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(54) **FAST DISSOLVING ORALLY CONSUMABLE SOLID FILM CONTAINING A TASTE MASKING AGENT AND PHARMACEUTICALLY ACTIVE AGENT AT WEIGHT RATIO OF 1:3 TO 3:1**

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See application file for complete search history.

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(57) **ABSTRACT**

Physiologically acceptable films, including edible films, are disclosed. The films include a water soluble film-forming polymer, such as pullulan, and a taste masked pharmaceutically active agent, such as dextromethorphan. The taste masking agent is preferably a sulfonated polymer ion exchange resin comprising polystyrene cross-linked with divinylbenzene, such as AMBERLITE. Methods for producing the films are also disclosed.

33 Claims, No Drawings

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FAST DISSOLVING ORALLY CONSUMABLE SOLID FILM CONTAINING A TASTE MASKING AGENT AND PHARMACEUTICALLY ACTIVE AGENT AT WEIGHT RATIO OF 1:3 TO 3:1

FIELD OF THE INVENTION

This invention relates to fast dissolving orally consumable films containing an agent to mask the taste of a pharmaceutically active agent therein, and more specifically to such films containing an ion exchange resin as the taste masking agent.

BACKGROUND OF THE INVENTION

It has been known to administer pharmaceutically active agents in an edible film vehicle.

For example, WO 99/17753 discloses rapidly dissolving films for delivery of drugs to be adsorbed in the digestive tract.

WO 98/26780 discloses a flat, foil, paper or wafer type presentation for the application and release of active substances in the buccal cavity. The specific active ingredient disclosed in WO 98/26780 is buprenorphine.

WO 98/20862 discloses a film for use in the oral cavity that can contain a cosmetic or pharmaceutical active substance.

WO 98/26763 discloses a flat, foil, paper or wafer like presentation for release of active substances into the buccal cavity. The particular active disclosed is apomorphine.

U.S. patent application Ser. No. 09/395,104 also discloses the delivery of pharmaceutical agents in a edible film vehicle.

U.S. Pat. No. 5,411,945 to Ozaki et al. discloses a pullulan binder and products produced therewith, including edible films (Example B-2). The products can include a variety of ingredients in addition to pullulan, such as other polysaccharides, antibacterial agents, flavor-imparting agents and pharmaceutically active substances (column 4, lines 5–15).

U.S. Pat. No. 3,784,390 Hijiya et al. discloses pullulan films and their use in coating and packing materials for foods, pharmaceuticals and other oxygen sensitive materials. All of the examples in this patent teach mixing pullulan in hot water.

It has also been known to combine ion exchange resins with pharmaceutically active agents to provide sustained release formulations.

For example, U.S. Pat. No. 6,001,392 to Wen et al. discloses a controlled-release syrup suspension for oral administration containing dextromethorphan adsorbed to a polystyrene sulfonate ion exchange resin. Pharmaceutical films are not disclosed.

U.S. Pat. No. 5,980,882 to Eichman discloses a method for improving the stability of a pharmaceutical composition that contains a drug-resin complex, comprising adding a chelating agent in an amount effective to reduce the rate of degradation of the drug in the drug-resin complex. Although Eichman teaches that complexing a drug with an ion exchange resin can mask the taste of the drug. Pharmaceutical films are not disclosed.

The inventors are not aware of any suggestion in the published art that ion exchange resins can act as taste

dissolving orally consumable films containing an ion exchange resin to mask the taste of a pharmaceutically active agent therein.

All references cited herein are incorporated herein by reference in their entireties.

SUMMARY OF THE INVENTION

The invention provides a consumable film adapted to adhere to and dissolve in a mouth of a consumer, wherein the film comprises at least one water soluble polymer, at least one pharmaceutically active agent and at least one taste masking agent.

Also provided is a method for preparing the consumable film of the invention, comprising:

dissolving water-soluble ingredients in water to provide an aqueous solution;

mixing at least one water soluble film former and at least one stabilizing agent to provide a film-forming mixture;

combining the film-forming mixture and the aqueous solution to provide a hydrated polymer gel;

mixing oils to form an oil mixture;

adding the oil mixture to the hydrated polymer gel and mixing to provide a uniform gel;

casting the uniform gel on a substrate; and

drying the cast gel to provide the film.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The invention provides a physiologically acceptable film that is particularly well adapted to adhere to and dissolve in a mouth of a consumer to deliver a pharmaceutically active agent. Preferred films according to the invention comprise a pharmaceutically active agent, an ion exchange resin, a film-forming agent, and at least one of the following additional ingredients: water, antimicrobial agents, plasticizing agents, flavoring agents, saliva stimulating agents, cooling agents, surfactants, stabilizing agents, emulsifying agents, thickening agents, binding agents, coloring agents, sweeteners, fragrances, triglycerides, preservatives, polyethylene oxides, propylene glycol, and the like.

The expression "physiologically acceptable" as used herein is intended to encompass compounds, which upon administration to a patient, are adequately tolerated without causing undue negative side effects. The expression encompasses edible compounds.

The expression "pharmaceutically active agents" as used herein is intended to encompass agents other than foods, which promote a structural and/or functional change in and/or on bodies to which they have been administered. These agents are not particularly limited; however, they should be physiologically acceptable and compatible with the film. Suitable pharmaceutically active agents include, but are not limited to:

A. antimicrobial agents, such as triclosan, cetyl pyridium chloride, domiphen bromide, quaternary ammonium salts, zinc compounds, sanguinarine, fluorides, alexidine, octonidine, EDTA, and the like;

B. non-steroidal anti-inflammatory drugs, such as aspirin, acetaminophen, ibuprofen, ketoprofen, diflunisal, fenoprofen calcium, naproxen, tolmetin sodium, indomethacin, and the like;

C. anti-tussives, such as benzonatate, caramiphen edisy-

D. decongestants, such as pseudoephedrine hydrochloride, phenylepherine, phenylpropanolamine, pseudoephedrine sulfate, and the like;

E. anti-histamines, such as brompheniramine maleate, chlorpheniramine maleate, carbinoxamine maleate, clemastine fumarate, dexchlorpheniramine maleate, diphenhydramine hydrochloride, diphenylpyraline hydrochloride, azatadine meleate, diphenhydramine citrate, doxylamine succinate, promethazine hydrochloride, pyrilamine maleate, tripelennamine citrate, triprolidine hydrochloride, acrivastine, loratadine, brompheniramine, dexbrompheniramine, and the like;

F. expectorants, such as guaifenesin, ipecac, potassium iodide, terpin hydrate, and the like;

G. anti-diarrheals, such a loperamide, and the like;

H. H_2-antagonists, such as famotidine, ranitidine, and the like;

I. proton pump inhibitors, such as omeprazole, lansoprazole, and the like;

J. general nonselective CNS depressants, such as aliphatic alcohols, barbiturates and the like;

K. general nonselective CNS stimulants such as caffeine, nicotine, strychnine, picrotoxin, pentylenetetrazol and the like;

L. drugs that selectively modify CNS function, such as phenyhydantoin, phenobarbital, primidone, carbamazepine, ethosuximide, methsuximide, phensuximide, trimethadione, diazepam, benzodiazepines, phenacemide, pheneturide, acetazolamide, sulthiame, bromide, and the like;

M. antiparkinsonism drugs such as levodopa, amantadine and the like;

N. narcotic-analgesics such as morphine, heroin, hydromorphone, metopon, oxymorphone, levorphanol, codeine, hydrocodone, xycodone, nalorphine, naloxone, naltrexone and the like;

O. analgesic-antipyretics such as salycilates, phenylbutazone, indomethacin, phenacetin and the like; and

P. psychopharmacological drugs such as chlorpromazine, methotrimeprazine, haloperidol, clozapine, reserpine, imipramine, tranylcypromine, phenelzine, lithium and the like.

The amount of pharmaceutically active agent that can be used in the rapidly dissolving films, according to the present invention, is dependent upon the dose needed to provide an effective amount of the pharmaceutically active agent. Examples of doses for specific pharmaceutically active agents that can be delivered per one strip of rapidly dissolving oral film are reviewed in Table A.

TABLE A

PHARMACEUTICALLY ACTIVE AGENT	PREFERRED DOSE
Chlorpheniramine Maleate	4 mg.
Brompheniramine Maleate	4 mg.
Dexchlorpheniramine	2 mg.
Dexbrompheniramine	2 mg.
Triprolidine Hydrochloride	2.5 mg.
Acrivastine	8 mg.
Azatadine Maleate	1 mg.
Loratidine	10 mg.
Phenylephrine Hydrochloride	10 mg.
Dextromethorphan Hydrobromide	10–30 mg.
Ketoprofen	12.5–25 mg.
Sumatriptan Succinate	35–70 mg.
Zolmitriptan	2.5 mg.
Loperamide	2 mg.
Famotidine	10 mg.
Nicotine	2 mg.
Diphenhydramine Hydrochloride	12.5–25 mg.
Pseudoephedrine Hydrochloride	30 mg.

Ion exchange resins preferred for use in the films of the invention are water-insoluble and consist of a pharmacologically inert organic or inorganic matrix containing covalently bound functional groups that are ionic or capable of being ionized under the appropriate conditions of pH. The organic matrix may be synthetic (e.g., polymers or copolymers of acrylic acid, methacrylic acid, sulfonated styrene, sulfonated divinylbenzene), or partially synthetic (e.g., modified cellulose and dextrans). The inorganic matrix can also be, e.g., silica gel modified by the addition of ionic groups. The covalently bound ionic groups may be strongly acidic (e.g., sulfonic acid), weakly acidic (e.g., carboxylic acid), strongly basic (e.g., quaternary ammonium), weakly basic (e.g., primary amine), or a combination of acidic and basic groups. In general, those types of ion exchangers suitable for use in ion exchange chromatography and for such applications as deionization of water are suitable for use in these controlled release drug preparations. Such ion exchangers are described by H. F. Walton in "Principles of Ion Exchange" (pp. 312–343). The ion exchange resins useful in the present invention have exchange capacities below about 6 milliequivalents per gram (meq/g) and preferably below about 5.5 meq/g.

The resin is crosslinked with a crosslinking agent selected from difunctional compounds capable of crosslinking polystyrenes; these are commonly known in the art. Preferably, the crosslinking agent is a divinyl or polyvinyl compound. Most preferably the crosslinking agent is divinylbenzene. The resin is crosslinked to an extent of about 3 to about 20%, preferably about 4 to about 16%, more preferably about 6 to about 10%, and most preferably about 8% by weight based on the total resin. The resin is crosslinked with the crosslinking agent by means well known in the art.

The size of the ion exchange resins should preferably fall within the range of about 20 to about 200 micrometers. Particle sizes substantially below the lower limit are difficult to handle in all steps of the processing. Particle sizes substantially above the upper limit, e.g., commercially available ion exchange resins having a spherical shape and diameters up to about 1000 micrometers, are gritty in liquid dosage forms and have a greater tendency to fracture when subjected to drying-hydrating cycles.

Representative resins useful in this invention include AMBERLITE IRP-69 (obtained from Rohm and Haas) and Dow XYS-40010.00 (obtained from The Dow Chemical Company). Both are sulfonated polymers composed of polystyrene cross-linked with 8% of divinylbenzene, with an ion exchange capacity of about 4.5 to 5.5 meq/g of dry resin (H+-form). Their essential difference is in physical form. AMBERLITE IRP-69 comprises irregularly-shaped particles with a size range of 47 to 149 micrometers, produced by milling the parent, large-sized spheres of AMBERLITE IRP-120. The Dow XYS-40010.00 product comprises spherical particles with a size range of 45 to 150 micrometers. Another useful exchange resin, Dow XYS-40013.00, is a polymer composed of polystyrene cross-linked with 8% of divinylbenzene and functionalized with a quaternary ammonium group; its exchange capacity is normally within the range of approximately 3 to 4 meq/g of dry resin.

The most preferred resin is AMBERLITE IRP-69. However, in less preferred embodiments, the taste masking agent need not be an ion exchange resin. In these embodiments, the taste masking agent can be, e.g., magnesium trisilicate. See, e.g., U.S. Pat. Nos. 4,650,663 and 4,581,232 to Peters et al. Taste can also be masked by polymers, such as

The film-forming agent used in the films according to the present invention can be selected from the group consisting of pullulan, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, polyvinyl pyrrolidone, carboxymethyl cellulose, polyvinyl alcohol, sodium alginate, polyethylene glycol, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl polymer, amylose, high amylose starch, hydroxypropylated high amylose starch, dextrin, pectin, chitin, chitosan, levan, elsinan, collagen, gelatin, zein, gluten, soy protein isolate, whey protein isolate, casein and mixtures thereof. A preferred film former is pullulan, in amounts ranging from about 0.01 to about 99 wt %, preferably about 30 to about 80 wt %, more preferably from about 45 to about 70 wt % of the film and even more preferably from about 60 to about 65 wt % of the film.

Unless specified otherwise, the term "wt %" as used herein with reference to the final product (i.e., the film, as opposed to the formulation used to create it), denotes the percentage of the total dry weight contributed by the subject ingredient. This theoretical value can differ from the experimental value, because in practice, the film typically retains some of the water and/or ethanol used in preparation.

In embodiments containing relatively high oil content, it is preferable to avoid substantial amounts of humectant in the film (and more preferable to have no humectant in the film), so as to avoid producing an overly moist, self-adhering film. In particular, it is preferred to formulate high oil content films with a plasticizing agent other than glycerin, which is also a humectant, and with a sweetener other than sorbitol, which is a mild humectant.

Saliva stimulating agents can also be added to the films according to the present invention. Useful saliva stimulating agents are those disclosed in U.S. Pat. No. 4,820,506. Saliva stimulating agents include food acids such as citric, lactic, malic, succinic, ascorbic, adipic, fumaric and tartaric acids. Preferred food acids are citric, malic and ascorbic acids. The amount of saliva stimulating agents in the film is from about 0.01 to about 12 wt %, preferably about 1 wt % to about 10 wt %, even more preferably about 2.5 wt % to about 6 wt %.

Preferred plasticizing agents include triacetin in amounts ranging from about 0 to about 20 wt %, preferably about 0 to about 2 wt %. Other suitable plasticizing agents include monoacetin and diacetin.

Preferred cooling agents include monomenthyl succinate, in amounts ranging from about 0.001 to about 2.0 wt %, preferably about 0.2 to about 0.4 wt %. A monomenthyl succinate containing cooling agent is available from Mane, Inc. Other suitable cooling agents include WS3, WS23, Ultracool II and the like.

Preferred surfactants include mono and diglycerides of fatty acids and polyoxyethylene sorbitol esters, such as, Atmos 300 and Polysorbate 80. The surfactant can be added in amounts ranging from about 0.5 to about 15 wt %, preferably about 1 to about 5 wt % of the film. Other suitable surfactants include pluronic acid, sodium lauryl sulfate, and the like.

Preferred stabilizing agents include xanthan gum, locust bean gum and carrageenan, in amounts ranging from about 0 to about 10 wt %, preferably about 0.1 to about 2 wt % of the film. Other suitable stabilizing agents include guar gum and the like.

Preferred emulsifying agents include triethanolamine stearate, quaternary ammonium compounds, acacia, gelatin, lecithin, bentonite, veegum, and the like, in amounts ranging

Preferred thickening agents include methylcellulose, carboxyl methylcellulose, and the like, in amounts ranging from about 0 to about 20 wt %, preferably about 0.01 to about 5 wt %.

Preferred binding agents include starch, in amounts ranging from about 0 to about 10 wt %, preferably about 0.01 to about 2 wt % of the film.

Suitable sweeteners that can be included are those well known in the art, including both natural and artificial sweeteners. Suitable sweeteners include, e.g.:

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

B. water-soluble artificial sweeteners such as the soluble saccharin salts, i.e., sodium or calcium saccharin salts, cyclamate salts, the sodium, ammonium or calcium salt of 3,4-dihydro-6-methyl-1,2,3-oxathiazine-4-one-2,2-dioxide, the potassium salt of 3,4-dihydro-6-methyl-1,2,3-oxathiazine-4-one-2,2-dioxide (acesulfame-K), the free acid form of saccharin, and the like;

C. dipeptide based sweeteners, such as L-aspartic acid derived sweeteners, such as L-aspartyl-L-phenylalanine methyl ester (aspartame) and materials described in U.S. Pat. No. 3,492,131, L-alpha-aspartyl-N-(2,2,4,4-tetramethyl-3-thietanyl)-D-alaninamide hydrate, methyl esters of L-aspartyl-L-phenylglycerin and L-aspartyl-L-2,5,dihydrophenylglycine, L-aspartyl-2,5-dihydro-L-phenylalanine, L-aspartyl-L-(1-cyclohexyen)-alanine, and the like;

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

E. protein based sweeteners such as thaumatoccous danielli (Thaumatin I and II).

In general, an effective amount of auxiliary sweetener is utilized to provide the level of sweetness desired for a particular composition, and this amount will vary with the sweetener selected. This amount will normally be 0.01% to about 10% by weight of the composition when using an easily extractable sweetener. The water-soluble sweeteners described in category A above, are usually used in amounts of about 0.01 to about 10 wt %, and preferably in amounts of about 2 to about 5 wt %. Some of the sweeteners in category A (e.g., glycyrrhizin) can be used in amounts set forth for categories B–E below due to the sweeteners' known sweetening ability. In contrast, the sweeteners described in categories B–E are generally used in amounts of about 0.01 to about 10 wt %, with about 2 to about 8 wt % being preferred and about 3 to about 6 wt % being most preferred. These amounts may be used to achieve a desired level of sweetness independent from the flavor level achieved from any optional flavor oils used. Of course, sweeteners need not be added to films intended for non-oral administration.

The flavorings that can be used include those known to the skilled artisan, such as natural and artificial flavors. These flavorings may be chosen from synthetic flavor oils and flavoring aromatics, and/or oils, oleo resins and extracts derived from plants, leaves, flowers, fruits and so forth, and combinations thereof. Representative flavor oils include: spearmint oil, cinnamon oil, peppermint oil, clove oil, bay

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