Chiodo
Attorney Docket Number:	1199-82
Receipt Date:	07-AUG-2009
Filing Date:	
Time Stamp:	14:50:34
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$968
RAM confirmation Number	909
Deposit Account	082461
Authorized User	

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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal of New Application	Utiltiy_Patent_Application_Transmittal.pdf	277351 2f59b0513b90f193635995bd55fd6ab44217ea5e	no	2
Warnings:					
Information:					
2	Application Data Sheet	Application_Data_Sheet.pdf	1346186 4e2f25c628b5fd4fdac2dfcbd414231e12c7c7af	no	6
Warnings:					
Information:					
3		application.pdf	231122 aa12b9e8b339eab3bb2c19e8f9b8481a4929cbca	yes	37

Multipart Description/PDF files in .zip description

Document Description	Start	End
Specification	1	32
Claims	33	36
Abstract	37	37

Warnings:					
Information:					
4	Oath or Declaration filed	declaration.pdf	554757 0dec40b1c7c065c9cc5fc97307556e343556f9a5	no	6
Warnings:					
Information:					
5	Fee Worksheet (PTO-875)	fee-info.pdf	38104 581acc199961ec0800cf665739a49b5604d6b32d	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	2447520		

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New International Application Filed with the USPTO as a Receiving Office

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Filing Date: **08/07/09**

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PATENT APPLICATION FEE DETERMINATION RECORD
Substitute for Form PTO-875

Application or Docket Number
12/537,571

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	82		N/A	
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	270		N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	110		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	31 minus 20 =	11	x$26	286	OR	x$52	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	7 minus 3 =	* 4	x$110	440		x$220	
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $270 ($135 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR						
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))			195			390	
			TOTAL	1188		TOTAL	

* If the difference in column 1 is less than zero, enter "0" in column 2.

APPLICATION AS AMENDED – PART II

		(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 ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
AMENDMENT A	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))					N/A		OR	N/A	
						TOTAL ADD'T FEE		OR	TOTAL ADD'T FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)	OR	RATE ($)	ADDITIONAL FEE ($)
AMENDMENT B	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))					N/A		OR	N/A	
						TOTAL ADD'T FEE		OR	TOTAL ADD'T 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.