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(54) **Title:** COMPOSITION FOR ADMINISTERING AN ACTIVE INGREDIENT AND METHOD FOR MAKING AND USING THE SAME

(57) **Abstract:** Provided herein are compositions for administering an active ingredient orally or transmucosally having a film layer, a coating applied to at least one side of the film layer, and an active ingredient in the film layer, coating, or both layers. In certain embodiments, the composition also includes an effervescent compound.

COMPOSITION FOR ADMINISTERING AN ACTIVE INGREDIENT AND METHOD FOR MAKING AND USING THE SAME

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation-in-part of and claims priority to the following applications:

1) U.S. Provisional Patent Application No. 60/981,389, filed October 19, 2007 **[57778.8006.US00]**.

2) U.S. Patent Application No. 10/713,544, filed November 14, 2003 **[57778.8001.US01]**, which claims the benefit of U.S. Provisional Patent Application Nos. 60/426,598, filed November 14, 2002 **[57778.8001.US00]** and 60/497,186, filed August 22, 2003 **[57778.8003.US00].**

3) U.S. Patent Application No. 10/402,273, filed March 28, 2003 **[57778.8002.US00]**.

4) U.S. Patent Application No. 10/921,770, filed August 18, 2004 **[57778.8003.US01]** which claims the benefit of U.S. Provisional Patent Application No. 60/497,186, filed August 22, 2003 **[57778.8003.US00].**

5) U.S. Patent Application No. 12/251,349, filed October 14, 2008 **[57778.8004.US01]**, which is a continuation of U.S. Patent Application No. 10/706,810, filed November 12, 2003 **[57778.8004.US00]** which claims the benefit of U.S. Provisional Patent Application No. 60/426,598, filed November 14, 2002 **[57778.8001.US00].**

6) U.S. Patent Application No. 11/417,676, filed May 3, 2006 **[57778.8005.US02]**,

which claims the benefit of U.S. Provisional Patent Application No. 60/677,679, filed May 3, 2005 **[57778.8005.US00]**;

and claims the benefit of U.S. Provisional Patent Application No. 60/677,717, filed May 4, 2005 **[57778.8005.US01]**;

and which is a continuation-in-part of U.S. Patent Application No. 10/713,544, filed November 14, 2002 **[57778.8001.US01]**, which claims the benefit of U.S. Provisional Patent Application Nos. 60/426,598, filed November 14, 2002 **[57778.8001.US00]** and 60/497,186, filed August 22, 2003 **[57778.8003.US00]**;

and which is a continuation-in-part of U.S. Patent Application No. 10/402,273, filed March 28, 2003 **[57778.8002.US00]**;

and which is a continuation-in-part of U.S. Patent Application No. 10/921,770, filed August 18, 2004 **[57778.8003.US01]** which claims the benefit of U.S. Provisional Patent Application No. 60/497,186, filed August 22, 2003;

and which is a continuation-in-part of U.S. Patent Application No. 10/706,810, filed November 12, 2003 **[57778.8004.US00]**, which claims the benefit of U.S. Provisional Patent Application No. 60/426,598, filed November 14, 2002 **[57778.8001.US00]**.

7) U.S. Patent Application No. 11/371,167, filed March 7, 2006,

which is a continuation-in-part of U.S. Patent Application No. 10/921,770, filed August 18, 2004 **[57778.8003.US01**], which claims the benefit of U.S. Provisional Patent Application No. 60/497,186, filed August 22, 2003 **[57778.8003.US00]**;

and which is a continuation-in-part of U.S. Patent Application No. 10/713,544, filed November 14, 2003, **[57778.8001.US01]**, which claims the benefit of U.S. Provisional Patent Application Nos. 60/426,598, filed November 14, 2002 **[57778.8001.US00]** and 60/497,186, filed August 22, 2003 **[57778.8003.US00]**;

and which is a continuation-in-part of U.S. Patent Application No. 10/402,273, filed March 28, 2003 **[57778.8002.US00]**.

The contents of all the applications listed above are incorporated herein by reference.

BACKGROUND

[0002] Pharmaceutical, herbal, or natural ingredients provide relief from symptoms associated with diseases and ailments, or boost the immune system or energy level of the user. Edible films have been known to deliver the active ingredients to the user. U.S. Patents 4,517,173, 4,876,092, and 5,047,244 disclose a two-layer film preparation having a water soluble layer containing film-forming polymers, additives, and pharmaceutical ingredients. The film preparation also contains a second layer that is water insoluble or impermeable for protecting the water soluble layer. U.S. Patents 5,166,233, 5,948,430, 6,419,904 B1, and U.S. Patent Application Publications 2001/0022964 A1 and 2002/0131990 disclose a

single film layer formed from a mixture of film-forming polymer(s), additives, and pharmaceutical or natural ingredients.

[0003] The edible films may be expensive and cumbersome to make and the therapeutic effect may be ill-timed or inconvenient. During the manufacturing of the film, the active ingredient, together with the film forming polymers and additives, undergo intensive heating and shear, which may cause the film to disintegrate or lose its efficacy. Films also have problems with sticking or adhering to each other while in container or when being pressed together during selection, and with bleeding of active ingredients from one film to another effecting dosage control. Therefore, a convenient and inexpensive film composition which is constructed to maintain its integrity when in contact with other film compositions, and which delivers the active ingredient efficiently and at a desired rate over time while allowing the active ingredient to retain its efficacy is in great demand.

SUMMARY

[0004] In an embodiment of the present invention a composition that effectively delivers an active ingredient to a subject orally or transmucosally is provided. The composition has a film layer, a coating applied on the film layer, and one or more active ingredients may be in the coating, the film layer, or in both the coating and the film layer. In certain embodiments, the coating is a powder matrix. In certain embodiments, the active ingredient may be in the form of a powder or may include a powder carrier. In certain embodiments the film layer and coating form a bi-layer composition. In other embodiments, the composition may include more than two layers.

[0005] In another embodiment, a composition is provided which includes a film layer, a coating, one or more active ingredients, and one or more effervescent compounds.

[0006] In certain embodiments, a composition may further contain auxiliary compositions. The active ingredient may be a pharmaceutical ingredient, an herbal ingredient, a nutritional supplement, or a mixture thereof. Optionally, the active ingredient may be in a controlled release dosage form.

[0007] In certain embodiments, a method for using the composition by administering the composition to a subject orally or transmucosally is provided. In certain embodiments, the composition will dissolve rapidly upon administration to an oral mucosa or other mucosal membrane.

[0008] Furthermore, in certain embodiments, a method for making a composition is provided which includes forming the film layer with an active ingredient, forming a coating, and applying the coating to the film layer. Optionally, the coating, rather than the film layer can be formed with an active ingredient or both the film layer and the coating may be formed with an active ingredient. These methods are applicable with various active ingredients and help ensure that the active ingredients retain their efficacy during the manufacturing process.

DETAILED DESCRIPTION

[0009] The following description of the invention is merely intended to illustrate various embodiments of the invention. As such, the specific modifications discussed are not to be construed as limitations on the scope of the invention. It will be apparent to one skilled in the art that various equivalents, changes, and modifications may be made without departing from the scope of the invention, and it is understood that such equivalent embodiments are to be included herein.

[0010] The terminology used in the description presented below is intended to be interpreted in its broadest reasonable manner, even though it is being used in conjunction with a detailed description of certain specific embodiments of the invention. Certain terms may even be emphasized below; however, any terminology intended to be interpreted in any restricted manner will be overtly and specifically defined as such in this detailed description section.

[0011] Where the context permits, singular or plural terms may also include the plural or singular term, respectively. Moreover, unless the word "or" is expressly limited to mean only a single item exclusive from the other items in a list of two or more items, then the use of "or" in such a list is to be interpreted as including (a) any single item in the list, (b) all of the items in the list, or (c) any combination of items in the list.

[0012] In certain embodiments of the invention, the composition has a soluble film layer, a coating applied on at least one side of the film layer, and an active ingredient that is contained in the coating, the film layer, or both the coating and film layer. The film layer may be soluble in water and/or saliva and/or other aqueous solutions. In other embodiments, the film layer may be hydrophobic.

[0013] The composition may be in the form of a thin film with any convenient shape suitable for administration, such as a film strip. In one embodiment, the film strip weighs about 10 to 80 mg per strip. Preferably, the film strip weighs about 20 to 70 mg per strip or about 30 to 60 mg per strip or about 50 mg per strip.

[0014] In certain embodiments of the composition, the active ingredient weighs about 0 to 40% of the composition. Preferably, the active ingredient weighs about 0.25 to 30% of the composition or about 5 to 25% of the composition or about 15 to 20% of the composition.

[0015] In one embodiment, the active ingredient may weigh up to about 20 mg per film strip. In another embodiment, the film strip delivers about 12.5 mg active ingredient. In yet another embodiment, the film strip delivers about 3 mg benzocaine and/or 3 mg menthol for sore throat and cough relief. In yet another embodiment, the film strip delivers about 20 mg caffeine to the user to provide hangover relief and boost energy.

[0016] The film strip may be in any shape that is suitable for oral administration or applicable to mucous membranes of various body parts of a subject. The film strip may be generally rectangular in shape. In one embodiment, the film strip may be generally rectangular in shape having a dimension of about $^{13}/_{16}$ inch by $1^{1}/_{4}$ inch. Alternatively, the film strip may be circular with a diameter of about 3/8 inch. Such a film strip may be suitable for application to the eye ball or mucous membranes located in other areas of the body.

[0017] The composition, e.g., film strip, is constructed to have an acceptable dissolution rate in the oral cavity or on various mucous membranes of a subject. The composition may dissolve in about 1 second to 5 minutes. Preferably, in about 1 second to 2 minutes, or more rapidly in about 1 to 60 seconds, or 1 to 30 seconds.

[0018] In certain embodiments, a film layer may have a thickness of about 0.01 to 3.00 mm. Preferably, the film layer has a thickness of about 0.03 to 1.10 mm or about 0.04 to 1.00 mm.

[0019] In certain embodiments, a film layer may be made from a polymer, softener, filler, or matrix. The film layer is constructed to have an acceptable dissolution rate in the oral cavity for a particular thickness. For example, if the film layer has a thickness of 50 microns, the film layer may dissolve in the oral cavity within about 15 seconds. The film layer may vary in thickness. The film layer may dissolve in about 1 second to 5 minutes. Preferably, in about 1 second to 2 minutes, or more rapidly in about 1 to 60 seconds, or 1 to 30 seconds.

[0020] The film layer may be made from a natural or synthetic polymer. In certain embodiments, the polymer is water soluble. In other embodiments, the polymer may be soluble in saliva and/or other aqueous solutions and/or the polymer may be hydrophobic. Preferably, the polymer has good film moldability, produces a soft flexible film and is safe for human consumption. The polymer may be a water-soluble cellulose derivative such as hydroxypropyl cellulose (HPC), methyl cellulose, hydroxypropyl alkylcellulose, carboxymethyl cellulose or the salt of carboxymethyl cellulose. Alternatively, the polymer may comprise an acrylic acid copolymer or its sodium, potassium or ammonium salt. The acrylic acid copolymer or its salt may be combined with methacrylic acid, styrene or vinyl type of ether as a comonomer, poly vinyl alcohol, poly vinyl pyrrolidone, polyalkylene glycol, hydroxy propyl starch, alginic acid or its salt, poly-saccharide or its derivatives such as trangacanth, bum gelatin, collagen, denatured gelatin, and collagen treated with succinic acid or anhydrous phthalic acid. The film layer may be made from pullulan, maltodextrin, pectin, alginates, carrageenan, guar gum, or other gelatins. The film layer may optionally contain additives known in the art.

[0021] In certain embodiments, the coating has a thickness of about 0.001 to 3.00 mm. Preferably, the coating has a thickness of about 0.007 to 1.00 mm or about 0.01 to 0.02 mm. In one embodiment, a coating is in the form of a powder matrix, and the active ingredient is in the powder matrix as a powder itself or with a powder carrier. The particle size of the powder matrix may be about 10 to 400 mesh. Preferably, the particle size is about 40 to 300 mesh.

[0022] In certain embodiments, the composition may contain one or more auxiliary compositions in the film layer, the coating, or both. Some auxiliary compositions serve as a suitable carrier for an active ingredient, others render desired texture and appeal to the composition. The auxiliary composition may be a dissolution-control agent, an absorption agent, a mucoadhesive agent, an adhesive, a buffering agent, a permeation enhancer, a flow agent, a softener, a cooling agent, a surfactant, a drying agent, an oil, a bulking agent, a filler, a pigment or a coloring agent, a flavoring agent, an odorant, or any combination thereof. In certain embodiments, the auxiliary composition is about 0.5 to 40 wt% of the composition. Preferably, it is about 1 to 30 wt% or about 1 to 20 wt% of the composition.

[0023] A dissolution-control agent can dissolve slowly over a selected period of time and may slow the release of active ingredient in the oral cavity or on the mucous membrane. The dissolution-control agent includes, e.g., gel forming compositions like carrageenan, gelatin, alginates, pullulan, PVP, and other hydrophilic materials; cyclodextrin; inert materials fibers, calcium, and fillers. In one embodiment, fibers may comprise carboxymethylcellulose.

[0024] An absorption agent absorbs water, saliva, or other aqueous solutions in the oral cavity or on other mucous membranes. One example of an absorption agent or absorbent is a mineral, such as magnesium trisilicate. In certain embodiments, an absorption agent may be used to slow the release of an active ingredient. In other embodiments, the absorption agent may be used to form a gel. The gel may cause the film strip to become chewable, similar to a very soft jelly-bean. For example, the gel may, when placed in the oral cavity or in contact with body fluid, absorb at least four times its weight of water or of saliva or other aqueous solutions in a selected period of time, or swell to at least three times its thickness in a selected period of time. The selected period of time can vary. In certain embodiments, the period of time is from about 1 second to 15 minutes or about 5 seconds to 5 minutes or about 10 seconds to 2 minutes. Examples include carboxymethylcellulose, pectin, modified starches, gelatin, and carrageenan. These compositions may be used alone or in combination. The gel may slow the dissolution of the active ingredient in certain embodiments, and thus, maintain the active ingredient in the oral cavity for a longer period of time. A gel may also be made to dissolve more rapidly is so desired.

[0025] The mucoadhesive agent, when placed in the oral cavity in contact with the mucosa therein, adheres to the mucosa. The mucoadhesive agent is especially effective in transmucous delivery of the active ingredient, as the mucoadhesive agent permits a close and extended contact of the composition with the mucosal surface by promoting adherence of the composition or drug to the mucosa, and facilitates the release of the active ingredient from the composition. The mucoadhesive agent is preferably a polymeric compound, such as a cellulose derivative but it may be also a natural gum, alginate, pectin, or such similar polymer. The concentration of the mucoadhesive agent in the coating, such as a powder matrix coating, may be adjusted to vary the length of time that the film adheres to the mucosa or to vary the adhesive forces generated between the film and mucosa. The mucoadhesive agent may adhere to oral mucosa or to mucosa or tissue in other parts of the body, including the mouth, nose, eyes, vagina, and rectum. Mucoadhesive agents include, e.g., carboxymethylcellulose, polyvinyl alcohol, polyvinyl pyrrolidone (povidone), sodiumalginate, methyl cellulose, hydroxyl propyl cellulose, hydroxypropylmethyl cellulose, polyethylene glycols, carbopol, polycarbophil, carboxyvinyl copolymers, propylene glycol alginate, alginic acid, methyl methacrylate copolymers, tragacanth gum, guar gum, karaya gum, ethylene vinyl acetate, dimenthylpolysiloxanes, polyoxyalkylene block copolymers, and hydroxyethylmethacrylate copolymers.

[0026] The buffering agent aids in the transmucosal delivery of the active ingredient in the composition. Generally, an active ingredient in an un-ionized form is more readily transported across the mucosal membrane. Therefore, the composition of certain embodiments of the present invention may include an agent for adjusting pH conditions to maximize or minimize the percentage of un-ionized active ingredient available in the oral cavity, and thus, to modulate the rate of mucosal absorption of an active ingredient. Buffering agents are important for those active ingredients that partially ionize within the pH range of the mouth, such as weak acid and weak base drugs. Generally, buffering agents are important when hydrophilic active ingredients are used because those drugs usually have lower mucosal permeability and dissolve more readily in saliva within the mouth. In one embodiment, the film layer includes one or more buffer forming agents, pH control agents, or both. In another embodiment, the powder matrix layer includes one or more buffer forming agents, pH

control agents, or both. In yet another embodiment, both layers include one or more buffer forming agents, pH control agents, or both.

[0027] The permeation enhancer improves the permeability of an active ingredient at the mucosal membrane. One or more permeation enhancers maybe used to modulate the rate of mucosal absorption of the active ingredient. Any effective permeation enhancers may be used, depending on the type of the active ingredient and the desired effect. Permeation enhancers include, for example, bile salts, such as sodium cholate, sodium glycocholate, sodium glycodeoxycholate, taurodeoxycholate, sodium deoxycholate, sodium lithocholate chenocholate, chenodeoxycholate, ursocholate, ursodeoxy-cholate, hyodeoxycholate, dehydrocholate, glycochenocholate, taurochenocholate, and taurochenodeoxycholate; sodium dodecyl sulfate (SDS), dimethyl sulfoxide (DMSO), sodium lauryl sulfate; salts and other derivatives of saturated and unsaturated fatty acids, surfactants, bile salt analogs, derivatives of bile salts, or such synthetic permeation enhancers as described in U.S. Pat. No. 4,746,508, which is hereby incorporated by reference.

[0028] In certain embodiments, the adhesives may be poorly water-soluble cellulose derivatives including ethyl cellulose, cellulose acetate and butyl cellulose; shellac; higher fatty acids including steric acid and palmitic acid.

[0029] The flow agent, when subjected to a curing process, flows to form a smoother or shinier coating on the exterior of the film layer. One preferred curing process includes heating the film layer with a powder coating to a selected temperature above 76°F to cause the auxiliary flow composition to soften and flow. Examples of auxiliary compositions are lipids (animal and vegetable fats), waxes, particularly low melting point waxes, and polyols, particularly low melting point polyols that may be admixed in a powder form or included in powder particles containing the active ingredient or other compositions. The active ingredient itself may have the property of flowing at an elevated temperature in excess of 76 °F to form a smoother or shinier coating.

[0030] In certain embodiments, the flow agent is a lipid, e.g., BENEFAT™ as used by DANISCO to designate salatrim, an abbreviation for long and short chain triglyceride molecules. Preferably, a lipid is in a powder form. If the lipid is in a

liquid form, it may optionally be plated on an absorbent to produce a flowable powder. The absorbent may be talc. Ideally, the melting point of the lipid is close to the temperature at which the film layer is dried. For example, the film layer along with the powder matrix layer applied to the film layer may be dried at about 200°F, and the lipid preferably has a softening point or melting temperature of about 200°F so that the drying temperature for the film layer is the ideal softening point or melting temperature for the lipid. If the melting temperature of the lipid is too low in comparison to the temperature at which the film layer is dried, the lipid may melt and run off the film. During the heating treatment of the composition, the lipid powder particles soften and flow to produce a smoother powder matrix layer on the film layer. The smoother powder matrix layer also helps improve the feel by an individual while inside the mouth, because the composition is not dry on the tongue.

[0031] The flavoring agent and/or odorant make the composition more palatable. At least one flavoring agent or odorant composition may be used. Any effective flavor or odor may be rendered. The flavoring agents may be natural or artificial, or both. The flavoring agent gives a flavor that is attractive to the user. In one embodiment, the flavoring agent may give the flavor of mint, Honey Lemon, orange, Lemon Lime, grape, Cran Razz, Vanilla Berry, Kids Grape, or cherry. In certain embodiments, the flavoring agent may be natural or artificial sweetener well known in the art. A suitable amount and method for adding the flavoring agent or odorant would be known to a person of skill in the art.

[0032] A bulking agent may include avicel, sugar alcohols including manitol, sorbitol, and xylitol, isomalt, lactic sugar, sorbitol dextrin, starch, anhydrous calcium phosphate, calcium carbonate, magnesium trisilicate, silica, and amylase.

[0033] In certain embodiments, moisture may exist in the powder matrix in the form of a minor amount of retained or bound water or other liquid, typically no more than about .001 to 10 wt% of the powder matrix or the composition. Optionally, the amount of moisture may be from about .001 to 8 wt% or about .01 to 5 wt% or about 1 to 3 wt%. The moisture in the powder matrix should not cause powder particles to stick or adhere to one another during the intermixing of powders to form the powder matrix or application of the powder matrix to the film layer. The moisture in the powder matrix should not cause individual film strips to stick or adhere to one another or to other materials, such as packaging or container materials. Any moisture should

also be sufficiently low not to cause a premature reaction or instability of active agents or effervescent compounds or any ingredient present in the powder matrix or composition.

[0034] In certain embodiments, combinations of auxiliary compositions may be used to achieve desired effects. In certain embodiments, the coating may be in the form of a powder matrix which includes an absorption agent to help prevent sticking and/or a softening agent to improve the feel and texture and/or a flavoring agent or sweetener to mask the bitter or unfavorable taste of an active ingredient which may be present in a film layer. Preferably, such a powder matrix contains a minimal amount of moisture or water content, e.g., from about .001-10 wt%, such that it can protect the film layer and any active ingredients in the film layer from moisture. The powder matrix maintains the stability of active agents present in the film layer and prevents sticking or adhesion of individual film strips to one another. For example, in one embodiment, an active agent such as glycerin is used. Glycerin is unstable and can become sticky or adhesive if exposed to certain amounts of moisture. The powder matrix, however, coats the film layer and protects the glycerin present in the film layer thereby maintaining the stability of the film strip and preventing sticking of the individual film strips to one another, e.g., while in container, or to other substances or materials that may come into contact with the film strips. In another embodiment an active agent, e.g., glycerin, may be present in the powder matrix where it is protected and its stability maintained.

[0035] In one embodiment, a film layer is coated with a powder matrix which includes magnesium trisilicate (talc) and/or starch and/or a flavoring agent such as acesulfame potassium to help mask the taste of an active ingredient present in the film or optionally present in the powder matrix. Preferably, the magnesium trisilicate and starch are present in a ratio of about 1:1. Preferably, the powder matrix has a low moisture or water content, e.g., from about .001-10 wt%, which protects and helps maintain the stability and integrity of the film strip.

[0036] In certain embodiments, combinations of auxiliary compositions may be used to achieve desired effects such as slowing the dissolution of an active ingredient. Less soluble fillers and fibers may be included in the powder matrix along with a high concentration of polymers having a high degree of ability to adhere to the oral mucosa lining in the mouth or to other mucosa membranes or linings.

[0037] In certain embodiments, the active ingredient may be a pharmaceutical ingredient, herbal ingredient or extract, a nutritional supplement, or a combination thereof. Suitable combinations of the active ingredients may provide synergistic or complementary effects to the user. Active ingredients may be combined to treat multi-symptom conditions.

[0038] A pharmaceutical ingredient is an agent that cures, treats, or prevents a disease or disease symptom or condition in a body or portion of a body.

[0039] The amount of pharmaceutical ingredient used in a composition depends on its type and desired therapeutic effect. For example, the pharmaceutical ingredient may be about 0.001 to 20 wt%. In certain embodiments, the pharmaceutically active ingredient or agent may be present in an amount ranging from about 0.5 to 40 wt% or about 1 to 30 wt% or about 5 to 15 wt% or about 0.5 to 15 wt%. The pharmaceutical ingredient may be in a controlled release, enteric release, delayed release, fast release, slow release, or immediate release form.

[0040] A variety of pharmaceutical or active ingredients may be used in the compositions described herein. Nonlimiting examples of such pharmaceutical or active ingredients and various uses for such ingredients are set forth herein.

[0041] In certain embodiments, the pharmaceutical ingredient may be used to treat sore throat (pharyngitis). Treatment may include a local anesthetic or narcotic agent, for examples, benzocaine, lidocaine, procaine-hydrochloride, and a mixture thereof; an oral sterilizing agent or antiseptics, for examples, phenol, chlorohexidine, cetylpyridinium, hexylresorcin, nitro-furazone, and a mixture thereof. In addition, the active ingredient for treating pharyngitis may include menthol and/or naturally occurring herbs, plants, vitamins, and/or oils which can relieve the symptoms of pharyngitis and cough.

[0042] The pharmaceutical ingredient may be used to treat cough. Treatment may include an antitussive, for example, dextromethorphan, benzonatate, caraminophen, chlophedianol, codeine, codeine phosphate, bisorlvon, camphor, menthol, theobromine, or a mixture thereof; an expectorant, for example, guaifenesin, ipecac, potassium iodide, terpin hydrate, or a mixture thereof; a mucolytic, for example, bromhexine.

[0043] The pharmaceutical ingredient may be used to treat symptoms arising from allergic reactions, nasal allergies, or hay fever including sneezing, runny nose, redness, inflammation and itching. Treatment may include an anti-histamine, for example, brompheniramine, cetirizine, chlorpheniramine, carbinoxamine, clemastine, cyproheptadine, dexchlorpheniramine, dimenhydrinate, diphenhydramine, doxylamine, fexofenadine, loratadine, promethazine, pyrilamine, tripelennamine, triprolidine, diphenhydramine hydrochloride, chlorophenylamine maleate, or a mixture thereof; corticosteroid, for example, fluticasone, mometasone, dexamethasone, or a mixture thereof.

[0044] The pharmaceutical ingredient may be used to treat nasal or sinus congestion related to the common cold or allergies. Treatment may include a decongestant agent, for example, pseudoephedrine, phenylepherine, phenylpropanolamine, or a mixture thereof.

[0045] The pharmaceutical ingredient may be used to treat headaches, joint pain, muscle pain, and other acute or chronic pain. Treatment may include an analgesic and/or non-steroidal anti-inflammatory anodynes, for example, aspirin, aminopyrin, acetoaminophen, ibufenac, ibuprofen, indomethasine, colehicine, sulpyrine, mephenamic acid, phenacetin, phenylbutazone, fulfenamic acid, probenecid, carprofen, ketoprofen, naproxen, diflunisal, fenoprofen calcium, tolmentin sodium, indomethacin, celecoxib, or a mixture thereof; anti-inflammatory steroids, for example, predonisone, predonisolone, predonisolone acetate, hydrocortisone, triamcinolone, dexamethasone, or betamethasone; anti-inflammatory enzymes, for example, (a)-chymotrysin; narcotic analgesics, for example, morphine, codeine, oxycodone, hydrocodone, buprenorphine, or a mixture thereof.

[0046] The pharmaceutical ingredient may be used to treat diarrhea. Treatment may include an anti-diarrhea agent, for example, loperamide, psyllium, or a mixture thereof.

[0047] The pharmaceutical ingredient may be used to control stomach acid levels and treat heartburn or ulcers. Treatment may include the use of any effective antacid, for example, sodium bicarbonate, calcium carbonate, aluminum-based compounds, magnesium compounds, aluminum-magnesium compounds or mixtures thereof; H2-antagonists, for examples, cimetidine, ranitidine, famotidine, nizatidine or

mixtures thereof; or protein pump inhibitor agent, for example, omeprazole, lansoprazole, esomeprozole, pantoprazole, rabeprazole, or a mixture thereof.

[0048] The pharmaceutical ingredient may be used to treat insomnia. Treatment may include a hypnotic agent, for example, quazepam, diazepam, lorazepam, zolpidem, zaleplon, eszopiclone, or a mixture thereof; an antihistamine, for example, diphenhydramine, doxylamine, or a mixture thereof.

[0049] The pharmaceutical ingredient may be used to treat motion sickness. Treatment may include an antihistamine, for example, diphenhydramine, dimenhydrinate, or a mixture thereof.

[0050] The pharmaceutical ingredient or an active ingredient may be used to treat erectile dysfunction. Treatment may include phosphodiesterase inhibitors, for example, sildenafil citrate, tadalafil, vardenafil, or a mixture thereof.

[0051] The pharmaceutical ingredient may be used to treat infection caused by microbial organisms. Treatment may include an antibiotic or antibacterial, including, for example, amikacin, betamethasone, clindamycin, clotrimazole, gentamicin, kanamycin, oxytetracycline, penicillin or a derivative, tetracycline or tetracycline hydrochloride, enrofloxacin, norfolzacin, ciproflozacin, danofloxacin, kitasaamycin tartrate, rozithromycin, diclazuril, peflozacin, sarafloxacin, cephaphalosporin derivative, erythromycin or a derivative, furadiomycin, leucomycin, or a mixture thereof; an anti-parasitic, for example, avermectins, praziquantel, or a mixture thereof.

[0052] The pharmaceutical ingredient may be an oral sterilizing agent, for example, chlorohexydine-hydrochloride, cetylpyridinium-chloride, hexylresorcin, or nitro-furazone; chemically therapeutic agent, for examples, sulfamethyzole or nalidixic; cardiac strengthening agent, for example, digatalis or digoxin; blood vein dilating agent, for example, nitroglycerine or papaverine-hydrochloride; periodontal disease treatment agent, for example, peptides; digesting organ curing agent, for example, azulene, or phenovalin, pepsin, vitamin U; enzyme, for example, lysozyme-chloride or trypsin; anti-diabetic agents such as insulin; blood pressure depressing agents; tranquilizers; styptic agent; sexual hormone; agent for curing virulent carcinoma.

[0053] In certain embodiments, the pharmaceutical ingredient is an active form of the therapeutic reagent. In certain embodiments, the pharmaceutical ingredients may be administered in the form of pharmaceutically acceptable salts, esters, amides, prodrugs, or a combination thereof. In certain embodiments, conversion of inactive ester, amide, or prodrug forms to an active form must occur prior to or upon reaching the target tissue or cell.

[0054] In certain embodiments, the film layer or coating may contain a pharmaceutically suitable carrier for a pharmaceutical ingredient. A suitable pharmaceutical carrier may be the auxiliary composition, namely, the absorption agents, buffering agents, bulking agents, coatings, dissolution control agents, flavors, mucoadherents, permeation enhancers, colors, sweeteners, or a mixture thereof. Optionally, the film layer or coating may include additional carriers, such as excipients known in the art, for the pharmaceutical ingredient.

[0055] In certain embodiments, herbal ingredients may be used for treating diseases, relieving ailments and symptoms, boosting the immune system or energy level, or improving the overall wellbeing of the user. Herbal ingredients refer to natural or cultivated herbal plant, or any portion thereof, including the fruit, stem, leave, flower, root, seed, or any extract or preparation thereof, such as essential oil, tincture, decoction, containing single chemical compound or a mixture of known or unknown compounds from further processing of the plant, that are safe for human consumption and have desired efficacy. Herbal ingredients may provide an alternative to the pharmaceutical ingredient, or a complement which balances the function of the pharmaceutical ingredient in combination, for users who prefer a holistic approach to life. Herbal ingredients containing high water or moisture content may be dried by heating or other conventional methods in order to remove the water or moisture content and to be used in a composition of certain embodiments of the present invention.

[0056] Herbal ingredients may be readily obtained from the market. Herbal ingredients may also be processed from harvested herbal plants. Processing techniques and extraction methods suitable for a particular herbal plant are usually known and practiced for generations. When multiple herbal ingredients are used, they may be mixed and processed together in a manner that retains their efficacy.

[0057] Herbal ingredients may provide allergy or pain relief. Echinacea extracts are used to treat rhinovirus colds and Nigella sativa (Black cumin) may be used to treat diverse ailments such as cough, pulmonary infections, asthma, influenza, allergy, hypertension, and stomach ache. Phytolacca (Pokeweed) may be used as a homeopathic remedy to treat many ailments topically or internally. Arnica (*Arnica montana*) is a mountain plant used for relief of bruises, sprains, stiffness, and muscle soreness, and as a tincture for anti-inflammatory treatment and pain relief. In one embodiment of the present invention, the active ingredient in the composition is Arnica extract, and the composition is used for homeopathic pain relief.

[0058] Herbal ingredients may be used for treating pharyngitis and cough. Such herbal ingredients include herbs, including Adrogrophis paniculata, Agrimony (agriminio eupatoria), bistort (polygonum bistora), blue gum tree (eucalytus globulus), club moss (lycopodium clavatum), fenugreek, garden thyme (thymus vulgaris), ginger, golden seal (hydrastid candenis), kava kava, lady's mantle (alchemilla vulgaris), lavender (lavedula spp.), lobelia, loosestrife (lythrum salicaria), Marsh cudweed (gnophthalum uliginosum), myrrh (commiphora molmol), peppermint (mentha piperita), phosphorous, poker root (phytolacca americana), pokeweed (phytolacca decandra), purple cone flower (echinacea puprea), purple sage (salvia officenalis), S. Benzoin, gum Benjamin, solanum, tea tree oil (melaeuca alternifolia), and wild indigo (baptisma tinctoria); trees and plant sources, including aloe, bee pollen, blackberry, camphor oil, cayenne, elderberry, gum arabic, honey, licorice extract, maitake extract, olive leaf extract, sage oils, sarsparilla, sweet oil of birch, shitake extract, slippery elm, and willow bark; essential oils and flavors, including cinnamon oil, clove oil, fennel seed oil, lemon oil, menthol, eucalyptus oil, peppermint oil, rosemary oil, spearmint oil, and wild cherry oil. Menthol and Pectin provide relief for cough.

[0059] Herbal ingredients may serve as an appetite suppressant, and thus, help lose weight or control weight. *Gymnema sylvestre* is an herb from the tropical forest of southern and central India. This herb alters the taste of sugar when placed in the mouth, thus fights sugar cravings. Extracts of Gymnema are not only used to curb sweet tooth but also for treatment of hyperglycemia, overweight, high cholesterol levels, anemia, and digestion. In one embodiment of the present invention, the active ingredient in the composition is Gymnema extract, and the composition is used as an appetite suppressant.

[0060] Herbal ingredients may be used to treat erectile dysfunction. For example, Asian Ginseng (*Panax ginseng*), Yohimbe, *Butea superba*, *Ginkgo biloba*, Horny goat weed, Muira puama (*Ptychopetalum olacoides*), and Damiana (*Turnera diffusa*) are used for treating erectile dysfunction.

[0061] Herbal ingredients may boost the function of the immune system and immune defense of the body, help fight fatigues, improve cognitive function, boost energy level, and provide hangover relief to the user.

[0062] Guarana (*Paullinia cupana;* syn. *P. crysan, P. sorbilis*), is a climbing plant in the Sapindaceae family, native to the Amazon basin. While Guarana fruit is about the size of a coffee berry, each contains about one seed having approximately three times more caffeine than the coffee bean. Caffeine is a stimulant of the central nervous system, cardiac muscle, as well as the respiratory system. In one embodiment of the present invention, Guarana extract may be used such that the caffeine amount in each film strip is about 20 mg.

[0063] American Ginseng (*Panax quinquefolius*) is an herbaceous perennial in the ivy family that is commonly used in medicine. Native to North America, it is also cultivated beyond the continent. The plant's root and leaves are used for medicinal purposes. American ginseng is believed to enhance the immune system, help the body fight off infection and disease. In several clinical studies, American ginseng improved the function of cells that play a role in immunity. In one embodiment of the present invention, the active ingredient is American Ginseng extract, and the composition is used to aid in prevention of mental and physical fatigue and increase cognitive function.

[0064] Ginkgo (*Ginkgo biloba*) is a unique tree in the family of Ginkgoaceae. Ginkgo leaf extract contains flavonoid, glycosides, and terpenoids (ginkgolides, bilobalides) and may be used as a memory enhancer and anti-vertigo agent. Ginkgo extract seems to improve the blood flow including microcirculation in small capillaries to most tissues, function as an anti-oxidant, and block the platelet aggregation which may cause cardiovascular, renal, respiratory, and central nervous system disorder. In one embodiment of the present invention, the active ingredient is Ginkgo extract, and the composition is used to improve blood flow to tissues and organs, as an antioxidant, improve cognitive function, or treat erectile dysfunction.

[0065] Cranberries are evergreen dwarf shrubs or trailing vines in the genus *Vaccinium*, subgenus *Oxycoccus*, or in the genus *Oxycoccus*. Cranberries contain polyphenol antioxidants and phytochemicals that are beneficial to the cardiovascular and immune system. Cranberry may be used against bacterial infections in the urinary system. Cranberry contains a high molecular weight non-dialyzable material that is able to inhibit and even reverse the formation of plaque by *Streptococcus mutan* pathogens that cause tooth decay. In one embodiment of the present invention, the active ingredient is Cranberry extract, and the composition is used to boost immune defense, prevent bacterial infection in the urinary tract, or prevent or treat dental decay.

[0066] Nutritional supplements are known to maintain the normal function of the body, treat disease, relieve ailments and disease symptoms, fight off fatigue, or boost the immune system or energy level of the user. Nutritional supplements may be combined with the herbal ingredient or the pharmaceutical ingredient.

[0067] Further, nutritional supplements may be used to orally replace nutrients lost during vomiting, diarrhea, heavy perspiration, fluid loss, or other natural nutrient deficiencies related the body's genetic makeup or current genetic state. Transmucosal nutrient supplements may be used in mild, moderate, or severe cases of nutrient loss.

[0068] Nutritional supplements include minerals, for example, Iron, Sodium, Calcium, Magnesium, Zinc, Molybdenum, Copper, Potassium, Manganese, Aluminum, Arsenic, Bromine, Cadmium, Chromium, Chlorine, Cobalt, Fluorine, Iodine, Molybdenum, Nickel, Phosphorus, Selenium, Silicon, Vanadium, Zinc; salts, for example, chlorides, bicarbonates, phosphates, and carbonates; carbohydrates, proteins, sugars such as glucose, and amino acids; Vitamins, for example, Vitamin A, Vitamin B family members including Vitamin B1 (Thiamine), B2 (Riboflavin), B3 (Niacin), B5 (Pantothenic Acid or Pantethine), B6 (Pyridoxine), B7 (Biotin or Vitamin H), B9 (Folic Acid), B12 (Cyanocobalamine), and unofficial B Vitamins including Choline and Inositol, Vitamin C, Vitamin D, Vitamin E, Vitamin K, Vitamin P (bioflavonoids); electrolytes, for example, primary ions of electrolytes including sodium (Na^+), potassium (K^+), calcium (Ca^{2+}), magnesium (Mg^{2+}), chloride (Cl^-), phosphate (PO_4^{3-}), and hydrogen carbonate (HCO_3).

[0069] Nutritional supplements for treating pharyngitis and cough include vitamins and minerals, including co-enzyme Q10, colloidal silver, Vitamin C, Vitamin E, and Zinc; and bacteria, for example, lactobacillus acidophilus.

[0070] In one embodiment, the active ingredients are Vitamin C and/or Zinc. The composition improves the immune defense in the user.

[0071] In another embodiment, the active ingredients are electrolytes. The composition provides electrolyte replacement and replenishment to the user.

[0072] In another embodiment, the active ingredients are Calcium and/or Magnesium. The composition is useful for maintaining bones and normal nerve transmission.

[0073] In another embodiment, the active ingredients are Guarana extract, Vitamin B12, and/or electrolytes. The composition provides hang over relief to the user.

[0074] In another embodiment, the active ingredients are Guarana extract and/or Vitamin B12. The composition provides energy to the user.

[0075] In another embodiment, the active ingredient may be Vitamin B1, B2, B6, B12, or any combination thereof. Vitamin B1 enhances circulation and is used in biosynthesis of acetylcholine. Vitamin B2 is essential for cell metabolism. Vitamin B6 regulates serotonin level in the body. Vitamin B12 promotes energy production. Therefore, the combined use of the vitamins also provides benefits to the user.

[0076] Exemplary formulations for compositions in certain embodiments of the present invention are provided in Tables 1 and 2 with the preferred ranges.

Table 1. Film Strip I.

Ingredients	Preferred Weight %	More Preferred Weight %
Water	0-25	5-15
N & A Cherry Oil	0-25	10-20
Carrageen	0-10	3-6
Acesulfame Potassium	0-0.1	0.2-0.6

Sucralose	0-5	1-3
Lecithin	0-1	0.2-0.6
Benzocaine	0-12	3-9
Pectin **	20-60	35-50
Glycerin	0-10	2-8
Sodium Benzoate	0-2	0.05-0.2
Polysorbate 80	0-0.5	0.05-0.35
Menthol	1-12	3-9
Carboxylmethyl cellulose	1-12	3-9

Note: in the above formulations, the finished film strip contains about 8-10 wt% moisture; ** Pectin may be replaced by up to 5% of Gelatin, Maltodextrin, modified food starch, TiO_2, or Acacia Gum.

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Table 2. Film Strip II.

Ingredients	Preferred Weight %	More Preferred Weight %	Most Preferred Weight %
Tapioca Starch	2-65	18-25	22.8
Pullulan	3-85	15-25	20
Pectin	1-30	15-25	20
Gum Arabic	0.05-8	2-4	3
Maltodextrin	2.5-15	4-6	5
Polysorbate	0.01-2	0.075-0.175	0.15
Sodium Saccharin	0.05-0.75	0.1-0.4	0.25
Alginate	5-30	8-12	10
Carrageenan	1-5	1.5-3	2.5
Clove oil	0.25-10	2-7	5

Cinnamon oil	0.25-10	2-7	5
Echinacea	1-10	1-3	2.5
Vitamin E	0.25-5	0.5-2	1
Slippery Elm	1-10	2-6	5
Aloe Vera	1-7.5	1.5-3.5	2

Note: wt% is dry weight, and the finished film strip contains about 8-10 wt% moisture.

[0077] In certain embodiments, active ingredients may be present in the coating, the film layer, or both the coating and the film layer. In certain embodiments, the composition contains multiple coatings coated on the film layer. In certain embodiments, coatings may have multiple active ingredients or agents, respectively. In certain embodiments, the composition may contain multiple layers of film layers and coatings. In certain embodiments, a film layer may have multiple active ingredients or agents. If desired, multiple powder matrix layers may be applied to the film layer. The film layer may comprise a laminate of two or more layers. In certain embodiments, the composition is a bi-layer having a film layer and a coating on the film layer. Preferably, the coating is a powder matrix coating.

[0078] In certain embodiments, the composition may be edible and dissolve in an oral cavity of the user, e.g., a composition in the form of an edible thin film strip. Alternatively, the composition may be adhesive to various mucous membranes of the body, e.g., to the eye. The composition may have an effective dissolution rate in the oral cavity. The effective dissolution rate depends on the specific application for the edible film. For example, for immediate delivery of the active ingredient, the film can be manufactured to rapidly dissolve in the oral cavity thus delivering the entire dosage of active ingredient at one time. The film can also be manufactured to dissolve over an extended period regulating the amount of active material delivered to the oral cavity over a desired length of time.

[0079] In certain embodiments, the active ingredient may be in a controlled-release dosage form. The active ingredient may be microencapsulated to provide

controlled-release effect. A controlled release dosage form is a dosage form where the active ingredient is released for a time course or location that is chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as a solution or an immediate release dosage form. Controlled-release dosage forms include, e.g., fast, medium, slow, enteric, delayed, and extended release.

[0080] In certain embodiments, the composition may include a mixture of different controlled-release or immediate release forms to obtain a desired dissolution rate, bioavailability, or bioequivalence profile for one or more active ingredients. The powder matrix coating may include one or more controlled-release active ingredients. Optionally, the film layer and/or powder matrix may include one or more controlled-release active ingredients.

[0081] In certain embodiments, the composition may have multiple individually coated units of active ingredients. Each individual unit may be made available from the formulation upon disintegration when the composition is administered to a subject.

[0082] The active ingredient may be coated with a nominal coating thickness. An effective nominal coating thickness depends on the active ingredient, the coating material, and the desired properties. In certain embodiments, the effective nominal coating thickness may be, e.g., about 50-250 microns or about 50-150 microns or about 50-100 microns.

[0083] An effective particle size of an individually coated unit depends on the active ingredient and the desired properties. The active ingredient may have a particle size greater than about 100 microns or smaller than about 100 microns. Preferably, the active ingredient has a particle size smaller than about 50 microns or smaller than about 25 microns or smaller than about 15 microns. The particle size of the microcapsules may be several to thousands of microns. Preferably, the size of the microcapsules is about 30 to 800 microns or about 40 to 250 microns.

[0084] The active ingredient particles or droplets or controlled release particles or droplets may be coated with a coating material. Typical coating materials may include fats, waxes, triglycerides, fatty acids, fatty alcohols, ethoxylated fatty acids and alcohols, stearates, sugars, poly(ethylene glycol), certain metals, gums, hydrocolloids,

latexes, polymer-based formulations such as polyethylene, ethyl cellulose, ethylene-vinyl acetate, ethylene-acrylic acid, polyamides, or enteric polymers.

[0085] The microencapsulation of active ingredients decreases the disintegration of the active ingredients by moisture and oxidation, evaporation, or sublimation. The active ingredient is protected from reacting with other ingredients, and the unpleasant taste of some active ingredients may be effectively masked.

[0086] One of ordinary skilled in the art understands that the rate at which an active ingredient is released from a microcapsule may be modified, depending on the relative amount and composition of the coating layer and that of the active ingredient, chemistry of the active ingredient, the environment, temperature, nature of the composition, and the microcapsule including its porosity and biodegradability.

[0087] In certain embodiments, the compositions as described herein may be administered to a subject, orally or transmucosally, with the composition containing an effective amount of the active ingredient.

[0088] Transmucosal delivery refers to the delivery of the active ingredient through nasal passage, oral/buccal membrane, or vaginal or urethral suppositories so that the active ingredient is absorbed by the vaginal or penile capillary beds.

[0089] A viscous polysaccharide matrix designed to trap foreign particles that may enter the system coats the mouth, nasal passage, vagina, and urethra. The defensive matrix prevents damage to delicate tissues and capillary beds which lie directly underneath the epithelium. Although the mucous membrane protects the body from foreign matter and pathogens, the area is much more permeable. This permeability allows active ingredients to quickly enter into circulation.

[0090] Transmucosal delivery generally provides rapid uptake of an active ingredient through the thin membrane. Transmucosal delivery offers direct absorption through the mucous membrane to the circulatory system, thus bypassing the gastrointestinal tract and first pass liver metabolism. Transmucosal delivery also provides rapid onset of the active ingredient as it directly enters the circulatory system and is transported to the site of need. Lower Dosage is needed as the delivery bypasses the digestive tract and first pass liver metabolism, and thus results in fewer side effects.

[0091] In certain embodiments, the method for making a composition as described herein includes the steps of separately forming a film layer with an active ingredient, forming the coating, and applying the coating to the film layer. Optionally, the coating may be formed with the active ingredient or both the coating and film layer may include an active ingredient.

[0092] Suitable polymer(s), additives, and methods for forming the film layer depend on the desired rate of dissolution, oral feel for the user, compatibility of the film layer and the active ingredient, production constraint, and cost. The film layer may be thick or thin.

[0093] Water, saliva, or other aqueous solution soluble polymers or generally hydrophobic polymers for making the film layer may be natural or synthetic. The polymer preferably has good film moldability, produces a soft flexible film, and is safe for human consumption. One such polymer may be a water-soluble cellulose derivative like hydroxypropyl cellulose (HPC), methyl cellulose, hydroxypropyl alkylcellulose, carboxymethyl cellulose, or the salt of carboxymethyl cellulose. A polymer may comprise an acrylic acid copolymer or its sodium, potassium, or ammonium salt. The acrylic acid copolymer or its salt may be combined with methacrylic acid, styrene, or vinyl ether as a comonomer, poly vinyl alcohol, poly vinyl pyrrolidone, polyalkylene glycol, hydroxy propyl starch, alginic acid or its salt, poly-saccharide or its derivatives such as trangacanth, bum gelatin, collagen, denatured gelatin, or collagen treated with succinic acid or anhydrous phthalic acid. Other exemplary polymers for producing the film layer include pullulan, maltodextrin, pectin, alginates, guar gum, xanthan gum, gelatin, starches (including corn, potato, rice or tapioca), modified starches, wheat gluten, carrageenan konjac, or locust bean gum.

[0094] In certain embodiments, the film layer may be prepared by forming a homogeneous mixture of the polymer(s) (e.g., water soluble polymers) and additives and optionally an active ingredient, applying the homogeneous mixture on a substrate, drying the mixture, and removing the formed film layer from the substrate. A method for making the film may be found, for example, in U.S. Patent 5,948,430, the contents of which are incorporated herein by reference.

[0095] The mixture of the polymers and additives and one or more active agents may be aerated as a liquid mass before being applied on the substrate to form the film layer. Optionally, the film layer may be partially cured before the coating is applied. Optionally, an active agent may be added to the film along with the polymers and/or additives or after the polymers and/or additives are added to create the film.

[0096] In certain embodiments, the coating may be prepared by admixing a powder matrix with or without an active ingredient in the form of a powder or with a powder carrier in a fluidized bed, and applying the powder mixture to the film layer through atomization, sifting, screening, static, mechanical agitation, or through a liquid carrier. The powder matrix is ordinarily made without solvent. The powder matrix may include auxiliary compositions for the desired property of the composition, as the suitable carrier for the active ingredient, or both.

[0097] The powder matrix may be mixed with auxiliary compositions and optionally with active ingredients to form the coating by using any conventional method. In certain embodiments, the powder matrix is admixed in a fluidized bed that minimizes the generation of shear and heat for certain compositions and active ingredients if present; another advantage of mixing or suspending powder in a fluidized bed is that the dry air suspending the powder particles tends to prevent agglomeration of the particles. In a fluidized bed, dry air or another gas is dispersed upwardly through a plurality of openings to suspend and intermix powder particles. The admixed powder matrix may be stored (i.e., suspended) in the fluidized bed, prior to the application to the film layer.

[0098] The powder matrix may be applied to the film layer in any known manner, including sifting, screening, atomization, static, mechanical agitation, and via a liquid carrier. In certain embodiments, for example, the powder matrix is atomized through a Nordson or similar static spray gun using compressed air. One such gun creates a fine mist spray of powder particles. The gun statically electrically charges the powder particles so they adhere to the surface of the film layer for receiving the powder particles. For another example, the powder particles are admixed with a liquid carrier to form a particle-liquid solution. The particle-liquid solution is sprayed on the film layer and the liquid carrier evaporates, leaving the powder particles on the film. The liquid carrier may not cause the powder particles to dissolve therein.

[0099] In certain embodiments, a powder matrix is applied to the film layer to form the coating after the film layer has been made. The powder matrix may be applied to one or both sides of the film layer. For example, the powder matrix may be brushed, rolled, spread, painted, or otherwise applied onto the film layer using any device known in the art which is suitable for such applications. Alternatively, the powder matrix may include ionized or magnetically charged particles that adhere the powder matrix to the film layer. The thickness of the powder matrix layer may vary, preferably in the range of 0.001 mm to 3.00 mm or 0.01 mm to 1.00 mm.

[00100] The film layer includes an upper outer surface on the top of the film layer and includes a lower outer surface on the bottom of the film and sides or edges forming the perimeter of the film. The upper outer surface is generally parallel to the lower outer surface or at any angle from .01 to 90 degrees. The top of the film may be generally parallel to the bottom of the film or at any angle from .01 to 90 degrees.

[00101] A composition may be cured through any heat treatment known in the art. For example, in certain embodiments, the composition may be heated by a microwave or infrared transmitter. The time for heating under the transmitter varies depending on the amount of moisture to be removed, but typically is about 15-20 seconds. The microwave/infrared bombardment facilitates proper heating by generating the heat in the composition. Subsequently, the composition is heated to 200°F in a convection oven. The length of time in the convection oven varies but is typically about 3-4 minutes. During the heat treatment, lipid powder particles that may be contained in the composition tend to soften and flow to produce a smoother powder matrix layer on the film layer. The smoother powder matrix layer also improves the feel to an individual of the composition in the mouth because the composition is not as dry on the tongue.

[00102] In certain embodiments, after a powder matrix layer is applied to a film layer, an additional layer or layers may be applied over the powder matrix layer to seal the powder matrix layer and slow the dissolution of the active ingredient from the film layer or powder matrix layer if so desired. When the active ingredient is in the film layer and the film layer protected with a dry powder matrix, the likelihood of adverse interactions between the active ingredient and moisture or compositions

comprising the powder matrix or lessened. Also, the active ingredient may be applied to the film layer in a dry powder form and maintain stability as well.

[00103] In certain embodiments, a controlled release dosage form may be prepared where an active ingredient is microencapsulated as individual units and applied to the film layer as the coating itself or together with the powder matrix coating. Microcapsules may be prepared by simple or complex coacervation, interfacial cross-linking, interfacial polymerization, mechanical microencapsulation, polymer dispersion, matrix microencapsulation, solvent evaporation, solvent extraction, spray drying, hot melt microencapsulation (congealing), or supercritical fluid method. One priority application of this application, U.S. Patent Application Publication 2006/0210610 A1 provides a detailed account of the methods, the contents of which has been incorporated herein.

[00104] In certain embodiments, a composition as described in any of the above embodiments may include one or more effervescent compounds. An effervescent compound is useful in promoting and enhancing the absorption of an active agent or medicament in the oral cavity across the buccal, sublingual, or gingival mucosa. Optionally, a composition with an effervescent compound may be used on other mucosal membranes in the body. An effervescent compound can serve as a penetration enhancer which facilitates an increase in the rate and extent of absorption and/or dissolution of an active agent or ingredient. An effervescent compound increases the permeability and/or the uptake of active agents into the blood stream of a subject (human or other animal). An effervescent may be used together with any of the active agents or ingredients described herein. An effervescent may be present in the film layer, coating, or both.

[00105] In certain embodiments, effervescent compounds have the effect of reacting and/or bubbling and releasing various types of gas which help alter the pH of an environment, for example, changing an acidic environment to a more basic environment. This may be beneficial for increasing permeability, absorption, and/or uptake of active agents. Effervescent compounds can evolve gas by means of a chemical reaction which takes place, e.g., upon exposure of the effervescent compound to water, saliva, and/or other aqueous solution in the mouth. The chemical reaction is usually the cause of a reaction between an acid source and a source of carbon dioxide such as, e.g., an alkaline carbonate or bicarbonate (other sources may

be used as well whether they be acidic, basic or neutralizers). The reaction of these two general compounds produces carbon dioxide gas upon contact with water, saliva, and/or other aqueous solutions. Effervescents also help stimulate saliva production which provides additional water to aid in further effervescent action. The increased rate of absorption and permeability of active agents is believed to arise from various mechanisms caused by the effervescent as it effervesces, such as, reducing the mucosal layer thickness and/or viscosity, inducing a change in the cell membrane structure, or increasing the hydrophobic environment within the cellular membrane.

[00106] In certain embodiments, an effervescent compound may include a carbonate source which reacts upon exposure to water and/or saliva in the oral cavity and/or to the natural acids present in the oral cavity. Carbonate sources may include dry solid carbonate and bicarbonate salt such as, e.g., sodium bicarbonate, sodium carbonate, potassium bicarbonate and potassium carbonate, magnesium carbonate and the like. In other embodiments, the effervescent may include two mutually reactive components, such as an acid source and a carbonate source which react together. The acid source may be any source safe for human or animal consumption and may include food acids, acid and hydrite antacids, e.g., citric, tartaric, amalic, fumeric, adipic, or succinics, while the carbonate source may be any of the carbonate sources described above. Reactants which evolve carbon dioxide, oxygen, or other gasses which are safe for human or animal consumption are also included as possible components of an effervescent compound. Any pH altering or pH adjusting compound, for example, a compound having the pH characteristics of a base or an acid may also be used as an effervescent.

[00107] In certain embodiments, the effervescent compound is incorporated into the coating of a composition. Various preparation techniques may be used to create a coating with an effervescent. The amount of effervescent may be about 1-30 wt% of the composition or coating or about 1-15 wt% or about 2-10 wt%. In one embodiment, the effervescent compound is added to a powder matrix coating prior to applying the powder matrix to the film layer to form an edible thin film multi layer composition having an effervescent compound. Preferably, the thin film strip is a bi-layer composition which dissolves rapidly upon administration to the oral cavity or to a mucous membrane located on another part of the body of a subject. The powder

matrix preferably has a low wt% of water or moisture, which allows the effervescent compound to remain inactive in the powder matrix until it is exposed, e.g., to an oral cavity. For example, the water or moisture content of the powder matrix is preferably about .001 to 10 wt% or about .01 to 8 wt% or about .1 to 5 wt%. In certain embodiments the water or moisture content is about 6 to 10 wt% By incorporating the effervescent into the powder matrix, the effervescent remains shielded and protected from any reactive compounds present in the film layer or other layers of the composition, or from moisture present in the film layer or other layers of the composition. In certain embodiments, the film layer has a wt% of water or moisture that is sufficiently low not to react with the effervescent compound. In certain embodiments, an effervescent compound may optionally be incorporated into the film layer. In another embodiment, the effervescent may be incorporated into both the coating and the film layer.

[00108] In certain embodiments, the composition includes an effervescent in the form of sodium bicarbonate which is incorporated into a powder matrix coating . Any active agent or ingredient for which enhanced absorption is desired, e.g., caffeine or other stimulant, may be incorporated into the film layer. The active agent may optionally be incorporated into the powder matrix coating. Upon exposure to the oral cavity, the sodium bicarbonate begins to effervesce by reacting with saliva and acids present in the oral cavity. This in turn increases the absorption and uptake of caffeine into the blood stream, across the buccal, sublingual, or gingival mucosa.

[00109] The above described thin film, thin film strip, and composition embodiments have many desirable properties, for example, 1) they minimizes the risk that the active ingredient or agent or medicament or other composition is degraded or damaged from moisture, heat, and shear; 2) they are configured such that individual film strips can be packaged together (without the need for individual packaging or wrapping) without blocking or bleeding of active agents between film strips, which would cause dosage amounts to be skewed and altered; and 3) they allow individual film strips to be packaged together, where the film strips can include various components that provide improved flexibility, stability, dissolvability, and hydrophobicity properties at concentrations or amounts that would normally cause the individual film strips to adhere and fuse to one another in the absence of individual packaging, separators or dividers. For example, glycerol, grapeseed oil, tryglicerides

from caprilic acid, soy lecithin, humectant, softeners, plasticizers, surfactants, polyalcohols and other similar compounds, or any combination thereof may be present in the film layer or coating of the thin film embodiments described herein, in an amount ranging from about 10% to about 15 % on a dry weight basis, preferably about 10% to about 12%.

[00110] In certain embodiment the above described various thin film, thin film strip, and composition embodiments may include various energy ingredients, e.g., enlyten energy ingredients. Other embodiments may include ingredients such as anti-diarrhea ingredients or immodium.

[00111] The following examples illustrate embodiments of the present invention, however, they do not limit the scope of the present invention. Modifications and variations within the scope of the present invention are known to one of ordinary skill in the art.

Example 1. Film Strip With Benzocaine and Menthol.

[00112] A composition in the form of a thin film strip which contains benzocaine and menthol for treating cough and providing sore throat relief is prepared as follows.

[00113] Hydropropyl cellulose 3.4 g and 0.4 ml of macrogol-400 (polyethylene glycol) are dissolved in 60 g ethanol to form a cellulose-alcohol solution. Distilled water 9 ml containing 90 mg dissolved predonisolone is added to the cellulose solution to form a film forming mixture. The mixture is poured into a film molding frame placed on a Teflon plate circumscribed by a 9.5 cm^2 frame. The mixture is dried to form a film layer having an upper outer surface on the top and a lower outer surface on the bottom generally parallel to the upper outer surface. The film layer has a thickness of 40 microns.

[00114] Benzocaine powder is combined with carboxymethyl cellulose powder, modified food starch, carrageenan, sucralose, talc, and menthol in a fluidized bed container to form a powder matrix. The powder matrix includes 3.76 wt% benzocaine, 2.6 wt% carboxymethyl cellulose, 85.43 wt% modified food starch, 3.76 wt% menthol, 2 wt% carrageenan, 0.45 wt% sucralose, and 2.0 wt% magnesium trisilicate (talc). The powder matrix is drawn from the fluidized bed container and is applied to the upper exposed surface of the film layer to a substantially uniform

thickness of 60 microns. The powder matrix is atomized through a Nordson or similar static spray gun using compressed air. See, for example, Nordson Corporation's KINETIC (TM) spray systems. The gun creates a fine mist spray of powder particles. The gun statically electrically charges the powder particles so they adhere to the upper surface of the film layer. The powder matrix may also be applied to the lower outer surface of the film layer. The powder matrix may also be applied by brushing, rolling or adhering via ionized or magnetically charged particles onto the film layer. The composition is prepared and may be applied to mucous membrane at various areas of the body.

Example 2. Film Strip With Calcium And Menthol.

[00115] A composition in the form of a thin film strip that contains Calcium and menthol for treating cough is prepared as follows.

[00116] The film layer is prepared by mixing and hydrating 1.5 wt% Xanthan gum, 1.5 wt% locust bean gum, 1 wt% carrageenan, and 9.5 wt% pullulan in hot purified water (86.5 wt%) to form a gel. The gel is stored in a refrigerator overnight at about 4°C to form a film layer having a thickness of 55 microns.

[00117] Coral calcium powder is combined with carboxymethyl cellulose powder, modified food starch, carrageenan, sucralose, talc, menthol, and a lipid (BENEFAT™) in a fluidized bed container to form a powder matrix. The powder matrix includes 3.76 wt% calcium, 2.6 wt% carboxymethyl cellulose, 73.43 wt% modified food starch, 3.76 wt% menthol, 2 wt% carrageenan, 0.45 wt% sucralose, 2.0 wt% magnesium trisilicate, and 12 wt% BENEFAT™.

[00118] The powder matrix is drawn from the fluidized bed container and applied to the upper exposed surface of the film layer to a uniform thickness of 150 microns. The powder matrix is atomized through a Nordson or similar static spray gun using compressed air. The powder matrix layer and film layer together form the composition.

Example 3. Circular Film Containing Antibiotics.

[00119] A composition in the form of a thin film strip which contains antibiotics for treating conjunctivitis is prepared as follows.

[00120] Hydropropyl cellulose 3.4 g and 0.4 ml macrogol-400 (polyethylene glycol) are dissolved in 60 g ethanol to form a cellulose-alcohol solution. Distilled water 9 ml containing 90 mg of dissolved predonisolone is added to the solution to form a mixture. The mixture is poured into a film molding frame placed on a Teflon plate circumscribed by the frame of 9.5 cm^2 and dried to form a film layer having a thickness of 30 microns.

[00121] Penicillin or other antibiotic suitable for treating conjunctivitis is combined with carboxymethyl cellulose powder in a fluidized bed container to form a powder matrix. The powder matrix includes 5.00 wt% antibiotic powder and 95 wt% carboxymethyl cellulose. The powder matrix is drawn from the fluidized bed container and applied to the upper exposed surface of the film layer at a substantially uniform thickness of 5.0 microns with a Nordson or similar static spray gun. The powder matrix may also be applied to the lower surface of the film layer.

[00122] A circular piece of 3/8 inch in diameter is cut from a composition containing the described film layer and applied powders. The circular piece is about 35 microns thick and includes a portion of the film layer and a portion of the powder matrix layer. The circular piece is placed in an individual's eye with the powder matrix layer contacting the tear layer of the eye. The amount of adhesive in the powder matrix layer is gauged so that the powder matrix layer does not absorb moisture too rapidly from the tear layer of the individual's eye.

Example 4. Pharmaceutical Composition Containing Sidenafil.

[00123] A composition in the form of a thin film strip which contains controlled release dosage form of Sidenafil for treating erectile dysfunction is prepared as follows.

[00124] Four batches of powder matrix are prepared by individually combining the slow, medium, fast, and immediate release sildenafil with carboxymethyl cellulose powder, modified food starch, carrageenan, sucralose, and talc in a fluidized bed container. Each batch is atomized, through a Nordson or similar static spray gun using compressed air, onto a film layer. Thus, four different batches of sildenafil film dosage formats (slow, medium, fast, and immediate release) are obtained.

[00125] The film layer has been obtained as described in Example 1. The powder matrix may be applied to the lower and/or upper surface of the film layer. The powder matrix layer is applied such that each provides about 25 mg sildenafil per strip.

Example 5. Pharmaceutical Composition Containing Tadalafil.

[00126] A composition in the form of a thin film strip which contains controlled release dosage form of Tadalafil for treating erectile dysfunction is prepared as follows.

[00127] Six batches of powder matrix are prepared by combining the slow, medium, fast, and immediate release tadalafil in different ratios, including batch 1: 100% immediate release; batch 2: 50% immediate release and 50% fast release; batch 3: 50% fast release and 50% medium release; batch 4: 50% medium release and 50% slow release; batch 5: 25% immediate release, 25% fast release, 25% medium release, and 25% slow release; batch 6: 33% fast release, 33% medium release, and 34% slow release.

[00128] Each batch is individually mixed with carboxymethyl cellulose powder, modified food starch, carrageenan, sucralose, and talc in a fluidized bed container to form a powder matrix. Each batch is atomized through a Nordson or similar static spray gun using compressed air onto the film layer as prepared in Example I, to produce six different batches of tadalafil film dosage formats. The powder matrix layer is applied such that each film strip has about 20 mg tadalafil.

Example 6. Pharmaceutical Composition Containing Loratadine.

[00129] A composition in the form of a film strip which contains controlled release dosage form of loratadine to provide allergy relief is prepared as follows.

[00130] Four batches of powder matrix are prepared by individually combining the slow, medium, fast, and immediate release loratadine with carboxymethyl cellulose powder, modified food starch, carrageenan, sucralose, and talc in a fluidized bed container. Each batch is atomized, through a Nordson or similar static spray gun using compressed air, onto a film layer as prepared in Example 1. Four different batches of loratadine film dosage formats (slow, medium, fast, and immediate

release) are obtained which provides loratadine at a final concentration of 10 mg per film strip.

Example 7. Pharmaceutical Composition Containing Desloratadine.

[00131] A composition in the form of a film strip which contains medium release desloratadine to provide allergy relief is prepared as follows.

[00132] One batch of powder matrix containing medium release desloratadine is prepared by combine medium release desloratadine with carboxymethyl cellulose powder, modified food starch, carrageenan, sucralose, and talc in a fluidized bed container. The powder matrix is atomized, through a Nordson or similar static spray gun using compressed air, onto a film layer as prepared in Example 1.
A film dosage form contains medium release desloratadine at a final concentration of 2.5 mg desloratadine per film unit.

Example 8. Pharmaceutical Composition Containing Desloratadine.

[00133] A composition in the form of a film strip which contains controlled release desloratadine to provide allergy relief is prepared as follows.

[00134] Four batches of powder matrix are prepared by individually combining the slow, medium, fast, and immediate release desloratadine with carboxymethyl cellulose powder, modified food starch, carrageenan, sucralose, and talc in a fluidized bed container. Each batch is atomized, through a Nordson or similar static spray gun using compressed air, onto a film layer as prepared in Example 1. Four different batches of film composition are prepared, and each film dosage format provides about 5 mg desloratadine.

[00135] In compositions containing pharmaceutical ingredients in a controlled release form as prepared in Examples 4-8, batches of the film dosage format may be individually tested for dissolution, bioavailability, and bioequivalence, and the results are compared to the respective reference listed compound. If necessary, the process is repeated with different controlled release formulations to achieve a desired result.

Example 9. Energy Strip Containing Guarana Extract.

[00136] A composition in the form of a thin film strip is prepared as described in Example 1 except that the active ingredient is Guarana extract so that each film strip contains about 33 wt% caffeine, in the amount of 20 mg caffeine per strip. Four strips of the composition provide the equivalent amount of caffeine as in one "Red Bull" energy drink. The composition boosts energy, improves cognitive function, and provides hangover relief to the user. The composition may optionally include Vitamine B-12 and/or electrolytes as well.

Example 10. Film Strip Containing Effervescent Compound.

[00137] A composition in the form of a thin film strip is prepared as described in any example or embodiment above. The film layer includes at least one active ingredient and the coating applied to at least one side of the film layer is a powder matrix coating which includes at least one effervescent compound. The effervescent compound is sodium bicarbonate, and the active ingredient is a stimulant. The amount of effervescent is in the range of about 1-30 wt%. The amount of active ingredient is as described in any example or embodiment above depending on the type of active ingredient and the condition to be treated.

CLAIMS

We claim:

1. A thin film composition for administering an active ingredient comprising

a film layer, wherein the film layer includes at least one active ingredient; and

a coating applied to at least one side of the film layer, wherein the coating comprises at least one effervescent compound.

2. The composition of claim 1, wherein the coating is a powder matrix.

3. The composition of claim 2, wherein the composition is an edible film strip that rapidly dissolves in an oral cavity and the amount of moisture in the powder matrix is about .001 to 10 wt%.

4. The composition of claim 3, wherein the composition dissolves in about 5 to 30 seconds upon contact with the oral cavity.

5. The composition of claim 3, wherein the film strip weighs about 10 to 80 mg per strip.

6 The composition of claim 2, wherein particle size of the powder matrix is about 10 to 400 mesh.

7. The composition of claim 1, wherein the active ingredient is present in the coating.

8. The composition of claim 1, further comprising an auxiliary composition selected from the group consisting of:

a dissolution-control agent, an absorption agent, a mucoadhesive agent, an adhesive, a buffering agent, a permeation enhancer, a flow agent, a softener, a cooling agent, a surfactant, a drying agent, an oil, a bulking agent, a filler, a pigment or coloring agent, a flavoring agent, an odorant, or a combination thereof.

9. The composition of claim 8, wherein the film layer comprises a polymer

and the powder matrix coating comprises an absorption agent and a flavoring agent.

10. The composition of claim 9, wherein the film layer comprises pectin and the powder matrix comprises magnesium trisilicate, starch, or acesulfame potassium.

11. The composition of claim 9, wherein the absorption agent and a starch are present in a ratio of about 1:1.

12. The composition of claim 8, wherein the flavoring agent gives a flavor of mint, Honey Lemon, orange, Lemon Lime, grape, Cran Razz, Vanilla Berry, Kids Grape, or cherry.

13. The composition of claim 1, wherein the active ingredient comprises a pharmaceutical ingredient.

14. The composition of claim 13, wherein the pharmaceutical ingredient is useful for treating pharyngitis, cough, allergic reaction, nasal or sinus congestion, headache, joint or muscle pain, diarrhea, heartburn or ulcer, insomnia, motion sickness, erectile dysfunction, microbial infection, periodontal disease, diabetic, as an oral sterilizing agent, an anti-microbial or antibiotic agent, a chemotherapeutic agent, cardiac strengthening agent, blood vein dilating agent, digesting organ curing agent, enzyme, blood pressure depressing agent, tranquilizer, styptic agent, sexual hormone, or agent for curing virulent carcinoma.

15. The composition of claim 14, wherein the pharmaceutical ingredient is selected from a group consisting of an active form of the following compounds benzocaine, dextromethorphan, famotidine, loperamide, diphenhydramine, ketoprofen, loratadine, desloratadine, tadalafil, sildenafil citrate, or a combination thereof.

16. The composition of claim 1, wherein the active ingredient comprises an herbal ingredient, a nutritional supplement, or both.

17. The composition of claim 16, wherein the active ingredient comprises menthol, pectin, Arnica extract, *Gymnema sylvestre* extract, American Ginseng extract, *Ginkgo Biloba* extract, cranberry, Guarana extract.

18. The composition of claim 16, further comprising Vitamin B12.

19. The composition of claim 1, wherein the active ingredient is an electrolyte.

20. The composition of claim 16, wherein the nutritional supplement is mineral, vitamin, or a combination thereof, or electrolytes.

21. The composition of claim 1, wherein the active ingredients are Vitamin C and Zinc or Calcium and Magnesium.

22. The composition of claim 1, wherein the active ingredient comprises Vitamin B1, Vitamin B2, Vitamin B6, Vitamin B12, Vitamin C, or a combination thereof.

23. The composition of claim 1, wherein the composition is edible and dissolves in an oral cavity of a subject to which the composition is administered.

24. An effervescent thin film composition comprising:

a film layer;

a coating applied to at least one side of said film layer, wherein the coating comprises at least one effervescent compound; and

an active ingredient.

25. The composition of claim 24, wherein an active ingredient is present in the film layer.

26. The composition of claim 24, wherein the active ingredient is present in the coating.

27. The composition of claim 24, wherein the coating is a powder matrix, the effervescent compound is sodium bicarbonate, and the active ingredient is a stimulant.

28. A method of making an effervescent thin film composition comprising:

providing a film layer having an active agent incorporated therein;

admixing a powder matrix with an effervescent compound;

brushing the powder matrix coating on one or more surfaces of the film

layer.

29. The composition of claim 1, wherein the effervescent compound is sodium bicarbonate, and the active ingredient is a stimulant.

30. The composition of claim 1, wherein the thin film composition is a film strip.

31. A package of thin film strips according to claim 30, wherein two or more film strips are packaged together without individual packaging or wrapping, wherein the active agents do not bleed or block between the film strips, and the dosage amounts are not skewed.

32. A package of thin film strips according to claim 31, wherein each film strip comprises glycerol, grapeseed oil, tryglicerides from caprilic acid, soy lecithin, humectant, softeners, plasticizers, surfactants, polyalcohols or any combination thereof in a film layer in an amount ranging from about 10% to about 15 % on a dry weight basis.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 08/80362

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 25/02; A61K 9/12 (2008.04)
USPC - 424/43
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)
USPC - 424/43

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC ? 424/43, 435, 439, 440, 46, 466

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST (PGPB, USPT, EPAB, JPAB); Google; Google Scholar
Search Terms Used: thin film, film layer, film strip, composition, active ingredient, effervescent, compound, dissolve, weight ratio, oral cavity, powder matrix, coating, auxiliary composition, absorption agent, flavoring agent, bulking agent, starch, nutritional, ...

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2006/0210610 A1 (Davidson et al.) 21 September 2006 (21.09.2006) ? [abstract], para [0008], para [0012], para [0023], para [0045], para [0033], para [0025], para [0047], para [0043], para [0040], para [0046], para [0056], para [0109], para [0127], para [0019], para [0022], para [0041], para [0027]	1-23, 27, 29-32
Y	US 2001/0006677 A1 (McGinity et al.) 05 July 2001 (05.07.2001) - para [0019]-[0020], para [0057], para [0075]-[0076]	1-23, 29-32
X --- Y	US 2007/0087036 A1 (Durschlag et al.) 19 April 2007 (19.04.2007) - para [0039], [abstract], para [0054], para [0033], para [0041], para [0015], [claim 29], para [0012], para [0100]	24-28 --- 17, 19, 21
Y	US 2007/0122455 A1 (Myers et al.) 31 May 2007 (31.05.2007) - para [0105], para [0103], para [0119], para [0124], para [0122]	31-32
A	US 2004/0247649 A1 (Pearce et al.) 09 December 2004 (09.12.2004)	1-32
A	US 2004/0136923 A1 (Davidson) 15 July 2004 (15.07.2004)	1-32

☐ Further documents are listed in the continuation of Box C. ☐

* 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 application or patent 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
08 December 2008 (08.12.2008)	22 DEC 2008
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

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