(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
27 September 2001 (27.09.2001)

PCT

(10) International Publication Number
WO 01/70194 A1

(51) International Patent Classification⁷: A61K 9/00, 9/20

(21) International Application Number: PCT/US01/02192

(22) International Filing Date: 23 January 2001 (23.01.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/535,005 23 March 2000 (23.03.2000) US

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(81) Designated States *(national)*: AE, AG, AL, AU, BA, BB, BG, BR, BZ, CA, CN, CR, CU, CZ, DM, DZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, MZ, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, UZ, VN, YU, ZA.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

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

WO 01/70194 A1

(54) Title: FAST DISSOLVING ORALLY CONSUMABLE FILMS CONTAINING AN ION EXCHANGE RESIN AS A TASTE MASKING AGENT

(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.

FAST DISSOLVING ORALLY CONSUMABLE FILMS CONTAINING AN ION EXCHANGE RESIN AS A TASTE MASKING AGENT

SPECIFICATION

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 No. 09/395,104 also discloses the delivery of pharmaceutical agents in a edible film vehicle.

U.S. Patent 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. Patent 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. Patent 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. Patent 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 masking agents in a fast dissolving orally consumable film. Accordingly, an object of this invention is to provide fast 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 edisylate, menthol, dextromethorphan hydrobromide, chlophedianol hydrochloride, and the like;

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. Patents Nos. 4,650,663 and 4,581,232 to Peters et al. Taste can also be masked by polymers, such as EUDRAGIT E (Rohm and Haas), and/or cellulosics, such as ethylcellulose, and the like.

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. Patent 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 from about 0 to about 5 wt%, preferably about 0.01 to about 0.7 wt% of the film.

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,dihydrophenyl-glycine, 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 oil, thyme oil, cedar leaf oil, oil of nutmeg, oil of sage, and oil of bitter almonds. Also useful are artificial, natural or synthetic fruit flavors such as vanilla, chocolate, coffee, cocoa and citrus oil, including lemon, orange, grape, lime and grapefruit and fruit essences including apple, pear, peach, strawberry, raspberry, cherry, plum, pineapple, apricot and so forth. These flavorings can be used individually or in admixture. Commonly used flavors include mints such as peppermint, artificial vanilla, cinnamon derivatives, and various fruit flavors, whether employed individually or in admixture. Flavorings such as aldehydes and esters including cinnamyl acetate, cinnamaldehyde, citral, diethylacetal, dihydrocarvyl acetate, eugenyl formate, p-methylanisole, and so forth may also be used. Generally, any flavoring or food additive, such as those described in Chemicals Used in Food Processing, publication 1274 by the National Academy of Sciences, pages 63-258, may be used. Further examples of aldehyde flavorings include, but are not limited to acetaldehyde (apple); benzaldehyde (cherry, almond); cinnamic aldehyde (cinnamon); citral, i.e., alpha citral (lemon, lime); neral, i.e. beta citral (lemon, lime); decanal (orange, lemon); ethyl vanillin (vanilla, cream); heliotropine, i.e., piperonal (vanilla, cream); vanillin (vanilla, cream); alpha-amyl cinnamaldehyde (spicy fruity flavors); butyraldehyde (butter, cheese); valeraldehyde (butter, cheese); citronellal (modifies, many types); decanal (citrus fruits); aldehyde C-8 (citrus fruits); aldehyde C-9 (citrus fruits); aldehyde C-12 (citrus fruits); 2-ethyl butyraldehyde (berry fruits); hexenal, i.e. trans-2 (berry fruits); tolyl aldehyde (cherry, almond); veratraldehyde (vanilla);

2,6-dimethyl- 5-heptenal, i.e. melonal (melon); 2-6-dimethyloctanal (green fruit); and 2-dodecenal (citrus, mandarin); cherry; grape; mixtures thereof; and the like.

The amount of flavoring employed is normally a matter of preference subject to such factors as flavor type, individual flavor, and strength desired. Thus, the amount may be varied in order to obtain the result desired in the final product. Such variations are within the capabilities of those skilled in the art without the need for undue experimentation. In general, amounts of about 0.1 to about 30 wt% are useable with amounts of about 2 to about 25 wt% being preferred and amounts from about 8 to about 10 wt% are more preferred.

The compositions of this invention can also contain coloring agents or colorants. The coloring agents are used in amounts effective to produce the desired color. The coloring agents useful in the present invention, include pigments such as titanium dioxide, which may be incorporated in amounts of up to about 5 wt%, and preferably less than about 1 wt%. Colorants can also include natural food colors and dyes suitable for food, drug and cosmetic applications. These colorants are known as FD&C dyes and lakes. The materials acceptable for the foregoing spectrum of use are preferably water-soluble, and include FD&C Blue No. 2, which is the disodium salt of 5,5-indigotindisulfonic acid. Similarly, the dye known as Green No. 3 comprises a triphenylmethane dye and is the monosodium salt of 4-[4-N-ethyl-p-sulfobenzylamino) diphenyl-methylene]-[1-N-ethyl-N-p-sulfonium benzyl)-2,5-cyclo-hexadienimine]. A full recitation of all FD&C and D&C dyes and their corresponding chemical structures may be found in the Kirk-Othmer Encyclopedia of Chemical Technology, Volume 5, Pages 857-884, which text is accordingly incorporated herein by reference.

The films can also include a triglyceride. Examples of triglycerides include vegetable oils such as corn oil, sunflower oil, peanut oil, olive oil, canola oil, soybean oil and mixtures thereof. A preferred triglyceride is olive oil. The triglyceride is added to the film in amounts from about 0.1 wt% to about 12 wt%, preferably in a range from about 0.5 wt% to about 9 wt%, of the film.

The films can include a preservative in amounts from about 0.001 wt% to about 5 wt%, preferably from about 0.01 wt% to about 1 wt% of the film. Preferred preservatives include sodium benzoate and potassium sorbate. Other suitable preservatives include, but are not limited to, salts of edetate (also known as salts of ethylenediaminetetraacetic acid, or EDTA, such as disodium EDTA) and parabens (e.g., methyl, ethyl, propyl or butyl-hydroxybenzoates, etc.) or sorbic acid. The preservatives listed above are exemplary, but each preservative must be evaluated on an empirical basis, in each formulation, to assure the compatibility and efficacy of the preservative. Methods for evaluating the efficacy of preservatives in pharmaceutical formulations are known to those skilled in the art.

The films can also include a polyethylene oxide compound. The molecular weight of the polyethylene oxide compound ranges from about 50,000 to about 6,000,000. A preferred polyethylene oxide compound is N-10 available from Union Carbide Corporation. The polyethylene oxide compound is added in amounts from about 0.1 wt% to about 5 wt%, preferably from about 0.2 wt% to about 4.0 wt% of the film.

The films can also include propylene glycol. The propylene glycol is added in amounts from about 1 wt% to about 20 wt%, preferably from about 5 wt% to about 15 wt% of the film.

Methods for preparing films according to the invention are capable of encapsulating the oil ingredients within the film-forming matrix and maintaining the integrity of the film, even when the film contains oils in amounts of 10 wt% or more.

In certain methods for preparing films according to the invention, the film-forming ingredients are mixed and hydrated with water separately from the water-soluble ingredients, which are mixed in aqueous solution separately from the organic ingredients and surfactants. In these methods, the final formulation is preferably produced by mixing the film-forming phase with the aqueous phase, then mixing in the organic phase, which includes surfactants, such as Polysorbate 80 and Atmos 300. This mass is mixed until emulsified. In other embodiments, the aqueous and film forming phases are combined into a single phase by dissolving the water soluble ingredients in the water and then adding the gums to hydrate. The organic phase is then added to this single aqueous phase.

The resulting formulation is cast on a suitable substrate and dried to form a film. The film is preferably air-dried or dried under warm air and cut to a desired dimension, packaged and stored. The film can contain from about 0.1% to about 10 wt% moisture, preferably from about 3 % to about 8 wt% moisture, even more preferably from about 4 to about 7 wt% moisture.

The film-forming phase can include pullulan and stabilizing agents such as xanthan gum, locust bean gum and carrageenan. These ingredients are mixed and then hydrated in water for about 30 to about 48 hours to form a gel. The water is preferably heated to a temperature of about 25 to about 45°C to promote hydration. The amount of water is about 40 to 80% of the gel. The resulting hydrated gel is then chilled to a temperature of about 20 to about 30°C for about 1 to about 48 hours. The water is preferably deionized.

In preferred embodiments, the aqueous phase includes water heated to a temperature of about 60 to 90°C, preferably 70 to 80°C, and ingredients such as the pharmaceutically active agent, ion exchange resin (or other masking agent), coloring agent, preservative and sweetener. The water is preferably deionized and the amount of water used is about 5 to about 80 wt% of the final gel mixture.

The pharmaceutically active agent is sorbed to the ion exchange resin (or other masking agent) without separating ion exchanged pharmaceutically active agent from unexchanged agent and counter ion salts.

Adsorption of the pharmaceutically active agent onto the ion exchange resin particles to form the pharmaceutically active agent/resin complex is a well known technique as shown in U.S. Pat. Nos. 2,990,332 and 4,221,778. In general, the pharmaceutically active agent is mixed with an aqueous suspension of the resin, and in less preferred embodiments, the complex is then washed and dried. Adsorption of pharmaceutically active agent onto the resin may be detected by measuring a change in the pH of the reaction medium, or by measuring a change in concentration of sodium or pharmaceutically active agent.

Binding of pharmaceutically active agent to resin can be accomplished according to four general reactions. In the case of a basic pharmaceutically active agent, these are: (a) resin (Na-form) plus pharmaceutically active agent (salt form); (b) resin (Na-form) plus pharmaceutically active agent (as free base); (c) resin (H-form) plus pharmaceutically active agent (salt form); and (d) resin (H-form) plus pharmaceutically active agent (as free base). All of these reactions except (d) have cationic byproducts, by competing with the cationic pharmaceutically active agent for binding sites on the resin, reduce the amount of pharmaceutically active agent bound at equilibrium. For basic pharmaceutically active agents, stoichiometric binding of pharmaceutically active agent to resin is accomplished only through reaction (d).

Four analogous binding reactions can be carried out for binding an acidic pharmaceutically active agent to an anion exchange resin. These are: (a) resin (Cl--form) plus pharmaceutically active agent (salt form); (b) resin (Cl--form) plus pharmaceutically active agent (as free acid); (c) resin

(OH--form) plus pharmaceutically active agent (salt form); and (d) resin (OH--form) plus pharmaceutically active agent (as free acid). All of these reactions except (d) have ionic by-products and the anions generated when the reactions occur compete with the anionic pharmaceutically active agent for binding sites on the resin with the result that reduced levels of pharmaceutically active agent are bound at equilibrium. For acidic pharmaceutically active agents, stoichiometric binding of pharmaceutically active agent to resin is accomplished only through reaction (d). The binding may be performed, for example, as a batch or column process, as is known in the art.

In less preferred embodiments, the adsorption complex, including pharmaceutically active agent and resin, is collected and washed with ethanol and/or water to insure removal of any unadsorbed pharmaceutically active agent. The complexes are usually air-dried in trays at room or elevated temperature.

The ratio of the pharmaceutically active agent adsorbate to ion exchange resin adsorbent in the adsorption complex is about 1:3 to about 3:1, preferably about 1:2 to about 2:1, most preferably about 1:1. The only limit to using ratios in excess of 1:3 is an economic and aesthetic one.

The amount of the pharmaceutically active agent adsorbed to the ion exchange resin is in the range from about 25 to about 75% by weight of the pharmaceutically active agent/resin adsorption complex (hereinafter referred to as the “pharmaceutically active agent/resin complex” or “complex”). More preferably, the amount of the pharmaceutically active agent adsorbed to the ion exchange resin is in the range from about 33 to about 77% by weight of the pharmaceutically active agent/resin complex. Most preferably, the amount of the pharmaceutically active agent adsorbed to the ion exchange resin is in the range from about 40 to about 60% by weight of the pharmaceutically active agent/resin complex.

The amount of pharmaceutically active agent/resin complex in the formulation is adjusted to deliver a predetermined dose of the pharmaceutically active agent over a predetermined period of time.

For example, a preferred antitussive film of the invention is administered at one dose every 12 hours to deliver a pharmaceutically effective amount of dextromethorphan over a period of approximately 12 hours to a patient in need of such administration. A typical adult dose of a film of the invention measuring 1" x 1.25" (2.54 cm x 3.18 cm) weighs about 60 to about 190 mg and contains about 20 to about 130 mg of pharmaceutically active agent/resin complex to deliver about 5 to about 65 mg of pharmaceutically active agent (e.g., dextromethorphan hydrobromide) when the average pharmaceutically active agent:ion exchange resin ratio is about 1:1.

In a particularly preferred embodiment of the invention, pullulan is present in the film in an amount of about 2 to about 6 mg/cm^2, dextromethorphan is present in the film in an amount of about 1.4 to about 3 mg/cm^2, and sulfonated polymer ion exchange resin is present in said film in an amount of about 1.4 to about 2 mg/cm^2.

The antitussive pharmaceutically active agents that are suitable for use in these preparations are acidic, amphoteric or most often basic antitussives. Examples of basic pharmaceutically active agents useful in the present invention include, but are not limited to dextromethorphan, diphenhydramine, caramiphen, carbapentane, ethylmorphine, noscapine and codeine. In addition, the antitussive embodiments of the invention can further comprise additional agents that are therapeutically effective to treat conditions other than coughing. That is, more than one type of pharmaceutically active agent can be included in a film of the invention. For example, in the case of a film containing an antitussive agent, the film can further comprise an antihistamine, sympathomimetic pharmaceutically active agent (nasal decongestant, bronchodilator), analgesic, antiinflammatory, cough suppressant and/or expectorant. Compounds which are antihistamines, sympathomimetic pharmaceutically active agents (nasal decongestant, bronchodilator), analgesic, antiinflammatory, cough suppressants and/or expectorants are well known to those of skill in the art and need not be discussed in detail herein.

In embodiments, a certain percentage of the films disclosed herein will contain non-coated pharmaceutically active agent/resin complexes. The remaining pharmaceutically active agent/resin complexes are further characterized by the presence of a coating. In the preferred embodiment of the present invention, about 20 to about 80% of the pharmaceutically active agent/resin complexes in the sustained-release compositions are coated, most preferably about 40 to about 60% of the pharmaceutically active agent/resin complexes. The coating is a water-permeable, diffusion barrier coating material. The presence of a coating allows one to selectively modify the dissolution profile as desired of a pharmaceutical composition comprising the pharmaceutically active agent/resin complexes of the present invention.

The coating materials can in general be any of a large number of conventional natural or synthetic film-forming materials used singly, in admixture with each other, and in admixture with plasticizers, pigments, etc. with diffusion barrier properties and with no inherent pharmacological or toxic properties. In general, the major components of the coating should be insoluble in water, and permeable to water and pharmaceutically active agent. However, it might be desirable to incorporate a water-soluble substance, such as methyl cellulose, to alter the permeability of the coating, or to incorporate an acid-insoluble, base-soluble substance to act as an enteric coating. The coating materials may be applied as a suspension in an aqueous fluid or as a solution in organic solvents. Suitable examples of such coating materials are described by R. C. Rowe in Materials used in Pharmaceutical Formulation. (A. T. Florence, editor), Blackwell Scientific Publications, Oxford, 1-36(1984), incorporated by reference herein. Preferably the water-permeable diffusion barrier is selected from the group consisting of ethyl cellulose, methyl cellulose and mixtures thereof Most preferably, the coating material is SURELEASE, manufactured by Colorcon which is water based ethyl cellulose latex, plasticized with dibutyl sebacate or with vegetable oils. Other non-limiting coating materials included within the scope of the present invention are AQUACOAT, manufactured by FMC Corporation of Philadelphia, which is ethylcellulose pseudolatex; solvent based ethylcellulose; shellac; zein; rosin esters; cellulose acetate; EUDRAGITS, manufactured by Rohm and Haas of Philadelphia, which are acrylic resins; silicone elastomers; poly(vinyl chloride) methyl cellulose; and hydroxypropylmethyl cellulose.

Conventional coating solvents and coating procedures (such as fluid bed coating and spray coating) can be employed to coat the particles. Techniques of fluid bed coating are taught, for example, in U.S. Patents Nos. 3,089,824, 3,117,027, and 3,253,944. The coating is normally applied to the pharmaceutically active agent/resin complex, but alternatively can be applied to the resin before complexing with the pharmaceutically active agent. Non-limiting examples of coating solvents include ethanol, a methylene chloride/acetone mixture, coating emulsions, methyl acetone, tetrahydrofuran, carbonetetrachloride, methyl ethyl ketone, ethylene dichloride, trichloroethylene, hexane, methyl alcohol, isopropyl alcohol, methyl isobutyl ketone, toluene, 2-nitropropane, xylene, isobutyl alcohol, n-butyl acetate.

It is preferred that the coated pharmaceutically active agent/resin complexes are coated in the range from about 40 to about 70% w/w pharmaceutically active agent/resin complex. More preferably, the pharmaceutically active agent/resin complex is coated in the range from about 45 to about 55% w/w pharmaceutically active agent/resin complex. Most preferably, the pharmaceutically active agent/resin complex is coated about 50% w/w pharmaceutically active agent/resin complex. Variation in the amount of coating and/or the use of coated/uncoated complex mixtures can be employed to selectively modify the dissolution profile as desired.

The average particle sizes of the non-hydrated coated and uncoated pharmaceutically active agent/resin complexes is about 60 to about 200 and about 60 to about 250 micrometers, respectively. More preferably, average particle sizes of the coated pharmaceutically active agent/resin complexes is between about 70 and about 190 micrometers, and most preferably about 70 to about 180 micrometers. More preferably, average particle sizes of the uncoated pharmaceutically active agent/resin complexes is between about 55 and about 160 micrometers, and most preferably about 60 to about 150 micrometers. It is desirable that about 85%, preferably about 95%, and most preferably about 98% of the resin particles have sizes within the ranges set forth above. Adjustments within these ranges can be made to accommodate desired aesthetic qualities of the final formulation product. It is more preferable that the resin dextromethorphan complex have particle sizes within these ranges as well.

In embodiments, it is possible to hydrate the film-forming ingredients and combine all of the ingredients without heating. This method comprises dissolving the water-soluble ingredients in water to form an aqueous mixture; mixing the film-forming ingredients in powder form to form a powder mixture; adding the powder mixture to the aqueous mixture to form a hydrated polymer gel; stirring the hydrated polymer at room temperature for about 30 minutes to about 48 hours; mixing the cooling agent, menthol and any other oils to form an oil mixture; adding the oil mixture to the hydrated polymer gel and mixing until uniform; deaerating the film until air bubbles are removed, casting the uniform mixture on a suitable substrate; and drying the cast mixture to form a film. This method hydrates the film-forming ingredients without heating the water, which can reduce energy costs in the manufacturing process and undesirable losses of volatile ingredients to evaporation. Further, mixing the oils in two steps minimizes the amount of flavor lost.

While not wishing to be bound by any theories, it is believed that the film-forming ingredients can be hydrated and mixed without heating due to an ionic effect known as the Donnan equilibrium. Hydrating the film-forming agents in the presence of electrolytes in solution effectively lowers the viscosity of the polymer gel being formed, thus increasing the efficiency of the hydrating process. The water-soluble ingredients of the formulation provide the electrolytes, which are dissolved in the hydration solution prior to addition of the film-forming ingredients. High-shear mixing also accelerates hydration, which delumps the powders, providing greater surface area for water contact. In addition, local heating effects, generated in the shear regions, provide energy for hydration without substantially raising the temperature of the mass.

Examples

The invention will be illustrated in more detail with reference to the following Examples, but it should be understood that the present invention is not deemed to be limited thereto.

Example 1

The ingredients listed in Table 1 were combined to provide a comparative example of an antitussive film in accordance with the following procedure:

A. The water was heated to 50°C. The potassium sorbate and sweeteners were dissolved in the water with mixing. The titanium dioxide was then added with further mixing to form Preparation A.

B. The film-forming ingredients (e.g., xanthan gum, locust bean gum, carrageenan and pullulan) were mixed in a separate container to form

Preparation B.

C. Preparation B was slowly added to Preparation A with rapid mixing, followed by overnight mixing at a reduced rate to provide Preparation C.

D. The glycerin and olive oil were combined in a separate container and then the menthol and monoammonium glycyrrhizinate (MAG) were dissolved therein by heating to 45°C to form Preparation D.

E. Preparation D was added to Preparation C with thorough mixing and then the flavor agents were added with continued mixing to provide Preparation E.

F. Dextromethorphan coated with ethyl cellulose was then added to Preparation E with mixing. The pH was adjusted as necessary to 6.0 using 10% citric acid solution to provide Preparation F (Examples 1-3 only).

Preparation F was poured on a mold and cast to form a film of a desired thickness at room temperature. The film was dried under warm air and cut to a desired dimension (dictated by, e.g., dosage and mouthfeel) for taste testing. The film was segmented into 1" x 1.25" (2.54 cm x 3.18 cm) dosage units, each of which had a thickness of 0.009±0.002 in (0.23±0.05 mm) and a weight of 70±3 mg.

A placebo film was also prepared in accordance with the foregoing to facilitate evaluation of, e.g., the taste and appearance of the active film.

Table 1

Material	% w/w in batch	g/batch	%w/w*	mg/dose*	%w/w* active film	% w/w actual batch
Coated Dextromethorphan (55% DM)		103.6291		27.3000	29.5775	9.3899
Xanthan Gum	0.0600	0.6000	0.2432	0.1581	0.1713	0.0544
Locust Bean Gum	0.0700	0.7000	0.2837	0.1844	0.1998	0.0634
Carrageenan	0.3000	3.0000	1.2159	0.7903	0.8563	0.2718
Pullulan	16.0000	160.0000	64.8466	42.1503	45.6666	14.4976
Potassium Sorbate	0.0600	0.6000	0.2432	0.1581	0.1713	0.0544
Accsulfame Potassium Salt	0.5000	5.0000	2.0265	1.3172	1.4271	0.4531
Aspartame NF	1.4000	14.0000	5.6741	3.6882	3.9958	1.2685
Purified Water	75.3264	753.2640				68.2534
Physcool	0.1000	1.0000	0.4053	0.2634	0.2854	0.0906
Menthol	1.0000	10.0000	4.0529	2.6344	2.8542	0.9061
Citric Acid	0.0710	0.7100	0.2878	0.1870	0.2026	0.0643
Cherry Flavor (Givudan)	0.1500	1.5000	0.6079	0.3952	0.4281	0.1359
Peppermint Flavor	0.5000	5.0000	2.0265	1.3172	1.4271	0.4531
Mono ammonium glycyrrhizinate (MAG)	0.0100	0.1000	0.0405	0.0263	0.0285	0.0091
Polysorbate 80 NF	0.3500	3.5000	1.4185	0.9220	0.9990	0.3171
Atmos 300	0.3500	3.5000	1.4185	0.9220	0.9990	0.3171
Glycerine	3.0000	30.0000	12.1587	7.9032	8.5625	2.7183
Olive Oil	0.5000	5.0000	2.0265	1.3172	1.4271	0.4531
FD&C green #3	0.0026	0.0260	0.0105	0.0068	0.0074	0.0024
Titanium Dioxide	0.2500	2.5000	1.0132	0.6586	0.7135	0.2265
Total w/o active		0.0000	100.0000	65.0000		
Total with active	100.0000	1103.6291		92.3000	100.0000	100.0000
* assuming that all water is evaporated						

The active film was gritty and bitter.

Example 2

Comparative films having the ingredients listed in Table 2 were prepared in accordance with the method of Example 1.

Table 2

Material	%w/w in batch	g/batch	%w/w* placebo film	mg/dose*	%w/w* active film	% w/w actual batch
Coated Dextromethorphan (53.5% DM)		106.4239		28.0374	30.1356	9.6187
Xanthan Gum	0.0600	0.6000	0.2432	0.1581	0.1699	0.0542
Locust Bean Gum	0.0700	0.7000	0.2837	0.1844	0.1982	0.0633
Carrageenan	0.3000	3.0000	1.2159	0.7904	0.8495	0.2711
Pullulan	16.0000	160.0000	64.8493	42.1520	45.3065	14.4610
Potassium Sorbate	0.0600	0.6000	0.2432	0.1581	0.1699	0.0542
Acesulfame Potassium Salt	0.5000	5.0000	2.0265	1.3173	1.4158	0.4519
Aspartame NF	1.4000	14.0000	5.6743	3.6883	3.9643	1.2653
Purified Water	75.3274	753.2740				68.0819
Physcool	0.1000	1.0000	0.4053	0.2635	0.2832	0.0904
Menthol	1.0000	10.0000	4.0531	2.6345	2.8317	0.9038
Citric Acid (used to adjust pH to 6.0)	0.0700	0.7000	0.2837	0.1844	0.1982	0.0633
Cherry Flavor (Givudan)	0.1500	1.5000	0.6080	0.3952	0.4247	0.1356
Peppermint Flavor	0.5000	5.0000	2.0265	1.3173	1.4158	0.4519
Mono ammonium glycyrrhizinate (MAG)	0.0100	0.1000	0.0405	0.0263	0.0283	0.0090
Polysorbate 80 NF	0.3500	3.5000	1.4186	0.9221	0.9911	0.3163
Atmos 300	0.3500	3.5000	1.4186	0.9221	0.9911	0.3163
Glycerine	3.0000	30.0000	12.1592	7.9035	8.4950	2.7114
Olive Oil	0.5000	5.0000	2.0265	1.3173	1.4158	0.4519
FD&C Green #3	0.0026	0.0260	0.0105	0.0069	0.0074	0.0024
Titanium Dioxide	0.2500	2.5000	1.0133	0.6586	0.7079	0.2260
Total w/o active		0.0000	100.0000	65.0000		
Total with active	100.0000	1106.4239		93.0374	100.0000	100.0000
* assuming that all water is evaporated						

The active film was gritty and bitter.

Example 3

Comparative films having the ingredients listed in Table 3 were prepared in accordance with the method of Example 1.

Table 3

Material	%w/w in batch	g/batch	%w/w* placebo film	mg/dose*	%w/w* active film	% w/w actual batch
Coated Dextromethorphan (60% DM)		94.7292		25.0000	27.7778	8.6532
Xanthan Gum	0.0600	0.6000	0.2436	0.1583	0.1759	0.0548
Locust Bean Gum	0.0700	0.7000	0.2842	0.1847	0.2053	0.0639
Carrageenan	0.3000	3.0000	1.2180	0.7917	0.8797	0.2740
Pullulan	16.0000	160.0000	64.9625	42.2256	46.9174	14.6155
Potassium Sorbate	0.0600	0.6000	0.2436	0.1583	0.1759	0.0548
Acesulfame Potassium Salt	0.5000	5.0000	2.0301	1.3196	1.4662	0.4567
Aspartame NF	1.4000	14.0000	5.6842	3.6947	4.1053	1.2789
Purified Water	75.3704	753.7040				68.8484
Physcool	0.1000	1.0000	0.4060	0.2639	0.2932	0.0913
Menthol	1.0000	10.0000	4.0602	2.6391	2.9323	0.9135
Citric Acid	0.0270	0.2700	0.1096	0.0713	0.0792	0.0247
Cherry Flavor (Givudan)	0.1500	1.5000	0.6090	0.3959	0.4399	0.1370
Peppermint Flavor	0.5000	5.0000	2.0301	1.3196	1.4662	0.4567
Mono ammonium glycyrrhizinate (MAG)	0.0100	0.1000	0.0406	0.0264	0.0293	0.0091
Polysorbate 80 NF	0.3500	3.5000	1.4211	0.9237	1.0263	0.3197
Atmos 300	0.3500	3.5000	1.4211	0.9237	1.0263	0.3197
Glycerine	3.0000	30.0000	12.1805	7.9173	8.7970	2.7404
Olive Oil	0.5000	5.0000	2.0301	1.3196	1.4662	0.4567
FD&C green #3	0.0026	0.0260	0.0106	0.0069	0.0076	0.0024
Titanium Dioxide	0.2500	2.5000	1.0150	0.6598	0.7331	0.2284
Total w/o active		0.0000	100.0000	65.0000		
Total with active	100.0000	1094.7292		90.0000	100.0000	100.0000
* assuming that all water is evaporated						

The active film was very thin, blue and gritty. Sensations of bitterness and numbness were minimal, but the flavor was not entirely agreeable.

Example 4

Films of the invention having the ingredients listed in Table 4 were prepared in accordance with the method of Example 1, except that Step F comprised adding uncoated dextromethorphan hydrobromide and AMBERLITE resin to Preparation E as separate ingredients.

Table 4

Material	%w/w in batch	g/batch	%w/w* placebo film	mg/dose*	%w/w* active film	% w/w actual batch
Dextromethorphan		17.0326		15.0000	15.7563	5.0951
Amberlite IRP69		17.2597		15.2000	15.9664	5.1630
Xanthan Gum	0.0600	0.1800	0.2439	0.1585	0.1665	0.0538
Locust Bean Gum	0.0700	0.2100	0.2845	0.1849	0.1943	0.0628
Carrageenan	0.3000	0.9000	1.2194	0.7926	0.8326	0.2692
Pullulan	16.0000	48.0000	65.0338	42.2720	44.4033	14.3587
Potassium Sorbate	0.0600	0.1800	0.2439	0.1585	0.1665	0.0538
Acesulfame Potassium Salt	0.5000	1.5000	2.0323	1.3210	1.3876	0.4487
Aspartame NF	1.4000	4.2000	5.6905	3.6988	3.8853	1.2564
Purified Water	75.3974	226.1922				67.6630
Physcool	0.1000	0.3000	0.4065	0.2642	0.2775	0.0897
Menthol	1.0000	3.0000	4.0646	2.6420	2.7752	0.8974
Citric Acid	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Cherry Flavor (Givudan)	0.1500	0.4500	0.6097	0.3963	0.4163	0.1346
Peppermint Flavor	0.5000	1.5000	2.0323	1.3210	1.3876	0.4487
Mono ammonium glycyrrhizinate (MAG)	0.0100	0.0300	0.0406	0.0264	0.0278	0.0090
Polysorbate 80 NF	0.3500	1.0500	1.4226	0.9247	0.9713	0.3141
Atmos 300	0.3500	1.0500	1.4226	0.9247	0.9713	0.3141
Glycerine	3.0000	9.0000	12.1938	7.9260	8.3256	2.6923
Olive Oil	0.5000	1.5000	2.0323	1.3210	1.3876	0.4487
FD&C green #3	0.0026	0.0078	0.0106	0.0069	0.0072	0.0023
Titanium Dioxide	0.2500	0.7500	1.0162	0.6605	0.6938	0.2244
Total w/o active		300.0000	100.0000	65.0000		
Total with active	100.0000	334.2922		95.2000	100.0000	100.0000
* assuming that all water is evaporated						

The active film had a pleasing appearance and taste.

Example 5

The ingredients listed in Table 5 were combined to provide an example of an antitussive film of the invention in accordance with the following procedure:

A. The water was heated to 75°C. Uncoated dextromethorphan hydrobromide was dissolved with mixing in the water, while maintaining the temperature at 75°C. AMBERLITE resin was then mixed into the water with heating for 4 to 5 hours at 70-80°C. Heating was stopped, water lost to evaporation was replaced, and the potassium sorbate and sweeteners were then added to the composition with mixing to form Preparation A.

B. The film-forming ingredients (e.g., xanthan gum, locust bean gum, carrageenan and pullulan) were mixed in a separate container to form Preparation B.

C. Preparation B was slowly added to Preparation A with rapid mixing, followed by overnight mixing at a reduced rate to provide Preparation C.

D. The menthol was dissolved with mixing in the alcohol in a separate container. The Physcool was then dissolved with mixing therein. The MAG, Polysorbate 80, Atmos 300 and flavors were then added to the mixture and mixed to enhanced uniformity to form Preparation D.

E. Preparation D, glycerine and mannitol were added to Preparation C with thorough mixing to provide Preparation E.

Preparation E was poured on a mold and cast to form a film of a desired thickness at room temperature. The film was dried under warm air and cut to a desired dimension (dictated by, e.g., dosage and mouthfeel) for taste testing. The film was segmented into 1.5 in^2 (9.7 cm^2) dosage units, each of which had a thickness of 0.009±0.002 in (0.23±0.05 mm) and a weight of 70±3 mg.

A placebo film was also prepared in accordance with the foregoing to facilitate evaluation of, e.g., the taste and appearance of the active film.

Table 5

Material	%w/w in batch	g/batch	mg/dose*	%w/w* film	% w/w actual batch
Dextromethorphan HBr		11.4615	15.0000	21.4286	9.2666
Amberlite IRP69		12.2256	16.0000	22.8571	9.8843
Xanthan Gum	0.0600	0.0600	0.0944	0.1348	0.0485
Locust Bean Gum	0.0700	0.0700	0.1101	0.1573	0.0566
Carrageenan	0.3000	0.3000	0.4718	0.6740	0.2425
Pullulan	16.0000	16.0000	25.1613	35.9447	12.9359
Potassium Sorbate	0.0600	0.0600	0.0944	0.1348	0.0485
Acesulfame Potassium Salt	0.5000	0.5000	0.7863	1.1233	0.4042
Aspartame NF	1.4000	1.4000	2.2016	3.1452	1.1319
Purified Water	70.2000	70.2000			56.7561
Alcohol USP	5.0000	5.0000			4.0425
Physcool	0.1000	0.1000	0.1573	0.2247	0.0808
Menthol	1.5000	1.5000	2.3589	3.3698	1.2127
Peppermint Flavor	0.1000	0.1000	0.1573	0.2247	0.0808
Raspberry Flavor (Givudan)	0.5000	0.5000	0.7863	1.1233	0.4042
Mono ammonium glycyrrhizinate (MAG)	0.0100	0.0100	0.0157	0.0225	0.0081
Polysorbate 80 NF	0.3500	0.3500	0.5504	0.7863	0.2830
Atmos 300	0.3500	0.3500	0.5504	0.7863	0.2830
Glycerine	1.5000	1.5000	2.3589	3.3698	1.2127
Mannitol USP	2.0000	2.0000	3.1452	4.4931	1.6170
Total w/o active		100.0000	39.0000		

The active film had a pleasing appearance and taste.

Example 6

Films of the invention having the ingredients listed in Table 6 were prepared in accordance with the method of Example 5.

Table 6

Material	%w/w in batch	g/batch	mg/dose*	%w/w*	%w/w
Dextromethorphan HBr		11.6538	15.0000	21.4286	9.3919
Amberlite IRP69		12.4308	16.0000	22.8571	10.0180
Xanthan Gum	0.0600	0.0600	0.0925	0.1321	0.0484
Locust Bean Gum	0.0700	0.0700	0.1079	0.1542	0.0564
Carrageenan	0.3000	0.3000	0.4625	0.6606	0.2418
Pullulan	16.0000	16.0000	24.6640	35.2343	12.8944
Potassium Sorbate	0.0600	0.0600	0.0925	0.1321	0.0484
Acesulfame Potassium Salt	0.5000	0.5000	0.7708	1.1011	0.4030
Aspartame NF	1.4000	1.4000	2.1581	3.0830	1.1283
Purified Water	69.7000	69.7000			56.1713
Alcohol USP	5.0000	5.0000			4.0295
Physcool	0.1000	0.1000	0.1542	0.2202	0.0806
Menthol	2.0000	2.0000	3.0830	4.4043	1.6118
Peppermint Flavor	0.1000	0.1000	0.1542	0.2202	0.0806
Raspberry Flavor (Givudan)	0.5000	0.5000	0.7708	1.1011	0.4030
Mono ammonium glycyrrhizinate (MAG)	0.0100	0.0100	0.0154	0.0220	0.0081
Polysorbate 80 NF	0.3500	0.3500	0.5395	0.7708	0.2821
Atmos 300	0.3500	0.3500	0.5395	0.7708	0.2821
Glycerine	1.5000	1.5000	2.3123	3.3032	1.2089
Mannitol USP	2.0000	2.0000	3.0830	4.4043	1.6118
Total w/o active		0.0000	39.0000		
Total with active	100.0000	124.0846	70.0000	100.0000	100.0000
* assuming that all water and alcohol is evaporated					

The active film had a pleasing appearance and taste.

Example 7

A film of the invention having the ingredients listed in Table 7 were prepared in accordance with the method of Example 5. The film was segmented into 1" x 1.25" (2.54 cm x 3.18 cm) dosage units, each of which had a thickness of 0.009±0.002 in (0.23±0.05 mm) and a weight of 63.6±3 mg.

Table 7

Material	%w/w in batch	kg/batch	mg/dose*	%w/w*	%w/w
Dextromethorphan HBr		1.3567	15.0000	23.5981	9.3918
Amberlite IRP69		1.4472	16.0000	25.1713	10.0180
Xanthan Gum	0.0600	0.0070	0.0772	0.1215	0.0484
Locust Bean Gum	0.0700	0.0081	0.0901	0.1417	0.0564
Carrageenan	0.3000	0.0349	0.3661	0.6075	0.2418
Pullulan	16.0000	1.8627	20.5941	32.3988	12.8944
Potassium Sorbate	0.0600	0.0070	0.0772	0.1215	0.0484
Acesulfame Potassium Salt	0.5000	0.0582	0.6436	1.0125	0.4030
Aspartame NF	1.4000	0.1630	1.8020	2.8349	1.1283
Purified Water	69.7000	8.1145			56.1714
Alcohol USP	5.0000	0.5821			4.0295
Physcool	0.1000	0.0116	0.1287	0.2025	0.0806
Menthol	2.0000	0.2328	2.5743	4.0498	1.6118
Peppermint Flavor	0.1000	0.0116	0.1287	0.2025	0.0806
Raspberry Flavor (Givudan)	0.5000	0.0582	0.6436	1.0125	0.4030
Mono ammonium glycyrrhizinate (MAG)	0.0100	0.0012	0.0129	0.0202	0.0081
Polysorbate 80 NF	0.3500	0.0407	0.4505	0.7087	0.2821
Atmos 300	0.3500	0.0407	0.4505	0.7087	0.2821
Glycerine	1.5000	0.1746	1.9307	3.0374	1.2089
Mannitol USP	2.0000	0.2328	2.5743	4.0498	1.6118
Total w/o active + resin		11.6420	32.5644		
Total with active + resin	100.0000	14.4459	63.5644	100.0000	100.0000
* assuming that all water and alcohol is evaporated					

The active film had a pleasing appearance and taste.

While the invention has been described in detail and with reference to specific examples thereof, it will be apparent to one skilled in the art that various changes and modifications can be made therein without departing from the spirit and scope thereof.

CLAIMS

WHAT IS CLAIMED IS:

1. A consumable film adapted to adhere to and dissolve in a mouth of a consumer, wherein said film comprises at least one water soluble polymer, at least one pharmaceutically active agent and at least one taste masking agent.

2. The consumable film according to claim 1, wherein said at least one water soluble polymer is a member selected from the group consisting of pullulan, hydroxyproplymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, polyvinyl pyrrolidone, carboxymethyl cellulose, polyvinyl alcohol, sodium alginate, polyethylene glycol, 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.

3. The consumable film according to claim 2, wherein said at least one water soluble polymer is pullulan.

4. The consumable film according to claim 1, wherein said at least one pharmaceutically active agent is a member selected from the group consisting of antimicrobial agents, non-steroidal anti-inflammatory agents, antitussives, decongestants, anti-histamines, expectorants, anti-diaherrals, H_2-antagonists, proton pump inhibitors, central nervous system agents, analgesics and mixtures thereof.

5. The consumable film according to claim 4, wherein the antimicrobial agent is a member selected from the group consisting of triclosan, cetyl pyridium chloride, domiphen bromide, quaternary ammonium salts, zinc compounds, sanguinarine, fluorides, alexidine, octonidine, EDTA and mixtures thereof.

6. The consumable film according to claim 4, wherein the non-steroidal anti-inflammatory agent is a member selected from the group consisting of aspirin, acetaminophen, ibuprofen, diflunisal, fenoprofen calcium, naproxen, tolmetin sodium, indomethacin, and mixtures thereof.

7. The consumable film according to claim 4, wherein the antitussive is a member selected from the group consisting of benzonatate, caramiphen edisylate, dextromethorphan, chlophedianol, diphenhydramine, salts thereof and mixtures thereof.

8. The consumable film according to claim 4, wherein the decongestant is selected from the group consisting of pseudoephedrine, phenylepherine, phenylpropanolamine, salts thereof and mixtures thereof.

9. The consumable film according to claim 4, wherein the anti-histamine is selected from the group consisting of brompheniramine maleate, chlorpheniramine maleate, carbinoxamine maleate, clemastine fumarate, dexchlorpheniramine maleate, diphenhydramine hydrochloride, diphenhydramine citrate, diphenylpyraline hydrochloride, doxylamine succinate, promethazine hydrochloride, pyrilamine maleate, tripelennamine citrate, triprolidine hydrochloride and mixtures thereof.

10. The consumable film according to claim 4, wherein the expectorant is selected from the group consisting of guaifenesin, ipecac, potassium iodide, terpin hydrate and mixtures thereof.

11. The consumable film according to claim 4, wherein the anti-diarrheal is loperamide.

12. The consumable film according to claim 4, wherein the H_2-antagonist is selected from the group consisting of famotidine, ranitidine and mixtures thereof.

13. The consumable film according to claim 4, wherein the proton pump inhibitor is selected from the group consisting of omeprazole,

lansoprazole, and mixtures thereof.

14. The consumable film according to claim 1, wherein the at least one taste masking agent is an ion exchange resin.

15. The consumable film according to claim 14, wherein the ion exchange resin is a sulfonated polymer comprising polystyrene cross-linked with divinylbenzene.

16. The consumable film according to claim 14, wherein the ion exchange resin is a sulfonated polymer comprising 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).

17. The consumable film according to claim 16, wherein the ion exchange resin has irregularly-shaped particles ranging in size from about 47 to about 149 micrometers.

18. The consumable film according to claim 16, wherein the ion exchange resin has spherical particles ranging in size from about 45 to about 150 micrometers.

19. The consumable film according to claim 14, wherein the ion exchange resin is a polymer composed of polystyrene cross-linked with 8% of divinylbenzene and functionalized with a quaternary ammonium group, and wherein an exchange capacity of said ion exchange resin is normally within a range of about 3 to about 4 meq/g of dry ion exchange resin.

20. The consumable film according to claim 1, wherein the at least one taste masking agent is magnesium trisilicate.

21. The consumable film according to claim 1, wherein said at least one water soluble polymer is pullulan, said at least one pharmaceutically active agent is dextromethorphan, and said at least one taste masking agent is a sulfonated polymer ion exchange resin comprising polystyrene cross-linked with divinylbenzene.

22. The consumable film according to claim 21, wherein said pullulan is present in an amount of about 40 to about 80 wt% of said film, said dextromethorphan is present in an amount of about 5 to about 40 wt% of said film, said sulfonated polymer ion exchange resin is present in an amount of about 5 to about 40 wt% of said film, and a ratio of said dextromethorphan to said sulfonated polymer ion exchange resin is 1:3 to 3:1.

23. The consumable film according to claim 22, wherein said pullulan is present in said film in an amount of about 2 to about 6 mg/cm^2, said dextromethorphan is present in said film in an amount of about 1.4 to about 2 mg/cm^2, and said sulfonated polymer ion exchange resin is present in said film in an amount of about 1.4 to about 2 mg/cm^2.

24. The consumable film according to claim 22, further comprising:

about 0.01 to about 5 wt% of at least one stabilizing agent;

about 0.001 to about 0.1 wt% of at least one of at least one coloring agent;

about 0.1 to about 70 wt% of water;

about 0.1 to about 15 wt% of at least one sweetening agent;

about 0.1 to about 15 wt% of at least one flavoring agent;

about 0.1 to about 4 wt% of at least one cooling agent;

about 0.1 to about 5 wt% of at least one surfactant;

about 0.1 to about 12 wt% of a triglyceride;

about 0.001 to about 5 wt% of a preservative;

about 0.1 to about 5 wt% of a polyethylene oxide compound; and

about 1 to about 20 wt% of propylene glycol.

25. A method for preparing the consumable film of claim 1, said method 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 said film-forming mixture and said aqueous solution to provide a hydrated polymer gel;

mixing oils to form an oil mixture;

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

casting the uniform gel on a substrate; and

drying the cast gel to provide said film.

26. The method of claim 25, wherein said at least one pharmaceutically active agent and said at least one taste masking agent are incorporated into said aqueous solution or into said uniform gel.

27. The method of claim 25, wherein said at least one taste masking agent is an ion exchange resin, and said at least one pharmaceutically active agent is sorbed to said ion exchange resin without separating ion exchanged pharmaceutically active agent from unexchanged agent and counter ion salts.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 01/02192

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/00 A61K9/20

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

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

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

WPI Data, PAJ, EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	EP 0 438 147 A (SCLAVO) 24 July 1991 (1991-07-24) claims 1-5,13 ---	1,2, 14-19
P,X	WO 00 42992 A (LAVIPHARM) 27 July 2000 (2000-07-27)	1-4
Y,P	claims 1,11,12,15,17,21,23,40 page 14, line 12 - line 21 page 18; table 1 -----	21-27

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

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search 10 May 2001	Date of mailing of the international search report 28/05/2001
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INTERNATIONAL SEARCH REPORT

Information on patent family members

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[51] Int. Cl^7
A61K 9/00
A61K 9/20

[12] 发明专利申请公开说明书

[21] 申请号 01806998.3

[43] 公开日 2003年5月21日

[11] 公开号 CN 1419441A

[22] 申请日 2001.1.23 [21] 申请号 01806998.3
[30] 优先权
[32] 2000.3.23 [33] US [31] 09/535,005
[86] 国际申请 PCT/US01/02192 2001.1.23
[87] 国际公布 WO01/70194 英 2001.9.27
[85] 进入国家阶段日期 2002.9.23
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权利要求书 4 页 说明书 25 页

[54] 发明名称 含有作为味道掩蔽剂的离子交换树脂的快速口溶食用膜

[57] 摘要

本发明公开了生理可接受膜，包括食用膜。该膜包括水溶成膜聚合物，例如支链淀粉，和味道掩蔽的药物活性剂，例如右甲吗南。味道掩蔽剂优选是磺化的聚合物离子交换树脂，其包括用二乙烯基苯交联的聚苯乙烯，例如 *AMBERLITE*。还公开了制备该膜的方法。

ISSN 1008-4274

知识产权出版社出版

1. 一种适合于附着和溶于消费者口中的食用膜，其中所述膜包括至少一种水溶聚合物、至少一种药物活性剂和至少一种味道掩蔽剂。

2. 根据权利要求1的食用膜，其中所述的至少一种水溶聚合物选自支链淀粉、羟丙基甲基纤维素、羟乙基纤维素、羟丙基纤维素、聚乙烯基吡咯烷酮、羧甲基纤维素、聚乙烯基醇、藻酸钠、聚乙二醇、黄原胶、黄芪胶、瓜尔豆胶、阿拉伯树胶、聚丙烯酸、甲基异丁烯酸酯共聚物、羧乙烯基聚合物、直链淀粉、高直链淀粉、羟丙基化高直链淀粉、糊精、果胶、几丁质、脱乙酰壳多糖、果聚糖、痂囊腔菌聚糖、胶原、明胶、玉米醇溶蛋白、面筋、大豆分离蛋白、乳清分离蛋白、酪蛋白及其混合物。

3. 根据权利要求2的食用膜，其中所述的至少一种水溶聚合物是支链淀粉。

4. 根据权利要求1的食用膜，其中所述的至少一种药物活性剂选自抗菌剂、非甾体消炎药、止咳药、减充血剂、抗组胺药、祛痰药、抗腹泻药、H_2-拮抗药、质子泵抑制剂、中枢神经系统药剂、止痛剂和其混合物。

5. 根据权利要求4的食用膜，其中抗菌剂选自三氯生、氯化十六烷基吡啶、溴化度米芬、季按盐、锌化合物、血根碱、氟化物、阿来西定，octonidine、EDTA和其混合物。

6. 根据权利要求4的食用膜，其中非甾体消炎药选自阿斯匹林、朴热息痛、布洛芬、二氟尼柳、非诺洛芬钙、萘普生、托美丁钠、消炎痛和其混合物。

7. 根据权利要求4的食用膜，其中镇咳药选自苯佐那酯，乙二磺酸卡腊米芬、右甲吗喃、氯苯达诺、苯海拉明，其盐和其混合物。

8. 根据权利要求4的食用膜，其中减充血剂选自假麻黄碱、去氧肾上腺素、苯丙醇胺，其盐和其混合物；

9. 根据权利要求4的食用膜，其中抗组胺药选自马来酸溴苯那敏、

马来酸氯苯那敏、马来酸卡比沙明、延胡索酸氯马斯汀、马来酸右氯本那敏、盐酸苯海拉明、盐酸二苯拉林、柠檬酸苯海拉明、琥珀酸多西拉敏、盐酸异丙嗪、马来酸美吡拉敏、柠檬酸曲吡那敏、盐酸曲普利啶和其混合物。

10. 根据权利要求 4 的食用膜，其中祛痰药选自愈创甘油醚、吐根、碘化钾、水合萜二醇和其混合物。

11. 根据权利要求 4 的食用膜，其中止泻剂是洛派丁胺。

12. 根据权利要求 4 的食用膜，其中 H_2-拮抗药选自法莫丁、雷尼替丁和其混合物。

13. 根据权利要求 4 的食用膜，其中质子泵抑制剂选自奥美拉唑、兰索拉唑和其混合物。

14. 根据权利要求 1 的食用膜，其中至少一种味道掩蔽剂是离子交换树脂。

15. 根据权利要求 14 的食用膜，其中离子交换树脂是包括用二乙烯基苯交联聚苯乙烯的磺化的聚合物。

16. 根据权利要求 14 的食用膜，其中离子交换树脂是包括用 8% 二乙烯基苯交联聚苯乙烯的磺化的聚合物，其具有的离子交换能力约 4.5 至 5.5meq/g 的干树脂(H^+-形式)。

17. 根据权利要求 16 的食用膜，其中不规则形状颗粒离子交换树脂的粒径大小是约 47 至约 149 微米。

18. 根据权利要求 16 的食用膜，其中球形颗粒的离子交换树脂的范围是约 45 至约 150 微米。

19. 根据权利要求 14 的食用膜，其中离子交换树脂是用 8% 二乙烯基苯交联的聚苯乙烯组成的聚合物，且具有季铵基作为功能基团；其中所述离子交换树脂的交换能力一般是约 3 至 4meq/g 的干离子交换树脂。

20. 根据权利要求 1 的食用膜，其中至少一种味道掩蔽剂是三硅酸镁。

21. 根据权利要求 1 的食用膜，其中所述的至少一种水溶聚合物是

支链淀粉，所述的至少一种药物活性剂是右甲吗南，且所述的至少一种味道掩蔽剂是包括用二乙烯基苯交联聚苯乙烯的磺化聚合物离子交换树脂。

22. 根据权利要求 21 的食用膜，其中所述的支链淀粉含量是所述膜的约 40 至约 80wt%，所述右甲吗南的含量是所述膜的约 5 至约 40wt%，所述磺化聚合物离子交换树脂的含量是所述膜的约 5 至约 40wt%，且所述右甲吗南与所述磺化聚合物的离子交换树脂的比例是 1:3 至 3:1。

23. 根据权利要求 22 的食用膜，其中所述的支链淀粉在所述膜中的含量是约 2 至约 $6mg/cm^2$，所述右甲吗南在所述膜中的含量是约 1.4 至约 $2mg/cm^2$，且所述磺化聚合物离子交换树脂在所述膜中的含量是约 1.4 至约 $2mg/cm^2$。

24. 根据权利要求 22 的食用膜，还包括：
约 0.01 至约 5wt%的至少一种稳定剂；
约 0.001 至约 0.1wt%的至少一种着色剂；
约 0.1 至约 70wt%的水；
约 0.1 至约 15wt%的至少一种甜味剂；
约 0.1 至约 15wt%的至少一种调味剂；
约 0.1 至约 4wt%的至少一种冷却剂；
约 0.1 至约 5wt%的至少一种表面活性剂；
约 0.1 至约 12wt%的甘油三酸酯；
约 0.001 至约 5wt%的防腐剂；
约 0.1 至约 5wt%的聚环氧乙烷化合物；和
约 1 至约 20wt%的丙二醇。.

25. 一种制备权利要求 1 的食用膜的方法，所述的方法包括：
将水溶成分溶于水中，得到水溶液；
将至少一种水溶膜成形剂和至少一种稳定剂混合，得到成膜混合物；
将所述成膜混合物和所述水溶液结合得到水合聚合物凝胶；
混合油形成油混合物；

将所述油混合物添加进所述水合聚合物凝胶，并混合得到均匀的凝胶；

在基底上浇铸均匀的凝胶；且

干燥浇铸的凝胶得到所述膜。

26 根据权利要求 25 的方法，其中将所述的至少一种药物活性剂和所述的至少一种味道掩蔽剂混入所述的水溶液或混入所述的均匀的凝胶。

27. 根据权利要求 25 的方法，其中所述的至少一种味道掩蔽剂是离子交换树脂，而所述的至少一种药物活性剂被吸附到所述的离子交换树脂，并不将离子交换药物活性剂与未交换剂和反荷离子盐分离。

含有作为味道掩蔽剂的离子交换树脂的快速口溶食用膜

本发明技术领域

本发明涉及快速口溶食用膜，该食用膜含有遮盖活性药剂味道的试剂，且更具体地说涉及含有作为味道掩蔽剂的离子交换树脂的膜。

本发明的背景技术

在食用膜载体中提供活性药剂已经是公知的。

例如，W099/17753 公开了用于将药物输送至消化道吸收的速溶膜。

W098/26780 公开了一种呈现出平面、箔、纸或圆片型的物质，该物质用于将口腔前庭中的活性物质施用和释放。在 W098/26780 中公开的具体活性成分是丁丙诺啡。

W098/20862 公开了一种利用口腔中含有的美容的或药物活性物质的膜。

W098/26763 公开了一种呈现出平面、箔、纸或圆片型的物质，该物质用于将口腔前庭中的活性物质释放。所公开的具体活性物质是阿朴吗啡。

U.S. 专利申请 No. 09/395,104 也公开了在食用膜载体中药剂的输送。

Ozaki 等人的 U.S. 专利 No. 5,411,945 公开了一种支链淀粉粘合剂以及由此制得的产品，包括食用膜(实施例 B-2)..除了支链淀粉以外该产品可以包括各种成分，例如其它多糖、抗菌剂、风味剂和药物活性物质(第 4 栏，第 5-15 行)。

Hijiya 等人的 U.S. 专利 No. 3,784,390 公开了支链淀粉膜，其用于食品、药品和其它氧敏物质的涂敷和包装物料。在该专利中的所有实施例均有将支链淀粉在热水中混合的教导。

将离子交换树脂与药物活性剂结合，以提供恒定释放的制剂已经是公知的。

例如，Wen 等人的 U.S. 专利 No.6,001,392 公开了用于口服的控制释放糖浆悬浮液，该悬浮液含有吸收至聚苯乙烯磺酸酯离子交换树脂的右甲吗南。没有公开药物膜。

Eichman 的 U.S. 专利 No.5,980,882 公开了一种提高药物组合物稳定性的方法，该药物组合物含有药物－树脂复合体，包括添加有效量的螯合剂，以降低在药物－树脂复合体中药物的降解速率。虽然 Eichman 教导了将药物和离子交换树脂复合可以遮盖药物的味道。没有公开药物膜。

本发明人在公开的技术中，没有发现任何有关离子交换树脂可以作为口中速溶食用膜中味道掩蔽剂的建议。因此，本发明的目的是提供口中速溶食用膜，该食用膜含有遮盖其中的药物活性剂味道的离子交换树脂。

本文所引用的所有参考文献均以全文被引入。

本发明概述

本发明提供一种适合于附着和溶于消费者口中的食用膜，其中该膜包括至少一种水溶聚合物、至少一种药物活性剂和至少一种味道掩蔽剂。

还提供了一种用于制备本发明食用膜的方法，包括：

将水溶成分溶于水中，得到水溶液；

将至少一种水溶膜成形剂和至少一种稳定剂混合，得到成膜混合物；

将成膜混合物和水溶液结合得到水合聚合物凝胶；

混合油形成油混合物；

将油混合物添加进水合聚合物凝胶，并混合得到均匀的凝胶；

在基底上浇铸均匀的凝胶；且

干燥浇铸的凝胶得到膜。

优选实施方案的详细描述

本发明提供一种生理可接受的膜，该膜特别适合于在消费者口中附着和溶解，以输送药物活性剂。根据本发明优选的膜包括药物活性剂、离子交换树脂、成膜剂和至少一种下述附加成分：水、抗菌剂、增塑剂、风味剂、唾液刺激剂、冷却剂、表面活性剂、稳定剂、乳化剂、增稠剂、粘合剂、色素、甜味剂、香料、甘油三酸酯、防腐剂、聚环氧乙烷和聚乙二醇等。

本文所使用的措辞“生理可接受”指的是包括基于对病人给药的化合物，所述的化合物具有充分的耐药性，不会导致不适当的消极副作用。该措辞包括食用化合物。

本文所使用的措辞“药物活性剂”是指除食品以外的试剂，其在被施用以后促进了体内和/或体表的结构和/或功能的改变。对这些试剂没有特别的限制；然而它们应是生理可接受的并且与膜是相容的。合适的药物活性剂包括但不仅限于：

A.抗菌剂，例如三氯生、氯化十六烷基吡啶、溴化度米芬、季按盐、锌化合物、血根碱、氟化物、阿来西定，octonidine 和 EDTA 等；

B.非甾体消炎药，例如阿斯匹林、朴热息痛、布洛芬、酮洛芬、二氟尼柳、非诺洛芬钙、萘普生、托美丁钠和消炎痛等；

C.止咳药，例如，苯佐那酯，乙二磺酸卡腊米芬、薄荷醇、氢溴酸右甲吗喃和盐酸氯苯达诺等；

D.减充血剂，例如盐酸假麻黄碱、去氧肾上腺素、苯丙醇胺和硫酸假麻黄碱等；

E.抗组胺药，例如马来酸溴苯那敏、马来酸氯苯那敏、马来酸卡比沙明、延胡索酸氯马斯汀、马来酸右氯本那敏、盐酸苯海拉明、盐酸二苯拉林、马来酸阿扎他定、柠檬酸苯海拉明、琥珀酸多西拉敏、盐酸异丙嗪、马来酸美吡拉敏、柠檬酸曲吡那敏、盐酸曲普利啶、阿伐斯汀、氯雷他定、溴苯那敏和右溴苯那敏等；

F.祛痰药，例如俞创甘油醚、吐根、碘化钾和水合萜二醇等；

G.抗腹泻药，例如洛派丁胺等；

H. H_2-拮抗药，例如法莫丁和雷尼替丁等；

I. 质子泵抑制剂，例如奥美拉唑和兰索拉唑等；

J. 一般未选择的 CNS 镇静剂，例如脂肪族醇和巴比妥类药物等；

K. 一般未选择的 CNS 兴奋剂，例如咖啡因、尼古丁、士的宁、木防己苦毒素和次戊基四唑等；

L. 选择性地改变 CNS 功能的药物，例如苯海因、苯巴比妥，朴米酮、卡马西平、乙琥胺、甲琥胺、苯琥胺、三甲双酮、安定，苯二氮杂䓬，苯乙酰脲、苯丁酰脲、乙酰唑胺、舒噻嗪和溴化物等；

M. 抗帕金森氏综合症药，例如左旋多巴和金刚烷胺等；

N. 麻醉药-止痛药例如吗啡、海洛因、氢吗啡酮、美托酮、羟吗啡酮、左吗啡、可待因、氢可酮、xycodone、烯丙吗啡、纳洛酮和纳曲酮等；

O. 止痛药-解热剂例如，水杨酸酯、保泰松、消炎痛和非那西汀等；和

P. 抗精神失常药，例如氯丙嗪、左美丙嗪、氟哌啶醇、氯氮平、利血平、丙咪嗪、反苯环丙胺、苯乙肼和锂等。

根据本发明的用于速溶膜的药物活性剂的量依赖于提供有效量的药物活性剂所需要的剂量。每条速溶口服膜可以输送的具体药物活性剂的剂量实例列于表 A 中。

表 A

药物活性剂	优选剂量
马来酸氯苯那敏	4mg.
马来酸溴苯那敏	4mg.
右氯苯那敏	2mg.
右溴苯那敏	2mg.
盐酸曲苯利啶	2.5mg.
阿伐斯汀	8mg.
马来酸阿扎他定	1mg.
氯雷他定	10mg.

盐酸苯福林	10mg.
氢溴酸右甲吗南	10-30mg.
酮洛芬	12.5-25mg.
琥珀酸舒马曲坦	35 - 70mg.
Zolmitriptan	2.5mg.
洛派丁胺	2mg.
法莫丁	10mg.
尼古丁	2mg.
盐酸苯海拉明	12.5-25mg.
盐酸假麻黄碱	30mg.

优选用于本发明膜的离子交换树脂是不溶于水的，且由药物惰性有机或无机基质组成，所述基质含以共价键结合的官能基团，所述的基团是离子的或在适当的pH条件下能够被离子化的。该有机基质可以是合成的(例如，丙烯酸、异丁烯酸、磺化的苯乙烯、磺化的二乙烯基苯的聚合物或共聚物)，或部分合成的(例如，变性纤维素和葡聚糖)。无机基质也可以是例如，通过添加离子基团而改性的硅胶。共价键离子基团可以是强酸、(例如，磺酸)、弱酸(例如，羧酸)、强碱(例如，季铵)、弱碱(例如，伯胺)、或酸和碱基团的组合。一般，适合用于离子交换色谱法，且以去离子水方式应用的离子交换树脂是适合用于控制药物制剂释放的那些种类。这样的离子交换树脂描述于H.F.Walton"离子交换原理(PrinciplesofIonExchange)"(312-343页)。用于本发明的离子交换树脂所具有的交换能力低于约6毫克当量每克(meq/g)且优选低于约5.5meq/g。

树脂用交联剂交联，该交联剂选自能够交联聚苯乙烯的双功能化合物；它们在本领域是公知的。优选，交联剂是二乙烯基或聚乙烯基化合物。最优选的交联剂是二乙烯基苯。基于树脂的总重量该树脂的交联程度是约3至约20%，优选约4至约16%，更优选约6至约10%，且最优选约8%。该树脂用交联剂以本领域公知的方式进行交联。

离子交换树脂的大小优选范围是约 20 至约 200 微米。粒径低于下限的，在加工的所有步骤中难以操作。粒径大于上限，例如，市售的、球形的离子交换树脂，直径直至约 1000 微米，在液体配药形式中具有砂砾感，且当经过干燥-水合循环很易于破碎。

用于本发明的典型树脂包括 AMBERLITEIRP-69(源自 Rohm 和 Haas) 和 DowXYS-40010.00(源自 TheDowChemicalCompany)。两者都是由用 8% 二乙烯基苯交联的聚苯乙烯组成的磺化的聚合物，具有的离子交换能力是约 4.5to5.5meq/g 的干树脂(H^+-形式)。其本质的区别在于物理结构。AMBERLITEIRP-69 包括粒径范围是 47 至 149 微米的不规则形状颗粒，是通过磨制大粒径球形的作为起源的 AMBERLITEIRP-120 而制备的。TheDowXYS-40010.00 产品包括粒径是 45to150 微米的球形颗粒。另一种有用的交换树脂 DowXYS-40013.00 是由用 8% 二乙烯基苯交联的聚苯乙烯组成的聚合物，且具有季铵基作为功能基团；其交换能力一般是约 3 至 4meq/g 的干树脂。

最优选的树脂是 AMBERLITEIRP-69。然而，只是在较少的优选实施方案中，不需要将离子交换树脂作为味道掩蔽剂。在这些实施方案中，味道掩蔽剂可以是例如，三硅酸镁。参见 Peters 等人的 U.S.4,650,663 和 4,581,232。味道也可以被聚合物例如 EUDRAGITE(Rohm 和 Haas)，和/或纤维素，例如乙基纤维素等所遮盖。

用于本发明膜的成膜剂可以选自支链淀粉、羟丙基甲基纤维素、羟乙基纤维素、羟丙基纤维素、聚乙烯基吡咯烷酮、羧甲基纤维素、聚乙烯基醇、藻酸钠、聚乙二醇、黄原胶、黄芪胶、瓜尔豆胶、阿拉伯树胶、聚丙烯酸、甲基异丁烯酸酯共聚物、羧乙烯基聚合物、直链淀粉、高直链淀粉、羟丙基化高直链淀粉、糊精、果胶、几丁质、脱乙酰壳多糖、果聚糖、痂囊腔菌聚糖、胶原、明胶、玉米醇溶蛋白、面筋、大豆分离蛋白、乳清分离蛋白、酪蛋白及其混合物。优选的成膜剂是支链淀粉，用量是膜的约 0.01 至约 99wt%，优选约 30 至约 80wt%，更优选约 45 至约 70wt%，且更加优选约 60 至约 65wt%。

除非另有说明，本文所用的术语"wt%"是针对最终产品的(即膜，与

制造它的制剂相对)，表示原料成分所构成的总干重量的百分数。该理论值与试验值可以是不同的，因为在实际情况下，膜一般保留了一些制备当中所使用的水和/或乙醇。

在实施方案中含有相当高的油，优选避免在膜中有大量的湿润剂(且更优选在膜中没有湿润剂)，以便于避免产生出过渡湿润、自粘附的膜。特别是优选配制成高油含量的膜，该膜具有除了甘油以外的增塑剂，而甘油也是一种湿润剂，并且含有除了山梨糖醇以外的甜味剂，而山梨糖醇是一种轻微的湿润剂。

也可以将唾液刺激剂添加到本发明的膜中. 有效的唾液刺激剂公开于US4,820,506中。唾液刺激剂包括食用酸例如柠檬酸、乳酸、苹果酸、琥珀酸、抗坏血酸、脂肪酸、富马酸和酒石酸。优选食用酸是柠檬酸、苹果酸和抗坏血酸。在膜中的唾液刺激剂的量是约0.01至约12wt%，优选约1wt%至约10wt%，更优选约2.5wt%至约6wt%。

优选增塑剂包括甘油三乙酸酯，其用量是约0至约20wt.%，优选0至约2wt.%。其它合适的增塑剂包括甘油一乙酸酯和甘油二乙酸酯。

优选冷却剂包括琥珀酸单芪酯，其含量是约0.001至约2.0wt%，优选约0.2至约0.4wt%. 含琥珀酸单芪酯的冷却剂是Mane, Inc市售的。其它合适的冷却剂包括WS3, WS23和UltracoolII等。

优选表面活性剂包括脂肪酸的甘油一酸酯和甘油二酸酯和聚氧化乙烯山梨糖醇酯，例如Atmos300和聚山梨酯80. 该表面活性剂在膜中的添加量是约0.5至约15wt%，优选约1至约5wt%。其它合适的表面活性剂包括pluronic acid、月桂基硫酸钠等。

优选的稳定剂包括黄原胶、槐树豆胶和角叉菜胶，在膜中的用量是约0至约10wt%，优选约0.1至约2wt%。其它合适的稳定剂包括瓜尔豆胶等。

优选的乳化剂包括三乙醇胺硬脂酸酯、季铵化合物、阿拉伯树胶、明胶、卵磷脂、膨润土和veegum等，在膜中的用量范围是约0至约5wt%，优选约0.01至约0.7wt%。

优选增稠剂包括甲基纤维素、羧甲基纤维素等，在膜中的用量范

围是约 0 至约 20wt%，优选约 0.01 至约 5wt%。

优选粘合剂包括淀粉，在膜中的用量范围是约 0 至约 10wt%，优选约 0.01 至约 2wt%。

合适的甜味剂可以包括本领域公知的那些甜味剂，包括天然的和人工的甜味剂。合适的甜味剂包括，例如：

A. 水溶甜味剂例如单糖、二糖和多糖，例如木糖、核糖、葡萄糖(右旋糖)、甘露糖、半乳糖、果糖(左旋糖)、蔗糖(糖)、麦芽糖、转化糖(来源于蔗糖的果糖和葡萄糖的混合物)、部分水解淀粉、淀粉糖浆干粉、二氢查耳酮、莫尼林、甜叶菊苷和甘草甜素；

B. 水溶人工甜味剂，例如可溶糖精盐，即糖精钠或糖精钙、环磺酸盐、3,4-二羟基-6-甲基-1、2、3-噁噻嗪-4-酮-2,2-二氧化物的钠、铵或钙盐、3,4-二羟基-6-甲基-1,2,3-噁噻嗪-4-酮-2,2-二氧化物的钾盐(双氧噁噻嗪钾)，和糖精的游离酸形式等；

C. 二肽基甜味剂，例如 L-天门冬氨酸衍生甜味剂，例如 L-门冬氨酰-L-苯丙氨酸甲基酯(阿斯巴甜)和描述于 US3,492,131 中的物质，L-α-门冬氨酰-N-(2,2,4,4--四甲基-3-thietanyl)-D-丙氨酸酰胺水合物、L-门冬氨酰-L-苯基甘油和 L-门冬氨酰-L-2,5 二羟基苯基甘油的甲基酯，L-门冬氨酰-2,5-二羟基-L-苯基丙氨酸、L-门冬氨酰-L-(1-cyclohexyen)-丙氨酸等；

D. 衍生自天然存在的水溶甜味剂的水溶甜味剂，例如公知的普通糖(蔗糖)的氯化衍生物，该产品被称为氯化蔗糖衍生物；和

E. 蛋白质基甜味剂，例如 thaumatoccousdanielli(非洲竹芋甜素 I 和 II)。

一般，针对具体的组合物所需的甜味水平使用有效量的辅助甜味剂，根据所选择的甜味剂，使用量是不同的。当使用易提取的甜味剂时，基于组合物的重量该用量是 0.01%至约 10%。使用上述 A 类的水溶甜味剂时，通常的用量是约 0.01 至约 10wt%，且更优选的量是约 2 至约 5wt%。在 A 类中的一些甜味剂(例如.，甘草甜素)由于该甜味剂公知的增甜效果可以采用其下面的 B－E 类所述的用量。相反，描述于 B－

E 类的甜味剂一般用量是约 0.01 至约 10wt%，优选约 2 至约 8wt%，且最优选约 3 至约 6wt%。这些用量可以用来实现所需的甜味水平，并独立于由任意香精油所实现的风味水平。当然不是用来口服的膜，就不需要添加甜味剂。

可以使用的风味剂包括本领域普通技术人员公知的那些物质，例如天然的和人工的风味剂。这些风味剂可以选自合成香精油和调味香料和/或油、含油树脂和源自植物、叶、花、果实等等的提取物，和其组合。典型的香精油包括：薄荷油、肉桂油、胡椒薄荷、丁香油、月桂油、百里香油、雪松叶油、肉豆蔻油、洋苏草油和苦杏仁油。同样有效的人工、天然或合成的水果风味剂，例如是香草、巧克力、咖啡、可可和柑桔油，包括柠檬、桔子、葡萄、酸橙和葡萄柚和水果香精包括苹果、梨、桃、草莓、覆盆子、樱桃、李子、菠萝、杏等等。这些风味剂可以单独使用，也可以混合使用。常用的风味剂包括薄荷例如胡椒薄荷、人工香草、肉桂衍生物和各种水果风味剂，既可以单独使用也可以混合使用。风味剂例如醛和酯包括乙酸肉桂酯、肉桂醛、柠檬醛、二乙缩醛、乙酸二氢香芹酯、甲酸丁香酯、对甲基茴香醚等等也可以被使用。一般，任何风味剂或食品添加剂，例如在“食品加工中的化学应用”(ChemicalsUsedinFoodProcessing)，由theNationalAcademyofSciences出版 1274，第 63－258 页中所描述的那些物质也可以被使用。醛风味剂的另外的实例包括但不仅限于乙醛(苹果)；苯甲醛(樱桃，杏仁)；肉桂醛(肉桂)；柠檬醛，即.，α柠檬醛(柠檬，酸橙)；橙花醛，即β柠檬醛(柠檬，酸橙)；癸醛(柑桔，柠檬)；乙基香草醛(香草，稀奶油)；洋茉莉醛，即.，胡椒醛(香草、稀奶油)；香草醛(香草，稀奶油)；α戊基肉桂醛(辛辣水果风味)；丁醛(奶油，奶酪)；戊醛(奶油，奶酪)；香茅醛(修饰剂，许多种类)；癸醛(柑桔水果)；C-8 醛(柑桔水果)；C-9 醛(柑桔水果)；C-12 醛(柑桔水果)；2-乙基丁醛(浆果)；己烯醛，即反式－2－己烯醛(浆果)；甲苯基醛(樱桃，杏仁)；藜芦醛(香草)；2,6-二甲基-5-庚烯醛，即.西瓜醛(甜瓜)；2-6-二甲基辛醛(青果)；和 2-十二烯醛(柑桔)；樱桃；葡萄；其混合物等。

风味剂的用量一般由这样一些因素确定的，例如风味类型、个体风味和所需的强度。因此，为了得到终产品所需的结果，用量可以是不同的。这种不同是本领域普通技术人员能够掌握的，不需要进行额外的试验。一般，用量是约 0.1 至约 30wt%，优选约 2 至约 25wt%且最优选约 8 至约 10wt%。

本发明的组合物也可以含有着色剂或色素。有效用量的着色剂产生所需的颜色。用于本发明的着色剂，包括颜料，例如二氧化钛，其添加量是约 5wt%，且优选小于约 1wt%。色素也可以包括天然食用色素和适合于食品、药物和化妆品的染料。这些色素公知的是 FD&C 染料和色淀。用于前述应用范围可接受的物质优选是水溶的，且包括 FD&CBlueNo.2，它是 5,5 靛蓝二磺酸二钠盐。类似地，公知染料 GreenNo.3 包括三苯甲烷染料，且是 4-[4-N-乙基-对-磺苄基氨基]二苯基-亚甲基]-[1-N-乙基-N-对苄基铳]-2,5-环-己二烯亚胺]的一钠盐。有关 FD&C 和 D&C 染料和其对应的化学结构的所有描述公开于 Kirk-Othmer Encyclopedia of Chemical Technology，5 卷，857~884 页，其全文在此引入作为参考。

该膜也可以包括甘油三酸酯。甘油三酸酯的实例包括植物油例如，玉米油、向日葵油花生油、橄榄油、加拿大菜籽油、大豆油和其混合物。优选的甘油三酸酯是橄榄油。在膜中的添加量是膜的约 0.1wt%至约 12wt%，优选约 0.5wt%至约 9wt%。

该膜可以含有膜的约 0.001wt%至约 5wt%的防腐剂，优选约 0.01wt%至约 1wt%。优选防腐剂包括苯甲酸钠和山梨酸钾。其它合适的防腐剂包括但不仅限于依地酸盐（也称为乙二胺四乙酸或 EDTA 的盐，例如乙二胺四乙酸二钠）和尼泊金酯类（例如.，甲基、乙基、丙基或丁基-羟基苯甲酸酯等.）或山梨酸。上述防腐剂只是例举，但每种防腐剂必须基于经验进行评估，在各种制剂中，确保防腐剂的相容性和功效。对在药物制剂中的防腐剂功效的评估方法是本领域普通技术人员所公知的。

该膜也可以包括聚环氧乙烷化合物。聚环氧乙烷化合物的分子量

范围约 50,000 至约 6,000,000。优选的聚环氧乙烷化合物是 UnionCarbideCorporation 的 N-10。基于膜的重量，该聚环氧乙烷化合物的添加量是约 0.1wt%至约 5wt%，优选约 0.2wt%至约 4.0wt%。

该膜也可以含有丙二醇。基于膜的重量，丙二醇的添加量是约 1wt%至约 20wt%，优选约 5wt%至约 15wt%。

根据本发明的膜的制备方法，能够将油成分包囊在成膜基质中，并保持膜的完整性，甚至于在膜的含油量为 10wt%或更多的情况下也是如此。

在制备本发明膜的特定方法中，将成膜成分混合，并与由水溶成分分离的水进行水合，水溶成分在与有机成分和表面活性剂分离的水溶液中混合。在这些方法中，优选通过将成膜相与水相混合，接着在包含表面活性剂，例如聚山梨酸酯 80 和 Atmos300 的有机相中混合而制备出最终的制剂。将该物质混合直至乳化。在其它的实施方案中，通过将水溶成分溶于水中，并接着将树胶添加进水合物，从而使水相和成膜相结合成单一的相。接着将有机相添加至该单一的水相。

将得到的制剂浇铸在合适的基底上，并干燥成膜。该膜优选是风干的或热风干燥的，并被切割成所需的大小、包装并贮藏。该膜可以含有约 0.1%至约 10wt%的水分，优选约 3%至约 8wt%的水分，更优选约 4 至约 7wt%的水分。

成膜相可以包括支链淀粉和稳定剂例如黄原胶、槐树豆胶和角叉菜胶。将这些成分混合，并在水中水合约 30 至 48 小时，以形成凝胶。所述水优选被加热至约 25℃至约 45℃的温度，以促进水合。水量是凝胶体量的约 40 至 80%。得到的水合凝胶接着被冷却至约 20 至约 30℃的温度，持续约 1 至约 48 小时。所述水优选是去离子水。

在优选的实施方案中水相包括被加热至约 60 至 90℃，优选 70 至 80℃的水，和例如药物活性剂、离子交换树脂(或其它掩蔽剂)、着色剂、防腐剂和甜味剂这样的成分。水优选是去离子水，用水量是最终凝胶混合物的约 5 至约 80wt%。

药物活性剂被吸附至离子交换树脂(或其它掩蔽剂)，并不将离子

交换药物活性剂与未交换剂和反荷离子盐分离。

如 U.S.2,990,332 和 4,221,778 中所示，将药物活性剂吸附至离子交换树脂颗粒上，以形成药物活性剂/树脂复合体是众所周知的技术。一般，将药物活性剂与树脂悬浮液混合，且在较少优选的实施方案中，复合体接着进行清洗和干燥。通过对反应介质的 pH 变化的测定，或通过对钠或药物活性剂中浓度变化的测定，来确定药物活性剂对树脂的附着。

药物活性剂对树脂的粘合可以通过四种常规反应实现。在碱性药物活性剂的情况下，它们是：(a)树脂(Na-形式) + 药物活性剂(盐形式)；(b)树脂(Na-形式) + 药物活性剂(作为自由碱)；(c)树脂(H-形式) + 药物活性剂(盐形式)；和(d)树脂(H-形式) + 药物活性剂(作为自由碱)。所有这些反应除(d)以外，均具有阳离子副产品，通过与阳离子药物活性剂竞争树脂上的粘合位置，使平衡粘合的药物活性剂的量降低。对于碱性药物活性剂，药物活性剂对树脂的化学计量粘合只通过反应(d)实现。

对于将酸性药物活性剂与阴离子交换树脂粘合，可以通过四种相似的粘合反应进行，它们是：(a)树脂(Cl-形式) + 药物活性剂(盐形式)；(b)树脂(Cl-形式) + 药物活性剂(作为自由酸)；(c)树脂(OH-形式) + 药物活性剂(盐形式)；和(d)树脂(OH-形式) + 药物活性剂(作为自由酸)。所有这些反应除(d)以外，均具有离子副产品，且当反应进行时，产生阴离子，与阴离子药物活性剂竞争树脂上的粘合位置，降低了平衡粘合的药物活性剂的量。对于酸性药物活性剂，药物活性剂对树脂的化学计量粘合只通过反应(d)实现。例如，在现有技术中公知的间歇或连续方法中可以进行粘合。

在较少的优选实施方案中，包括药物活性剂和树脂的吸附复合体，用乙醇和/或水收集和清洗，以确保任何未吸附的药物活性剂的去除。该复合体通常是在房间中的托盘或升高的温度下被风干。

在吸附复合体中，吸附的药物活性剂与离子交换树脂吸附剂的比例是约 1:3 至约 3:1，优选 1:2 至约 2:1，最优选约 1:1。只是对使用比

例超过 1:3 有限制，这样才能经济和完美。

基于药物活性剂/树脂吸附复合体(下文称为"药物活性剂/树脂复合体"或"复合体")的重量，吸附到离子交换树脂的药物活性剂的量的范围是约 25 至约 75%。基于药物活性剂/树脂吸附复合体的重量，更优选吸附到离子交换树脂上的药物活性剂的量是约 33 至约 77%。基于药物活性剂/树脂吸附复合体的重量，最优选吸附到离子交换树脂上的药物活性剂的量是约 40 至约 60%。

在制剂中的药物活性剂/树脂复合体的量被调节成在预定的时间内输送预定剂量的药物活性剂。

例如，每 12 小时服用一次本发明优选的镇咳药膜，用以在这样的给药方式中，在约 12 小时的时间里输送病人所需的药物有效量的右甲吗南。当平均的药物活性剂：离子交换树脂比例是约 1：1 时，测定的 1"x1.25"(2.54cmx3.18cm)本发明膜的一般成人剂量重量是约 60 至约 190mg 且含约 20 至约 130mg 的药物活性剂/树脂复合体的，用以输送约 5 至约 65mg 的药物活性剂(例如，轻溴酸右甲吗南)。

在本发明特别优选的实施方案中，膜中支链淀粉的含量是约 2 至约 6mg/cm^2，膜中右甲吗南的量是约 1.4 至约 3mg/cm^2，而所述膜中磺化的聚合物离子交换树脂的量是约 1.4 至约 2mg/cm^2。

适合用于这些制剂的镇咳药物活性剂是酸性的、两性的或最通常是碱性的镇咳药。用于本发明的碱性药物活性剂的实例包括，但不仅限于右甲吗南、苯海拉明、卡腊米芬、carbapentane、乙基吗啡、那可丁和可卡因。另外，本发明的镇咳药实施方案还可以包括添加剂，这些添加剂对咳嗽以外的情况也有治疗效果。即，超过一种以上的药物活性剂可以被包含在本发明的膜中。例如，在含有镇咳剂的情况下，该膜还可以含有抗组胺药、拟交感神经药物活性剂(鼻减充血剂、支气管扩张药)，镇痛剂、消炎药、咳嗽抑制剂和/或祛痰药，作为抗组胺药、拟交感神经药物活性剂(鼻减充血剂、支气管扩张药)，镇痛剂、消炎药、咳嗽抑制剂和/或祛痰药的化合物是本领域技术人员所公知的，不需要在此进行详细论述。

在实施方案中，本文所公开的膜中的一定百分含量含有非涂敷的药物活性剂/树脂复合体。其余的药物活性剂，其特征在于还含有涂层。在本发明优选的实施方案中，持续释放的组合物中约20至约80%药物活性剂/树脂复合体被涂敷，最优选约40至约60%的药物活性剂/树脂复合体被涂敷。该涂层是水可渗透的、扩散屏障涂料。涂层的存在使所需的药物组合物的溶解模式进行选择性地修正，所述的药物组合物含有本发明的药物活性剂/树脂复合体。

一般，涂料可以是任何大量的常规天然或合成的成膜物料，可以单独使用，或彼此混合使用，且在混合物中有增塑剂、颜料等，具有扩散屏障特性，而不具有固有的药理性或毒性。一般，涂层的主要成分应是不溶于水的，并是水和药物活性剂可渗透的。然而，优选可以混入水溶物质，例如甲基纤维素，以改变涂层的渗透性，或混入不溶于酸，溶于碱的物质，以作为肠溶性涂层。该涂料可以以水性液体中的悬浮液或有机溶剂中的溶液的形式使用。这样涂料的合适的实例描述于R.C.Rowe的“用于药物制剂的物料(MaterialsusedinPharmaceuticalFormulation)”.(A.T.Florence,编辑),BlackwellScientificPublications,Oxford,1-36(1984)，在此引入作为参考。优选水可渗透扩散屏障选自乙基纤维素、甲基纤维素和其混合物，最优选，涂料是SURELEASE,由Colorcon制造，其是水基乙基纤维素胶乳，由癸二酸二丁酯或植物油增塑。包括在本发明范围内的其它非限制性涂料是Philadelphia的FMC公司制造的AQUACOAT,它是乙基纤维素假胶乳；溶剂基乙基纤维素；虫胶；玉米醇溶蛋白；甘油松香酯；乙酸纤维素；由Philadelphia的RohmandHaas制造的EUDRAGITS，它是丙烯酸树脂；聚硅氧烷弹性体；聚氯乙烯甲基纤维素和羟丙基甲基纤维素。

可以采用常规的涂料溶剂和涂敷工艺(例如流化床涂敷和喷涂)来涂敷所述颗粒。在例如US3,089,824,US3,117,027和US3,253,944中有流化床涂敷技术的教导。一般对药物活性剂/树脂复合体进行涂敷，但也可以在与药物活性剂复合之前对树脂涂敷。涂敷溶剂的非限制性

实例包括乙醇、二氯甲烷/丙酮混合物、涂敷乳液、甲基丙酮、四氢呋喃、四氯化碳、甲基乙基酮、二氯乙烯、三氯乙烯、己烷、甲基醇、异丙基醇、甲基异丁基酮、甲苯、2-硝基丙烷、二甲苯、异丁基醇、正乙酸丁酯。

优选涂敷的药物活性剂/树脂复合体是药物活性剂/树脂复合体的约40至约70%w/w。更优选，涂敷的药物活性剂/树脂复合体是药物活性剂/树脂复合体的约45至约55%。最优选，涂敷的药物活性剂/树脂复合体是药物活性剂/树脂复合体的约50%。可以采用不同涂敷量和/或使用涂敷的/未涂敷的复合体混合物来选择性地改变所需的溶解模式。

非水合涂敷的和未涂敷的药物活性剂/树脂复合体的平均粒径分别是约60至约200和约60至约250微米。更优选，涂敷的药物活性剂/树脂复合体的平均粒径是约70至约190微米，且最优选约70至约180微米。更优选，未涂敷的药物活性剂/树脂复合体的平均粒径是约55至约160微米，且最优选约60至约150微米。理想有约85%，优选约95%，且最优选约98%的树脂颗粒，在上述粒径范围内的。在这些范围内调节，使其达到最终制剂产品所需的美观品质。更优选，树脂右甲吗南复合体的粒径也在这些范围内。

在实施方案中，可以将成膜成分水合，并在不需要加热的情况下，混合所有的这些成分。该方法包括将水溶成分溶于水中，形成水性混合物；将粉状的成膜成分混合形成粉状混合物；将粉状混合物添加到水性混合物中，以形成水合聚合物凝胶；在室温下将水合聚合物搅拌约30分钟至约48小时；将冷却剂，薄荷醇和任意其它油混合，形成油混合物；将油混合物添加至水合聚合物凝胶，并混合直至均匀；对膜脱气直至消除气泡，将上述均匀的混合物浇注至合适的基底上；并对浇注的混合物干燥形成膜。水合成膜成分的该方法不需要对水加热，这就降低了在制造过程中的能量消耗，并降低了挥发性成分蒸发所导致的令人不快的损失。而且，将油在两个步骤中混合使风味剂的损失量最少。

虽然并不希望被任何理论所束缚，但相信由于公知的唐南平衡离子效应，成膜成分可以被水合，且混合不需要加热。在溶液中有电解质的情况下，水合成膜剂，有效地降低了形成的聚合物凝胶的粘度，从而增加了水合效率。该制剂的水溶成分提供了电解质，在将成膜成分添加之前，电解质溶于水合溶液中。高剪切混合同样加速了水合，并打碎了粉末，提供了与水接触的更多的表面积。另外，在剪切区域中产生的局部热效应，提供了水合的能量，基本上不会升高物质的温度。

实施例

参照下述实施例，对本发明进行更详细的说明，但这并不意味着是对本发明的限制。

实施例 1

以下述步骤，将列于表 1 中成分混合，用以得到镇咳药膜的对比实施例:

A. 将水加热至 50℃。将山梨酸钾和甜味剂溶于水中，并混合。并接着添加二氧化钛，进一步混合形成制剂 A。

B. 将成膜成分(例如，黄原胶、槐树豆胶、角叉菜胶和支链淀粉)在单独的容器中混合形成制剂 B。

C. 将制剂 B 缓慢地添加至制剂 A 并快速混合，接着在降低的速率下过夜混合，用以提供制剂 C。

D. 在单独的容器中将甘油和橄榄油混合，并接着通过加热至 45℃将薄荷醇和甘草酸一铵盐(MAG)溶于其中，形成制剂 D。

E. 将制剂 D 添加至制剂 C，并进行彻底混合，并接着在连续混合的情况下添加风味剂，以形成制剂 E。

F. 接着将用乙基纤维素涂敷的右甲吗南添加进制剂 E 并混合。使用 10%的柠檬酸溶液将 pH 调节至所需的 6.0，得到制剂 F(只在实施例 1 - 3 中)。

将制剂 F 倾斜在模子上，并在室温下浇铸形成所需厚度的膜。对膜进行热风干燥，且为了味道测试，切割成所需的大小(由剂量和口感决定)。该膜被分割成 1″x1.25″(2.54cmx3.18cm)剂量单位，各自的厚

度是0.009±0.002英寸(0.23±0.05mm)和703mg的重量。

同样根据前述制备安慰剂膜，以便于对例如活性膜的味道和外观进行评定。

表1

原料	配料中的%w/w	g/配料	%w/w*	mg/剂量*	%w/w*活性膜	%w/w实际配料
涂敷的右甲吗南(55%DM)		103.6291		27.3000	29.5775	9.3899
黄原胶	0.0600	0.6000	0.2432	0.1581	0.1713	0.0544
槐树豆胶	0.0700	0.7000	0.2837	0.1844	0.1998	0.0634
角叉菜胶	0.3000	3.0000	1.2159	0.7903	0.8563	0.2718
支链淀粉	16.0000	160.0000	64.8466	42.1503	45.6666	14.4976
山梨酸钾	0.0600	0.6000	0.2432	0.1581	0.1713	0.0544
双氧噁噻嗪钾盐	0.5000	5.0000	2.0265	1.3172	1.4271	0.4531
阿斯巴甜NF	1.4000	14.0000	5.6741	3.6882	3.9958	1.2685
纯净水	75.3264	753.2640				68.2534
Physcool	0.1000	1.0000	0.4053	0.2634	0.2854	0.0906
薄荷醇	1.0000	10.0000	4.0529	2.6344	2.8542	0.9061
柠檬酸	0.0710	0.7100	0.2878	0.1870	0.2026	0.0643
樱桃香精(Givudan)	0.1500	1.5000	0.6079	0.3952	0.4281	0.1359
薄荷香精	0.5000	5.0000	2.0265	1.3172	1.4271	0.4531
甘草酸一铵盐(MAG)	0.0100	0.1000	0.0405	0.0263	0.0285	0.0091
聚山梨酸酯80NF	0.3500	3.5000	1.4185	0.9220	0.9990	0.3171
Atmos300	0.3500	3.5000	1.4185	0.9220	0.9990	0.3171
甘油	3.0000	30.0000	12.1587	7.9032	8.5625	2.7183
橄榄油	0.5000	5.0000	2.0265	1.3172	1.4271	0.4531
FD&C 绿#3	0.0026	0.0260	0.0105	0.0068	0.0074	0.0024
二氧化钛	0.2500	2.5000	1.0132	0.6586	0.7135	0.2265
总w/o活性		0.0000	100.0000	65.0000		
总活性	100.0000	1103.6291		92.3000	100.0000	100.0000
*假定所有的水被蒸发						

该活性膜是有砂砾感和苦的。

实施例2

根据实施例1的方法制备的对比膜，其具有的成分列于表2中.

表2

原料	配料中的%w/w	g/配料	%w/w* 安慰剂膜	mg/剂量*	%w/w* 活性膜	%w/w 实际配料
涂敷的右甲吗南(53.5%DM)		106.4239		28.0374	30.1356	9.6187
黄原胶	0.0600	0.6000	0.2432	0.1581	0.1699	0.0542
槐树豆胶	0.0700	0.7000	0.2837	0.1844	0.1982	0.0633
角叉菜胶	0.3000	3.000	1.2159	0.7904	0.8495	0.2711
支链淀粉	16.0000	160.0000	64.8493	42.1520	45.3065	14.4610
山梨酸钾	0.0600	0.6000	0.2432	0.1581	0.1699	0.0542
双氧噁噻嗪钾盐	0.5000	5.0000	2.0265	1.3173	1.4158	0.4519
阿斯巴甜NF	1.4000	14.0000	5.6743	3.6883	3.9643	1.2653
纯净水	75.3274	753.2740				68.0819
Physcool	0.1000	1.0000	0.4053	0.2635	0.2832	0.0904
薄荷醇	1.0000	10.0000	4.0531	2.6345	2.8317	0.9038
柠檬酸(用于调节pH至6.0)	0.0700	0.7000	0.2837	0.1844	0.1982	0.0633
樱桃香精(Givudan)	0.1500	1.5000	0.6080	0.3952	0.4247	0.1356
薄荷香精	0.5000	5.0000	2.0265	1.3173	1.4158	0.4519
甘草酸一铵盐(MAG)	0.0100	0.1000	0.0405	0.0263	0.0283	0.0090
聚山梨酸酯80NF	0.3500	3.5000	1.4186	0.9221	0.9911	0.3163
Atmos300	0.3500	3.5000	1.4186	0.9221	0.9911	0.3163
甘油	3.0000	30.0000	12.1592	7.9035	8.4950	2.7114
橄榄油	0.5000	5.0000	2.0265	1.3173	1.4158	0.4519
FD&C 绿#3	0.0026	0.0260	0.0105	0.0069	0.0074	0.0024
二氧化钛	0.2500	2.5000	1.0133	0.6586	0.7079	0.2260
总w/o活性		0.0000	100.0000	65.0000		
总活性	100.0000	1106.4239		93.0374	100.0000	100.0000
*假定所有的水被蒸发						

该活性膜是有砂砾感和苦的。

实施例3

根据实施例1的方法制备的对比膜，其具有的成分列于表3中。

表 3

原料	配料中的%w/w	g/配料	%w/w* 安慰剂膜	mg/剂量*	%w/w* 活性膜	%w/w 实际配料
涂敷的右甲吗南(60%DM)		94.7292		25.0000	27.7778	8.6532
黄原胶	0.0600	0.6000	0.2436	0.1583	0.1759	0.0548
槐树豆胶	0.0700	0.7000	0.2842	0.1847	0.2053	0.0639
角叉菜胶	0.3000	3.0000	1.2180	0.7917	0.8797	0.2740
支链淀粉	16.0000	160.0000	64.9625	42.2256	46.9174	14.6155
山梨酸钾	0.0600	0.6000	0.2436	0.1583	0.1759	0.0548
双氧噁噻嗪钾盐	0.5000	5.0000	2.0301	1.3196	1.4662	0.4567
阿斯巴甜 NF	1.4000	14.0000	5.6842	3.6947	4.1053	1.2789
纯净水	75.3704	753.7040				68.8484
Physcool	0.1000	1.0000	0.4060	0.2639	0.2932	0.0913
薄荷醇	1.0000	10.0000	4.0602	2.6391	2.9323	0.9135
柠檬酸	0.0270	0.2700	0.1096	0.0713	0.0792	0.0247
樱桃香精(Givudan)	0.1500	1.5000	0.6090	0.3959	0.4399	0.1370
薄荷香精	0.5000	5.0000	2.0301	1.3196	1.4662	0.4567
甘草酸一铵盐(MAG)	0.0100	0.1000	0.0406	0.0264	0.0293	0.0091
聚山梨酸酯 80NF	0.3500	3.5000	1.4211	0.9237	1.0263	0.3197
Atmos300	0.3500	3.5000	1.4211	0.9237	1.0263	0.3197
甘油	3.0000	30.0000	12.1805	7.9173	8.7970	2.7404
橄榄油	0.5000	5.0000	2.0301	1.3196	1.4662	0.4567
FD&C 绿#3	0.0026	0.0260	0.0106	0.0069	0.0076	0.0024
二氧化钛	0.2500	2.5000	1.0150	0.6598	0.7331	0.2284
总 w/o 活性		0.0000	100.0000	65.0000		
总活性	100.0000	1094.7292		90.0000	100.0000	100.0000
*假定所有的水被蒸发						

该活性膜非常薄，呈蓝色并有砂砾感。苦和麻木的感觉极小，但风味还不能被完全接受。

实施例 4

除了步骤 F 包括向作为单独成分的制剂 E 添加未涂敷的氢溴酸右甲吗南和 AMBERLITE 树脂以外，根据实施例 1 的方法制备的本发明膜，其具有的成分列于表 4 中。

表 4

原料	配料中的%w/w	g/配料	%w/w* 安慰剂膜	mg/剂量*	%w/w* 活性膜	%w/w 实际配料
右甲吗南		17.0326		15.0000	15.7563	5.0951
Amberlite IRP69		17.2597		15.2000	15.9664	5.1630
黄原胶	0.0600	0.1800	0.2439	0.1585	0.1665	0.0538
槐树豆胶	0.0700	0.2100	0.2845	0.1849	0.1943	0.0628
角叉菜胶	0.3000	0.9000	1.2194	0.7926	0.8326	0.2692
支链淀粉	16.0000	48.0000	65.0338	42.2720	44.4033	14.3587
山梨酸钾	0.0600	0.1800	0.2439	0.1585	0.1665	0.0538
双氧嗯噻嗪钾盐	0.5000	1.5000	2.0323	1.3210	1.3876	0.4487
阿斯巴甜 NF	1.4000	4.2000	5.6905	3.6988	3.8853	1.2564
纯净水	75.3974	226.1922				67.6630
Physcool	0.1000	0.3000	0.4065	0.2642	0.2775	0.0897
薄荷醇	1.0000	3.0000	4.0646	2.6420	2.7752	0.8974
柠檬酸	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
樱桃香精(Givudan)	0.1500	0.4500	0.6097	0.3963	0.4163	0.1346
薄荷香精	0.5000	1.5000	2.0323	1.3210	1.3876	0.4487
甘草酸一铵盐(MAG)	0.0100	0.0300	0.0406	0.0264	0.0278	0.0090
聚山梨酸酯 80NF	0.3500	1.0500	1.4226	0.9247	0.9713	0.3141
Atmos300	0.3500	1.0500	1.4226	0.9247	0.9713	0.3141
甘油	3.0000	9.0000	12.1938	7.9260	8.3256	2.6923
橄榄油	0.5000	1.5000	2.0323	1.3210	1.3876	0.4487
FD&C 绿#3	0.0026	0.0078	0.0106	0.0069	0.0072	0.0023
二氧化钛	0.2500	0.7500	1.0162	0.6605	0.6938	0.2244
总 w/o 活性		300.0000	100.0000	65.0000		
总活性	100.0000	334.2922		95.2000	100.0000	100.0000
*假定所有的水被蒸发						

该活性膜具有令人满意的外观和口味。

实施例 5

以下述步骤，将列于表 5 中成分混合，用以得到本发明镇咳药膜的实施例：

A. 将水加热至 75℃。将未涂敷的氢溴酸右甲吗南溶于水中，并混合，同时保持 75℃的水温。接着将 AMBERLITE 树脂混合进水中，并在 70－80℃下加热 4－5 小时。停止加热，补充因蒸发而损失的水，且将山梨酸钾和甜味剂添加进该组合物并混合，形成制剂 A。

B. 将成膜成分(例如，黄原胶、槐树豆胶、角叉菜胶和支链淀粉)在单独的容器中混合形成制剂 B。

C. 将制剂 B 缓慢地添加至制剂 A 并快速混合，接着在降低的速率下过夜混合，用以提供制剂 C。

D. 在单独的容器中，将薄荷醇混合溶解进醇中。Physcool 接着被混合溶解于其中。接着将 MAG、聚山梨酸酯 80、Atmos300 和风味剂添加进该混合物中，并混合，以提高其均匀性，来形成制剂 D。

E. 向制剂 C 添加制剂 D、甘油和甘露糖醇进行彻底的混合，得到制剂 E。

将制剂 E 倾斜在模子上，并在室温下浇铸形成所需厚度的膜。对膜进行热风干燥，且为了味道测试，切割成所需的大小(由剂量和口感决定)。该膜被分割成 1.5 英寸 ^{2}(9.7cm^2)剂量单位，各自的厚度是 0.009±0.002 英寸(0.23±0.05mm)和 70±3mg 的重量。

同样根据前述制备安慰剂膜，以便于对例如活性膜的味道和外观进行评定。

表 5

原料	配料中的%w/w	g/配料	mg/剂量*	%w/w*膜	%w/w 实际配料
氢溴酸右甲吗南		11.4615	15.0000	21.4286	9.2666
AmberliteIRP69		12.2256	16.0000	22.8571	9.8843
黄原胶	0.0600	0.0600	0.0944	0.1348	0.0485
槐树豆胶	0.0700	0.0700	0.1101	0.1573	0.0566
角叉莱胶	0.3000	0.3000	0.4718	0.6740	0.2425
支链淀粉	16.0000	16.0000	25.1613	35.9447	12.9359
山梨酸钾	0.0600	0.0600	0.0944	0.1348	0.0485
双氧噁噻嗪钾盐	0.5000	0.5000	0.7863	1.1233	0.4042
阿斯巴甜 NF	1.4000	1.4000	2.2016	3.1452	1.1319
纯净水	70.2000	70.2000			56.7561
醇 USP	5.0000	5.0000			4.0425
Physcool	0.1000	0.1000	0.1573	0.2247	0.0808
薄荷醇	1.5000	1.5000	2.3589	3.3698	1.2127
薄荷香精	0.1000	0.1000	0.1573	0.2247	0.0808
覆盆子香精(Givudan)	0.5000	0.5000	0.7863	1.1233	0.4042
甘草酸一铵盐(MAG)	0.0100	0.0100	0.0157	0.0225	0.0081
聚山梨酸酯 80NF	0.3500	0.3500	0.5504	0.7863	0.2830
Atmos300	0.3500	0.3500	0.5504	0.7863	0.2830
甘油	1.5000	1.5000	2.3589	3.3698	1.2127
甘露糖醇 USP	2.0000	2.0000	3.1452	4.4931	1.6170
总 w/o 活性		100.0000	39.0000		

该活性膜具有令人愉快的外观和口味。

实施例 6

根据实施例 5 的方法制备的本发明膜，其具有的成分列于表 6 中。

表 6

原料	配料中的%w/w	g/配料	mg/剂量*	%w/w*	%w/w
氢溴酸右甲吗南		11.6538	15.0000	21.4286	9.3919
AmberliteIRP69		12.4308	16.0000	22.8571	10.0180
黄原胶	0.0600	0.0600	0.0925	0.1321	0.0484
槐树豆胶	0.0700	0.0700	0.1079	0.1542	0.0564
角叉菜胶	0.3000	0.3000	0.4625	0.6606	0.2418
支链淀粉	16.0000	16.0000	24.6640	35.2343	12.8944
山梨酸钾	0.0600	0.0600	0.0925	0.1321	0.0484
双氧噁噻嗪钾盐	0.5000	0.5000	0.7708	1.1011	0.4030
阿斯巴甜 NF	1.4000	1.4000	2.1581	3.0830	1.1283
纯净水	69.7000	69.7000			56.1713
醇 USP	5.0000	5.0000			4.0295
Physcool	0.1000	0.1000	0.1542	0.2202	0.0806
薄荷醇	2.0000	2.0000	3.0830	4.4043	1.6118
薄荷香精	0.1000	0.1000	0.1542	0.2202	0.0806
覆盆子香精(Givudan)	0.5000	0.5000	0.7708	1.1011	0.4030
甘草酸一铵盐(MAG)	0.0100	0.0100	0.0154	0.0220	0.0081
聚山梨酸酯 80NF	0.3500	0.3500	0.5395	0.7708	0.2821
Atmos300	0.3500	0.3500	0.5395	0.7708	0.2821
甘油	1.5000	1.5000	2.3123	3.3032	1.2089
甘露糖醇 USP	2.0000	2.0000	3.0830	4.4043	1.6118
总 w/o 活性		0.0000	39.0000		
总活性	100.0000	124.0846	70.0000	100.0000	100.0000
*假定所有的水和醇被蒸发					

该活性膜具有令人愉快的外观和口味。

实施例 7

根据实施例 5 的方法制备的本发明的膜，其具有的成分列于表 7 中。该膜被分割成 1″x1.25″(2.54cmx3.18cm)剂量单位，各自的厚度是 0.009±0.002 英寸(0.23±0.05mm)和 63.6±3mg 的重量。

表 7

原料	配料中的%w/w	kg/配料	mg/剂量*	%w/w*	%w/w
氢溴酸右甲吗南		1.3567	15.0000	23.5981	9.3918
AmberliteIRP69		1.4472	16.0000	25.1713	10.0180
黄原胶	0.600	0.0070	0.0772	0.1215	0.0484
槐树豆胶	0.0700	0.0081	0.0901	0.1417	0.0564
角叉菜胶	0.3000	0.0349	0.3661	0.6075	0.2418
支链淀粉	16.0000	1.8627	20.5941	32.3988	12.8944
山梨酸钾	0.0600	0.0070	0.0772	0.1215	0.0484
双氧噁噻嗪钾盐	0.5000	0.0582	0.6436	1.0125	0.4030
阿斯巴甜 NF	1.4000	0.1630	1.8020	2.8349	1.1283
纯净水	69.7000	8.1145			56.1714
醇 USP	5.000	0.5821			4.0295
Physcool	0.1000	0.0116	0.1287	0.2025	0.0806
薄荷醇	2.0000	0.2328	2.5743	4.0498	1.6118
薄荷香精	0.1000	0.0116	0.1287	0.2025	0.0806
覆盆子香精(Givudan)	0.5000	0.0582	0.6436	1.0125	0.4030
甘草酸一铵盐(MAG)	0.0100	0.0012	0.0129	0.0202	0.0081
聚山梨酸酯 80NF	0.3500	0.0407	0.4505	0.7087	0.2821
Atmos300	0.3500	0.0407	0.4505	0.7087	0.2821
甘油	1.5000	0.1746	1.9307	3.0374	1.2089
甘露糖醇 USP	2.0000	0.2328	2.5743	4.0498	1.6118
总 w/o 活性+树脂		11.6420	32.5644		
总活性 + 树脂	100.0000	14.4459	63.5644	100.0000	100.0000
*假定所有的水和醇被蒸发					

该活性膜具有令人愉快的外观和口味。

参照其具体的实施例本发明已经得到了详细的说明，可以进行对本领域普通技术人员而言是显而易见的各种改变和修正，而这并不脱离本发明的实质和范围。