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A B O G A D O S

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SUPERINDUSTRIA Y COMERCIO
Radicacion : 00001050 00000002 Folios: 84
Fecha (AMD): 2000-04-10 16:09:50
Tramite : 002 PATENTES D 1 REGISTRO/ 329 COMPLEME
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

2292/P

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES
E. S. D.

Re: Expediente No. 00001050
Solicitud de Patente en nombre de
THE PROCTER & GAMBLE COMPANY.

Yo, JIMENA ESCOBAR URIBE, identificada como aparece al pie de mi firma, domiciliada en Santafé de Bogotá, en la Carrera 11 A No. 94-76 Of. 305, obrando como apoderada de la sociedad THE PROCTER & GAMBLE COMPANY., solicitante de la patente de la referencia, anexo al presente memorial los siguientes documentos:

Copias certificadas de las solicitudes de Patente Números 60/115,378 y 60/156,539 presentadas en Estados Unidos de América los días 11 de Enero de 1999 y 29 de septiembre de 1999, respectivamente, con la debida traducción de lo pertinente, incluyendo los capítulos reivindicatorios.

Señor Superintendente,

JIMENA ESCOBAR URIBE
C.C.39.779.452 de usaquén
T.P. 68228
Cód. 5376

ESTADOS UNIDOS DE AMERICA
A TODOS AQUELLOS A QUIENES EL PRESENTE LLEGUE:

DEPARTAMENTO DE COMERCIO DE LOS ESTADOS UNIDOS
Oficina de Patentes y Marcas de los Estados Unidos

Enero 12, 2000

La presente es para certificar que el anexo es una copia fiel de los registros de la Oficina de Patentes y Marcas de los Estados Unidos, de los documentos de la solicitud de patente identificada más adelante, que cumplieron con los requerimientos para concederse una fecha de presentación de acuerdo con el titulo 35 del Código de los Estados Unidos, sección 111.

Número de Solicitud: 60/115,378

Fecha de Presentación: Enero 11, 1999

Por la autoridad del
Comisionado de Patentes y Marcas

(fdo) T. LAWRENCE
Oficial Certificador
Sello oficial de la Oficina de Patentes y Marcas de los Estados Unidos de América.

REIVINDICACIONES

1. Una composición que comprende un activo farmacéutico en un disolvente anhídrido, hidrófilo, miscible en agua en donde el activo farmacéutico en su forma no ionizado tiene un porcentaje de valor de solubilidad en el disolvente a temperatura ambiente que es igual o superior a 0,075% y el activo farmacéutico está en su forma libre, no ionizada como una dispersión monomolecular en el disolvente.

2. La composición según la Reivindicación 1 en donde los activos farmacéuticos tienen un peso molecular inferior a 500 gramos por mol, es capaz de ser ionizada cuando está en un disolvente acuoso y tiene un coeficiente de partición octanol-agua cuando está en la forma no ionizada de por lo menos 100.

3. La composición según la Reivindicación 2 en donde los activos farmacéuticos se seleccionan del grupo que consiste de agentes antitusivos, antihistaminas, antihistaminas no sedantes, descongestionantes, expectorantes, analgésicos mucolíticos, agentes antiinflamatorios antipiréticos, anestésicos locales y mezclas de estos.

4. La composición según la Reivindicación 3 en donde la concentración de activos farmacéuticos en el disolvente es inferior o igual a 125% del porcentaje del valor de solubilidad del activo antes mencionado.

5. La composición según la Reivindicación 4 en donde el activo farmacéutico está presente en el disolvente a un nivel de 0,075% a 25,0% en peso de la composición.

6. La composición según la Reivindicación 5 en donde el activo farmacéutico está presente en el disolvente a un nivel de 0,28% a 10.0% en peso de la composición

7. La composición según la Reivindicación 1 en donde un disolvente anhídrido, hidrófilo, miscible en agua comprende de 60% a 99,975% en peso de la composición.

8. La composición según la Reivindicación 7 en donde el disolvente anhídrido, hidrófilo, miscible en agua comprende de 70% a 99% en peso de la composición.

9. La composición según la Reivindicación 8 que en donde el disolvente anhídrido, hidrófilo, miscible en agua comprende de 85% a 98% en peso de la composición.

10. La composición según las Reivindicación 7 en donde el disolvente anhídrido, hidrófilo, miscible en agua es seleccionado del grupo que consiste en propilenglicol, etanol, poli(etilenglicol) o PEG, carbonato de propileno, monoetiléter del dietilenglicol, poloxamer, glicofurol, glicerol y mezclas de estos.

11. Un método para el tratamiento de las enfermedades respiratorias utilizando la composición liquida de la Reivindicación 1 en donde el método comprende la administración oral de dicha composición en un volumen de dosificación total no mayor a 3.0 mls.

12. El método según la Reivindicación 11 en donde la composición está ubicada contra cualquiera de las membranas mucosas de la boca.

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PA 195100

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

January 12, 2000

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: ***60/115,378***
FILING DATE: ***January 11, 1999***

By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

T. Lawrence

T. LAWRENCE
Certifying Officer

"Express Mail" mailing label number EJ302200277US

Date of Deposit January 11, 1999

I hereby certify that this paper/fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231

John M. Howell 33,713
Attorney mailing application Reg. No.

Signature of Attorney mailing application

A/PROV 54

PTO/SB/16 (6-95)
Approved for use through 04/11/98. OMB 0651-0037
Patent and Trademark Office, U.S. DEPARTMENT OF COMMERCE

PROVISIONAL PATENT APPLICATION COVER SHEET

This is a request for filing a PROVISIONAL PATENT APPLICATION under 37 CFR §1.53(b)(2).

Docket Number	7387P	Type a plus sign (+) inside this box ⇒	+

INVENTOR(s) / APPLICANT(s)

LAST NAME	FIRST NAME	MIDDLE INITIAL	RESIDENCE (CITY AND EITHER STATE OR FOREIGN COUNTRY)
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TITLE OF THE INVENTION (280 characters max)

COMPOSITIONS HAVING IMPROVED DELIVERY OF ACTIVES

CORRESPONDENCE ADDRESS

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STATE	OH	ZIP CODE	45040	COUNTRY	USA

ENCLOSED APPLICATION PARTS *(check all that apply)*

X Specification Number of Pages: 17 + Abstract _ Small Entity Statement

_ Drawing(s) Number of Sheets: _ _ Other (specify) _

METHOD OF PAYMENT *(check one)*

_	A check or money order is enclosed to cover the Provisional filing fees	PROVISIONAL FILING FEE AMOUNT(S)	$150.00
X	The Commissioner is hereby authorized to charge filing fees specified under 37 CFR §1.19(f) and credit Deposit Account Number: 16-2480		

The invention was made by an agency of the United States Government or under a contract with an agency of United States Government.

X No

_ Yes, the name of the U. S. Government agency and the Government contract number are: _____

Respectfully submitted,

SIGNATURE John M Howell Date Jan 11, 1999

TYPED or PRINTED NAME John M. Howell REGISTRATION NO. 33,713 (*if appropriate*)

_ Additional inventors are being named on separately numbered sheets attached hereto

PROVISIONAL PATENT APPLICATION FILING ONLY

Burden Hour Statement: This form is estimated to take .2 hours to complete. Time will vary depending upon the needs of the individual cases. Any comments on the amount of time you are required to complete this form should be sent to the Office of Assistance Quality and Enhancement Division, Patent and Trademark Office, Washington, DC 20231, and to the Office of Information and Regulatory Affairs, Office of Management and Budget (Project 0651-0037), Washington, DC 20503. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Box Provisional Patent Application; Assistant Commissioner for Patents, Washington, D.C. 20231.

P&G Case 7387P

COMPOSITIONS HAVING IMPROVED DELIVERY OF ACTIVES

Douglas J. Dobrozsi
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TECHNICAL FIELD

The present invention pertains to compositions having improved delivery of pharmaceutical active ingredients. These compositions comprise pharmaceutical actives in an anhydrous, hydrophilic solvent. These compositions may take the form of liquid elixirs placed into the mouth and eventually swallowed, or can be delivered via liquid-filled lozenges, metered liquid dosing devices, atomizers and liquid-releasing, edible capsules. Such compositions are particularly useful for treating symptoms associated with respiratory illnesses.

BACKGROUND OF THE INVENTION

Routes for delivering pharmaceutical actives include delivering actives by intranasal, pulmonary, buccal, sublingual, transdermal, and rectal administration. These routes tend to be used for avoiding first-pass metabolism of drugs that are swallowed. "First past metabolism" refers to the arrangement and order of placement of the metabolizing enzymes within the body of a human, with respect to the path followed by substances that enter the gastrointestinal tract by swallowing, and are absorbed into the general blood circulation. Items swallowed by humans, including food, drink, and medicines, enter the stomach and from there flow into the intestine. Many of the chemicals associated with the food, drink, or medicine pass through the mucosal membranes in the gastrointestinal tract and into the blood in the mesenteric veins draining from the intestine. The blood flow from the mesenteric veins passes into the liver. Metabolizing enzymes in the mucosal membranes of the intestine and in the liver can chemically alter the nature of substances passing from the intestine, through the liver, and into the common blood circulation of the body. Since all swallowed medicines are subject to the metabolizing capacity of the intestinal mucosal membranes and the liver before entering the general blood circulation of the body, frequently only a small fraction of those substances go unmetabolized, and reach the general blood circulation

Avoiding first pass metabolism can increase the bioavailability, or blood concentrations of the administered compound. Metabolic formation of metabolites of the administered compound, however, can at the same time decrease. Where formation of metabolites from the first pass metabolism is desirable, avoiding the first pass metabolism is not preferred since it logically leads to lower amounts of the metabolite in the blood. Furthermore, the blood concentrations of the active substance can increase, leading to potential toxicity or side effects attributable to the active per se. Reducing the amount of active in the dose for avoiding toxicity, concomitantly decreases the circulating blood levels of the active metabolite. This results in loss of therapeutic affect and ultimately, benefit to the patient. In order to provide a medication that is effective and avoids unwanted side effects, the composition and its means of delivery must be modified.

Respiratory illnesses covers a broad range of ailments, including viral infections and allergic reaction to inhaled allergens. Viral infections in the upper respiratory tract of humans leads to illness usually referred to as colds, or influenza. Such an illness is quite common in the general population and can be the cause of significant discomfort and suffering. Allergen inhalation also negatively impacts a fair number in the population at the same or even at a greater degree than those having a viral infection.

There are no generally regarded effective and convenient methods for preventing viral infections or allergies. In the case of viral infections, the body's natural defense mechanisms fight the infection for a period of time normally ranging from 3 days to 2 weeks. This being the case, the most commonly employed medicines treat the uncomfortable, problematic symptoms of these respiratory ailments. These symptoms include stuffy and runny noses, soreness and inflammation in the nose and throat, fits of coughing, general aches in the body, fever, and headache. Of these symptoms, coughing in uncontrollable fits is considered by many to be the most problematic and uncomfortable. Coughing disrupts normal respiration, leading to increased headache and sore throat as well as loss of sleep to the sufferer and others living with the sufferer

The compositions used to treat the above mentioned symptoms generally fall into one of the following pharmacological classifications: antihistamines; decongestants; antitussives; expectorants; mucolytics; analgesics, antipyretic and anti-inflammatory agents. The compositions are manufactured in a number of product forms, the most common being liquid syrups and elixirs for swallowing, mouth drops and lozenges as well as inhalants and topical creams or lotions that release volatile agents that are inhaled through the nose into respiratory tract. The compositions are typically swallowed immediately, or slowly dissolved in the mouth. They typically contain actives such as

guafenesin, that aids the body in the removal of excess respiratory mucus or phlegm, diphenhydramine, that lessens the negative effects including coughing and other symptoms due to histamine produced in the body in response to the viral infection, and dextromethorphan, that acts within the part of the human brain controlling the coughing reflex. Among these actives, dextromethorphan is the most commonly used active in the world for relief of cough.

Dextromethorphan, by virtue of it's physicochemical, absorption, and bioavailability properties, is a very good candidate for increasing bioavailability via methods of administration other than swallowing. For example it has been reported in patents and pharmaceutical literature that substantial increases in bioavailability can be achieved using intranasal formulations; see H. Char *et al*, Nasal Delivery of 14-C Dextromethorphan in Rats, Journal of Pharmaceutical Sciences 81:750, 1992.

What has not been realized until now is that after careful and diligent research into pharmaceutic, therapeutic, and side effect properties of active compounds, compositions can be made to positively improve the therapeutic effect without increased side effects or toxicity.

SUMMARY OF THE INVENTION

An object, therefore, of the present invention is to provide improved compositions for treating the symptoms associated with respiratory ailments, particularly minimizing fits of coughing. The compositions are in the form of an anhydrous, hydrophilic liquids providing rapid delivery of actives including antitussives; antihistamines (including non-sedating antihistamines); decongestants; expectorants; mucolytics; analgesic, antipyretic and anti-inflammatory agents and local anesthetics for treating the symptoms of respiratory illnesses. The compositions can be dosed using a variety of product forms and, or package delivery options. The compositions of the present invention provide desired activity while minimizing potential side effects of the active compounds. It is also an objective of the subject invention to provide methods for achieving rapid transmucosal delivery of the aforementioned compositions.

Definitions and Terms

The following are definitions of terms found in the present specification:

1. transmucosal delivery:

Refers to application of drugs to the mucosal membranes of the oral cavity, including buccal (cheek), lips, gums, palates, and tongue, with the goal of the drug passing through the skin covering these places and entering the bloodstream.

2. therapeutic dose

Refers to the amount of the substance that when administered to a person in the proper form, will produce the desired effect within the body with minimal undesired side.

3. pharmaceutical active/active:

Refers to the chemical molecule which exerts the desired effect on the body, when administered in the proper amount and form

4. active metabolites

Refers to the chemical species of the pharmaceutical active upon the active undergoing metabolism.

5. monomolecular dispersion

Refers to the fact that molecules of the active are free and unencumbered from diffusion by association in crystalline or amorphous solid forms, or poly molecular association.

6. percent solubility value

Refers to the equilibrium solubility limit or maximum solubility of a molecule in a solvent at usual room temperature, expressed as the weight percent of the molecule in the composition.

DETAILED DESCRIPTION OF THE INVENTION

The compositions of the present invention comprise pharmaceutical actives referred to herein as "actives" for treating illnesses, particularly symptoms associated with respiratory ailments such as colds, influenza as well as allergy. These actives are most frequently used for treating the most problematic symptoms including a stuffy and runny nose, soreness and inflammation in the nose and throat, fits of coughing, general aches in the body, fever, and headache. In the present invention, when actives are combined with anhydrous solvents, the actives obtain enhanced transmucosal delivery into the blood In the case that active metabolites contribute to the desired therapeutic effect, this enhanced delivery is achieved without appreciably lowering the level of the corresponding active metabolites. Furthermore, the level of active in the blood is maintained at a level that avoids unwanted side effects brought on by too high of levels of active in the blood.

The composition comprises a pharmaceutical active in an hydrophilic, water-miscible, anhydrous solvent wherein the pharmaceutical active in its unionized form has a percent solubility value in the solvent at ambient temperature that is equal to or greater than 0.075% and the pharmaceutical active is in its free, unionized form as a monomolecular dispersion in the solvent.

The pharmaceutical active of the present invention has a molecular weight of less than 500 grams per mole, is capable of being ionized when in an aqueous solvent and has

an octanol-water partition coefficient when in the unionized form of at least 100. The octanol-water partition coefficient is disclosed in A. Martin, P. Bustamante, and A.H.C. Chun, Physical Pharmacy, Fourth Edition, Lea and Febiger publishers, Philadelphia, 1993, page 237; herein incorporated by reference.

The actives that comprise compositions of the present invention fall into at least one of the following pharmacological classifications: antitussives; antihistamines; non-sedating antihistamines; decongestants; expectorants; mucolytics, analgesic, antipyretic anti-inflammatory agents, local anesthetics and mixtures thereof. References that describe the use of such actives include J. G. Hardman, The Pharmacologic Basis of Therapeutics, Ninth Edition, McGraw-Hill, New York, 1995. Antitussives useful in the present invention include, but, are not restricted to the group consisting of codeine, dextromethorphan, dextrorphan, diphenhydramine, hydrocodone, noscapine, oxycodone, pentoxyverine and mixtures thereof. Antihistamines useful in the present invention include, but, are not restricted to the group consisting of acrivastine, azatadine, brompheniramine, chlorpheniramine, clemastine, cyproheptadine, dexbrompheniramine, dimenhydrinate, diphenhydramine, doxylamine, hydroxyzine, meclizine, pheninamine, phenyltoloxamine, promethazine, pyrilamine, tripelennamine, triprolidine and mixtures thereof. Non-sedating antihistamines useful in the present invention include, but, are not restricted to the group consisting of astemizole, cetirizine, ebastine, fexofenadine, loratidine, terfenadine, and mixtures thereof. Decongestants useful in the present invention include, but, are not restricted to the group consisting of phenylpropanolamine, pseudoephedrine, ephedrine, phenylephrine, oxymetazoline, and mixtures thereof Expectorants useful in the present invention include, but, are not restricted to the group consisting of ammonium chloride, guafenesin, ipecac fluid extract, potassium iodide and mixtures thereof. Mucolytics useful in the present invention include, but, are not restricted to the group consisting of acetylcycsteine, ambroxol, bromhexine and mixtures thereof. Analgesic, antipyretic and anti-inflammatory agents useful in the present invention include, but, are not restricted to the group consisting of acetaminophen, aspirin, diclofenac, diflunisal, etodolac, fenoprofen, flurbiprofen, ibuprofen, ketoprofen, ketorolac, nabumetone, naproxen, piroxicam, caffeine and mixtures thereof. Local anesthetics useful in the present invention include, but, are not restricted to the group consisting of lidocaine, benzocaine, phenol, dyclonine, benzonotate and mixtures thereof.

Actives in compositions of the present invention are soluble in the anhydrous solvent. The concentration of actives in the solvent is preferably less than or equal to 125% of the percent solubility value, more preferably less than or equal to the percent solubility

value of the pharmaceutical active. To maximize the benefits of the compositions of the present invention, the active is preferably in solution as monomolecular dispersion. The actives useful in the present invention are present in the solvent system at a level from about 0.075% to about 25.0%, preferably from about 0.28% to 10.0% by weight of the composition.

It is preferred that the active is in it free, unionized form as a monomolecular dispersion in said solvent system. In the cases where either the salt forms or ionized forms of the drug active exist, it is preferred to use the uncharged free (non salt) form of the drug in the present invention.

Actives of particularly use are those that arrest uncontrollable fits coughing. Of the antitussives available, dextromethorphan is preferred. Dextromethorphan is known to have pharmacological activity as an antitussive agent and is described in US Patent 5,196,436, Smith; incorporated herein by reference. As used herein, "dextromethorphan" means racemethorphan, 3-methoxy-17-methylmorphinan (dl-cis-1,3,4,9,10,10a-hexahydro-6-methoxy-11-methyl-2H-10,4a-iminoethanophenanthrene and pharmaceutically-acceptable salts thereof. Compositions of the present comprising dextromethorphan preferably comprise from about 0.1% to about 9.3%, more preferably from about 0.26% to about 6.2% and most preferably from about 1.16% to about 4.6% dextromethorphan. Other safe and effective amounts of other cough/cold drug actives may be included in such dextromethorphan-containing compositions.

The unionized form of the pharmaceutical active is maintained using an anhydrous solvent. By anhydrous it is meant that the solvent contains less than about 5 % water. The anhydrous solvent of the present invention comprises from about 60% to about 99.975%, preferably from 70% to about 99% and most preferably from about 85% to about 98% by weight of the composition.

The anhydrous solvent of the present invention is normally liquid at ambient or room temperatures. It is water-soluble or water-miscible. The solvents are selected from the group consisting propylene glycol, ethanol, poly(ethylene glycol) or PEG, propylene carbonate, diethylene glycol monoethyl ether, poloxamer, glycofurol, glycerol, and mixtures thereof. There are mixtures of these solvents that are particularly preferred for certain product forms of the present invention. For example, if the product form is an elixir, liquid capsule or liquid containing lozenge, the solvent is a combination of propylene glycol, ethanol, and PEG. If the product form is a spray, the solvents is a combination of propylene glycol, ethanol, PEG and usually propylene carbonate. The level of each solvent

that makes up these mixtures is partially dependent on aesthetic benefits sought by the formulator.

Optional Ingredients

Ingredients normally associated with cold and influenza treatment medicines can be used with the pharmaceutical actives disclosed herein. Such ingredients are disclosed in US Patent 5,196,436, incorporated herein by reference. Additionally, the following ingredients may be used in the present invention:

Buffers and mixtures of buffering agents, including basic buffers as single components with pKa of from 8 to 11, include triethanolamine, salts of amino acids, including alkaline salts of glycine, glycylglycine, glutamine or other amino acids, alkaline salts of phosphate, carbonate and mixtures thereof. The buffers provide compositional resistance to pH changes upon dilution of the composition with saliva within the range of 8 to10.

Sweeteners, including aspartame, saccharin and its salts, Sucralose™ (sold by the McNeil Specialty Products Co., New Brunswick, NJ); Prosweet™ (sold by the Virginia Dare Extract Co., New York, NY); Magnasweet™ (sold by MAFCO Worldwide Corp., Licorice Division, Camden, NJ); ammonium glycyrrhizinate, its salts, Talin™ (Thaumatin) and its diluted products, such as Talin GA90, (sold by the Talin Food Company, Birkenhead, England); and Acesulfame K, and mixtures thereof.

Flavorants, include anise, oil of peppermint, oil of clove, eucalyptus, lemon, lime, honey lemon, red fruit, mint, grapefruit, orange, cherry cola and mixtures thereof.

Sensory agents. Also useful herein are sensory agents selected from the group consisting of coolants, salivating agents, warming agents. Preferably these agents are present in the compositions at a level of from about 0.001% to about 10 %, preferably from about 0.1% to about 1%, by weight of the composition.

Suitable cooling agents include carboxamides, menthols, thymol, camphor, capsicum, phenol, eucalyptus oil, benzyl alcohol, salicyl alcohol, ethanol, clove bud oil, and hexylresorcinol, ketals, diols, and mixtures thereof. Preferred coolants are the paramenthan carboxyamide agents such as N-ethyl-p-menthan-3-carboxamide (WS-3 supplied by Sterling Organics), taught by U.S. Patent 4,136,163, issued January 23, 1979, to Watson et al., which is incorporated herein by reference in its entirety. Another preferred paramenthan carboxyamide agent is N,2,3-trimethyl-2-isopropylbutanamide, known as "WS-23", and mixtures of WS-3 and WS-23.

Additional preferred coolants are selected from the group consisting of menthol, 3-1-menthoxypropane-1,2-diol, known as TK-10 supplied by Takasago Perfumery Co., Ltd.,

Tokyo, Japan, menthone glycerol acetal known as MGA, manufactured by Haarmann and Reimer, menthyl lactate known as Frescolat® manufactured by Haarmann and Reimer, and mixtures thereof.

Additonal cooling agents include cyclic sulphones and sulphoxides and others, all of which are described in U.S. Patent 4,032,661, issued June 28, 1977, to Rowsell et al., which is herein incorporated by reference.

The terms "menthol" and "menthyl" as used herein include dextro- and levoratotory isomers of these compounds and racemic mixtures thereof.

TK-10 is described in detail in U.S. Patent 4,459,425, issued July 10, 1984 to Amano et al. and incorporated herein by reference.

Salivating agents of the present invention include Jambu® manufactured by Takasago Perfumery Co., Ltd., Tokyo, Japan.

Warming agents include capsicum and nicotinate esters, such as benzyl nicotinate.

METHOD OF USE

In terms of the methods of delivery of the active, it is generally accepted that oral mucosal delivery inside the mouth must be targeted to the sub-lingual region in order to achieve a very rapid therapeutic effect; see D. Harris and J.R. Robinson, Drug Delivery via the Mucus Membranes of the Oral Cavity, Journal of Pharmaceutical Sciences 81: 1, 1992. Such dosage forms are designed to be placed under the tongue, on the floor of the mouth, and held there for some extended time. The inventors have found, however, that a large increase in bioavailability with very rapid absorption can be achieved when the subject compositions are placed against any of the mucosal membranes of the mouth, even onto the tongue and swallowed. The form of the invention is a liquid elixir solution. It is intended to be applied to any of the mucosal membranes within the mouth. This can be achieved using a medicine dropper that is calibrated to indicate the proper amount to be administered, and squirting the elixir onto the tongue prior to swallowing. The elixir can be atomized into mouth and throat and then swallowed. It can be encapsulated into some sort of shell which makes it portable and convenient to transport and administer without having to measure the quantity of liquid elixir. Examples of encapsulation shell includes hard candies as are used for lozenges, gelatin, or starch-based shells. The elixir may be packaged into a small, disposable vial which can readily be opened and squirted into the mouth, the entire vial containing exactly one therapeutic dose. Typical dosage forms of the composition of the present invention contain no more than about 3 ml., preferable from about 0.2 ml. to about 3ml..

One preferred form is to encapsulate the liquid into a shell of hard candy or gelatin. The shell containing substances to pretreat the mucosa and thereby enhance the absorption of the active from the liquid center. The pretreatment occurs by sucking or chewing the shell material, and the advantage is gained by separating in time the treatment of the mucosa, which occurs first, followed by the presentation of the active to be absorbed. Examples of substances for pretreatment of the mucosal membranes are membrane penetration enhancers that are commonly known in the art, examples including menthol, peppermint oil, surfactants such as polysorbate 80 or poloxamer. Another example of a mucosal membrane pretreatment are buffers as listed above, which would precondition salivary micro environment pH in the range of 8 to 11.

EXAMPLES

Example I

Liquid Elixir

Item #	Material	% Comp. (w/w)
1	Dextromethorphan Base	2.055
2	Ethanol (100 %)	10.000
3	Polyethylene Glycol 600	81.88
4	Propylene Glycol	5.000
5	Sodium Saccharin	0.300
6	Pro-Sweet Liquid K	0.700
7	Monoammonium Glycyrrhizinate	0.050
8	Anethole	0.0075
9	Green Shade	0.003
	Total	100.000

Add a portion of Ethanol to the active (Dextromethorphan Base) and solid sweetening agents (Sucralose, Monoammonium Glycyrrizinate) and continuously mix at low heat (30°C). To this vessel add the additional solvents (Propylene Glycol, Polyethylene Glycol 600) and liquid sweeteners (Pro-sweet Liquid K). Mix until all materials are in solution, about 2 hours time. Prepare a premix of flavorants and colorants in the remaining portion of ethanol, and add to the vessel containing the nearly completed solution. Mix until a homogenous solution is obtained, and filter through a US # 100 mesh sieve (product density = 1.07 g/ml.). Fill into amber glass bottles, and cap with an integrated cap / calibrated medicine dropper assembly.

About 1.0 ml. of the elixir dropped onto the tongue and then swallowed. Dextromethorphan is rapidly absorbed into the blood.

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Example II

Liquid Elixir

Item #	Material	% Comp. (w/w)
1	Dextromethorphan Base	2.055
2	Ethanol (100 %)	10.000
3	Polyethylene Glycol 600	78.285
4	Propylene Glycol	5.000
5	Triethanolamine	3.740
6	Sucralose	0.150
7	Pro-Sweet Liquid K	0.700
8	Monoammonium Glycyrrhizinate	0.050
9	Flavorant	0.015
10	Colorant	0.005
	Total	100.000

Add a portion of Ethanol to the active (Dextromethorphan Base) and solid sweetening agents (Sucralose, Monoammonium Glycyrrizinate) and continuously mixed at low heat (30°C). To this vessel add the additional solvents (Propylene Glycol, Polyethylene Glycol 600), liquid sweeteners (Pro-sweet Liquid K), and buffer (Triethanolamine, a liquid). Mix until all materials are in solution, about 2 hours time. Prepare a premix of flavorants and colorants in the remaining portion of ethanol, and add to the vessel containing the nearly completed solution. Mix until a homogenous solution is obtained, and filter through a US # 100 mesh sieve (product density = 1.07 g/ml.). Fill into amber glass bottles, and cap with an integrated cap / calibrated medicine dropper assembly.

About 1.0 ml. of the elixir dropped onto the tongue and then swallowed. Dextromethorphan is rapidly absorbed into the blood.

Example III

Liquid Spray

Item #	Material	% Comp. (w/w)
1	Dextromethorphan Base	3.425
2	Ethanol (100 %)	5.350
3	Polyethylene Glycol 400	50.155
4	Propylene Carbonate	40.000
5	Sucralose	0.300
6	Pro-Sweet Liquid K	0.700
7	Monoammonium Glycyrrhizinate	0.050
8	Flavorant	0.015
9	Green Shade CSL-15689*	0.005
	Total	100.000

* - obtained from the Warner Jenkins Co., St. Louis, MO, USA.

Add a portion of Ethanol to the active (Dextromethorphan Base) and solid sweetening agents (Sucralose, Monoammonium Glycyrrizinate) and continuously mixed at low heat (30°C). To this vessel add the additional solvents (Propylene Carbonate, Polyethylene Glycol 400) and liquid sweeteners (Pro-sweet Liquid K). Mix until all materials are in solution, about 2 hours time. Prepare a premix of flavorants and colorants in the remaining portion of ethanol, and add to the vessel containing the nearly completed solution. Mix until a homogenous solution is obtained, and filter through a US # 100 mesh sieve (product density = 1.075 g/ml.). Fill into manually operated atomization pump and bottle. An example is manufactured by Calmar-Albert GmbH, the Mistette Mark II fitted with a 16 mm high viscosity head assembly which delivers 0.2 ml./actuation.

Three individual actuations are sprayed into the mouth. Dextromethorphan is rapidly absorbed into the blood, and during spraying some portion of the sprayed liquid contacts the throat area, providing the additional benefit such as numbing of the irritated cough receptors there.

Example IV

Liquid Spray

Item #	Material	% Comp. (w/w)
1	Dextromethorphan Base	3.425
2	Ethanol (100 %)	5.350
3	Polyethylene Glycol 400	46.415
4	Propylene Carbonate	40.000
5	Triethanolamine	3.740
6	Sucralose	0.300
7	Pro-Sweet Liquid K	0.700
8	Monoammonium Glycyrrhizinate	0.050
9	Flavorant	0.015
10	Colorant	0.005
	Total	100.000

Add a portion of Ethanol to the active (Dextromethorphan Base) and solid sweetening agents (Sucralose, Monoammonium Glycyrrizinate) and continuously mixed at low heat (30°C). To this vessel add the additional solvents (Propylene Carbonate, Polyethylene Glycol 400), liquid sweeteners (Pro-sweet Liquid K) and buffer (Triethanolamine, a liquid). Mix until all materials are in solution, about 2 hours time. Prepare a premix of flavorants and colorants in the remaining portion of ethanol, and add to the vessel containing the nearly completed solution. Mix until a homogenous solution is obtained, and filter through a US # 100 mesh sieve (product density = 1.075 g/ml.). Fill into manually operated atomization pump and bottle. An example is manufactured by

Calmar-Albert GmbH, the Mistette Mark II fitted with a 16 mm high viscosity head assembly.

Three individual actuations are sprayed into the mouth. Dextromethorphan is rapidly absorbed into the blood, and during spraying some portion of the sprayed liquid contacts the throat area, providing the additional benefit such as numbing of the irritated cough receptors there.

Example V

Liquid Centered Lozenge

Item #	Material	% Comp. (w/w)
1	Dextromethorphan Base	2.055
2	Ethanol (100 %)	2.000
3	Purified Water	5.000
4	Polyethylene Glycol 600	84.875
5	Propylene Glycol	5.000
6	Sucralose	0.300
7	Pro-Sweet Liquid K	0.700
8	Monoammonium Glycyrrhizinate	0.050
9	Flavorant	0.015
10	Colorant	0.005
	Total	100.000

Add a portion of Ethanol to the active (Dextromethorphan Base) and solid sweetening agents (Sucralose, Monoammonium Glycyrrizinate) and continuously mixed at low heat (30°C). To this vessel add the additional solvents (Propylene Glycol, Polyethylene Glycol 600) and liquid sweeteners (Pro-sweet Liquid K). Mix until all materials are in solution, about 2 hours time. Prepare a premix of flavorants and colorants in the remaining portion of ethanol and water, and add to the vessel containing the nearly completed solution. Mix until a homogenous solution is obtained, and filter through a US # 100 mesh sieve (product density = 1.07 g/ml.). Make individual filled lozenges containing about 1.0 ml. of liquid per lozenge by a commonly used method such as extrusion

A person places a liquid filled lozenge into the mouth and sucks on the lozenge until the liquid fill is released. Some cough relief is obtained through the action of sucking on the shell of the lozenge. When the liquid center is released, dextromethorphan is rapidly absorbed into the blood.

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Example VI

Liquid Centered Lozenge

Item #	Material	% Comp. (w/w)
1	Dextromethorphan Base	2.055
2	Ethanol (100 %)	2.000
3	Purified Water	5.000
4	Polyethylene Glycol 600	79.875
5	Propylene Glycol	5.000
6	Sodium Glycinate	5.000
7	Sucralose	0.300
8	Pro-Sweet Liquid K	0.700
9	Monoammonium Glycyrrhizinate	0.050
10	Flavorant	0.015
11	Colorant	0.005
	Total	100.000

Add a portion of Ethanol to the active (Dextromethorphan Base) and solid sweetening agents (Sucralose, Monoammonium Glycyrrizinate) and continuously mixed at low heat (30°C). To this vessel add the additional solvents (Propylene Glycol, Polyethylene Glycol 600) and liquid sweeteners (Pro-sweet Liquid K). Prepare an aqueous premix of buffer (Sodium Glycinate) and add to the vessel. Mix until all materials are in solution, about 2 hours time. Prepare a premix of flavorants and colorants in the remaining portion of ethanol, and add to the vessel containing the nearly completed solution. Mix until a homogenous solution is obtained, and filter through a US # 100 mesh sieve (product density = 1.07 g/ml.). Make individual filled lozenges containing about 1.0 ml. of liquid per lozenge by a commonly used method such as extrusion

A person places a liquid filled lozenge into the mouth and sucks until the liquid fill is released. Some cough relief is obtained through the action of sucking on the shell of the lozenge. When the liquid center is released, dextromethorphan is rapidly absorbed into the blood, and relief from coughing is obtained within 10 minutes time.

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Example VII

Liquid Elixir

Items #	Material	% Comp. (w/w)
1	Dextromethorphan Base	2.055
2	Pseudoephedrine Base	4.593
3	Ethanol (100%)	10.000
4	Polyethylene Glycol 600	73.689
5	Propylene Glycol	5.000
6	Triethanolamine	3.740
7	Sucralose	0.150
8	Pro-Sweet Liquid K	0.700
9	Monoammonium Glycyrrhizinate	0.050
10	Flavorant	0.015
11	Colorant	0.005
	Total	100

The composition is made according to the direction of Examples I and II.

Example VIII

Liquid Elixir

Items #	Material	% Comp. (w/w)
1	Chlorpheniramine Base	0.263
2	Pseudoephedrine Base	4.593
3	Ethanol (100%)	10.000
4	Polyethylene Glycol 600	79.224
5	Propylene Glycol	5.000
6	Sucralose	0.150
7	Pro-Sweet Liquid K	0.700
8	Monoammonium Glycyrrhizinate	0.050
9	Flavorant	0.015
10	Colorant	0.005
	Total	100

The composition is made according to the direction of Examples I and II.

Example IX

Liquid Elixir

Items #	Material	% Comp. (w/w)
1	Acetoaminophen	27.169
2	Dextromethorphan Base	1.195
2	Pseudoephedrine Base	2.671
3	Ethanol (100%)	10.000
4	Polyethylene Glycol 1000 and PEG 600	25.019
5	Polyethylene Glycol 600	22.765
6	Propylene Glycol	4.350
7	Polyvinyl pyrrolidone K-17PF	2.170
8	Triethanolamine	3.740
9	Sucralose	0.150
10	Pro-Sweet Liquid K	0.700
11	Monoammonium Glycyrrhizinate	0.050
12	Flavorant	0.015
13	Colorant	0.005
	Total	100

Procedure: Dissolve Dextromethorphan Base and Pseudoephedrine Base in portion of alcohol to make a premix. In separate container heat PEG 1000, PEG 600, PVP-K17pf and propylene glycol to @ 70°C. Once all material is melted and in clear liquid form add Acetoamonophen and continue to heat to 110-120 °C with continuous mixing. Remove heat once liquid is clear. Cool it to room temperature. Add the mixture to the Dextromethorphan and Pseudoephedrine premix. Also add liquid sweetener (Pro-sweet Liquid K) and buffer (Triethanolamine).

Mix until all materials are in solution. Prepare a premix of flavorants and colorants in the remaining portion of alcohol, and add to the vessel containing the nearly completed solution. Mix until homogeneous and filter through a US #100 mesh sieve. Fill in a amber glass bottles, and cap with an integrated cap/ calibrated medicine dropper assembly.
About 1.84 grams of the elixir is dropped onto the tongue and then swallowed.

WE CLAIM:

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1. A composition comprising a pharmaceutical active in an hydrophilic, water-miscible, anhydrous solvent wherein the pharmaceutical active in its unionized form has a percent solubility value in the solvent at ambient temperature that is equal to or greater than 0.075% and the pharmaceutical active is in it free, unionized form as a monomolecular dispersion in the solvent.

2. The composition according to claim 1 wherein the pharmaceutical actives have a molecular weight of less than 500 grams per mole, is capable of being ionized when in an aqueous solvent and has an octanol-water partition coefficient when in the unionized form of at least 100.

3. The composition according to claim 2 wherein the pharmaceutical actives are selected from the group consisting of antitussives, antihistamines, non-sedating antihistamines, decongestants, expectorants, analgesic mucolytics, antipyretic anti-inflammatory agents, local anesthetics and mixtures thereof.

4. The composition according to claim 3 wherein the concentration of pharmaceutical actives in the solvent is less than or equal to 125% of the percent solubility value of said active.

5. The composition according to claim 4 wherein the pharmaceutical active is present in the solvent at a level from about 0.075% to about 25.0% by weight of the composition.

6. The composition according to claim 5 wherein the pharmaceutical active is present in the solvent at a level from about 0.28% to 10.0% by weight of the composition.

7. The composition according to claim 1 wherein the an hydrophilic, water-miscible, anhydrous solvent comprises from about 60% to about 99.975% by weight of the composition.

8. The composition according to Claim 7 wherein the an hydrophilic, water-miscible, anhydrous solvent comprises from about 70% to about 99% by weight of the composition.

9. The composition according to claim 8 wherein the an hydrophilic, water-miscible, anhydrous solvent comprises from about 85% to about 98% by weight of the composition.

10. The composition according to claim 7 wherein the hydrophilic, water-miscible, anhydrous solvent is selected from the group consisting propylene glycol, ethanol, poly(ethylene glycol) or PEG, propylene carbonate, diethylene glycol monoethyl ether, poloxamer, glycofurol, glycerol and mixtures thereof.

11. A method for treating respiratory illnesses using a liquid composition of claim 1 wherein the method comprises oral administration of said composition having a total dosage volume of no more than 3.0 mls.

12. The method according to claim 11 wherein the composition is placed against any of the mucosal membranes of the mouth.

Date Recue/Date Received 2020-09-25

ABSTRACT

COMPOSITIONS HAVING IMPROVED DELIVERY OF ACTIVES

The present invention pertains to compositions having improved delivery of pharmaceutical actives. These compositions comprise pharmaceutical actives in an anhydrous solvent. These compositions may take the form of liquid elixirs placed into the mouth and eventually swallowed, or can be delivered via liquid-filled drops, metered liquid dosing devices, atomizers and liquid-releasing, edible capsules.

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Diciembre 03, 1999

La presente es para certificar que el anexo es una copia fiel de los registros de la Oficina de Patentes y Marcas de los Estados Unidos, de los documentos de la solicitud de patente identificada más adelante, que cumplieron con los requerimientos para concederse una fecha de presentación de acuerdo con el titulo 35 del Código de los Estados Unidos, sección 111.

Número de Solicitud: 60/156,539

Fecha de Presentación: Septiembre 29, 1999

Por la autoridad del
Comisionado de Patentes y Marcas

(fdo) W. MONTGOMERY
Oficial Certificador
Sello oficial de la Oficina de Patentes y Marcas de los Estados Unidos de América.

COMPOSICIONES QUE TIENEN ESTABILIDAD MEJORADA

Douglas J. Dobrozsi

CAMPO TECNICO

El presente invento pertenece a la estabilidad mejorada de composiciones que suministran ingredientes activos farmacéuticos, particularmente aquellos que tienen baja solubilidad en agua. Estas composiciones tienen excepcional estabilidad cuando son usadas en varias formas de producto incluyendo tabletas, elíxires líquidos puestos en la boca y eventualmente deglutidos o pueden ser suministrados a través de pastillas rellenas de líquido, dispositivos de dosificación líquida medida, atomizadores y cápsulas comestibles liberadoras de líquido. Tales composiciones son particularmente útiles para tratar síntomas asociados con enfermedades respiratorias.

ANTECEDENTES DEL INVENTO

Las vías de suministro de activos farmacéuticos incluyen el suministro de activos por medio de administración intranasal, pulmonar, bucal, sublingual, transdérmica y rectal. Estas vías tienden a ser usadas para evitar el metabolismo de primer paso de drogas que son deglutidas. "El metabolismo de primer paso" se refiere a la disposición y orden de colocación de las enzimas metabolizantes dentro del

cuerpo de un humano, con respecto al curso seguido por las sustancias que entran al tracto gastrointestinal por deglutido y son absorbidas en la circulación sanguínea general. Los artículos deglutidos por los humanos, incluyendo alimento, bebida y medicinas, entran al estómago y desde allí fluyen al intestino. Muchos de los químicos asociados con el alimento, bebida y medicinas pasan a través de las membranas mucosas en el tracto gastrointestinal y a la sangre en las venas mesentéricas que drenan del intestino. El flujo sanguíneo desde las venas mesentéricas pasa al hígado. Las enzimas metabolizantes en las membranas mucosas del intestino y el hígado pueden alterar químicamente la naturaleza de las sustancias que pasan desde el intestino a través del hígado y a la circulación sanguínea común del cuerpo. Ya que todas las medicinas deglutidas están sometidas a la capacidad de metabolización de las membranas mucosas del intestino y del hígado, antes de entrar a la circulación sanguínea general del cuerpo, frecuentemente solamente una pequeña fracción de esas sustancias van no metabolizadas y alcanzan la circulación sanguínea general.

Al evitar el primer paso de metabolismo se puede aumentar la biodisponibilidad o concentraciones en la sangre del compuesto administrado. La formación metabólica de metabolitos del compuesto administrado, sin embargo, puede al mismo tiempo disminuir. Donde es deseable la formación de metabolitos a partir del primer paso de metabolismo, no es preferido evitar el primer paso de metabolismo, ya que ello lógicamente conduce a menores cantidades del metabolito en la sangre. Adicionalmente, las concentraciones en la sangre de la

sustancia activa pueden aumentar, llevando a toxicidad potencial o efectos secundarios atribuibles al activo en sí. Reducir la cantidad de activo en la dosis para evitar la toxicidad, concomitantemente disminuye los niveles de metabolito activo en la circulación sanguínea. Esto da como resultado pérdida de efecto terapéutico y finalmente, de beneficio para el paciente. Con el fin de proveer un medicamento que sea efectivo y evite efectos secundarios no deseados, la composición y su medio de suministro debe ser modificada.

Las enfermedades respiratorias cubren un amplio rango de dolencias, incluyendo infecciones virales y reacción alérgica a alergenos inhalados. Las infecciones virales en el tracto respiratorio superior de los humanos, conducen a enfermedades usualmente denominadas como resfriados o influenza. Tales enfermedades son muy comunes en la población general y pueden ser la causa de incomodidad y sufrimiento significativo. La inhalación de alergenos también impacta negativamente una buena cantidad de la población en el mismo o mayor grado que aquella que sufre infecciones virales.

No hay métodos considerados generalmente efectivos y convenientes para prevenir las infecciones virales o alergias. En el caso de las infecciones virales, los mecanismos de defensa natural del cuerpo, combaten la infección por un período de tiempo que varía desde 3 días hasta 2 semanas. Siendo este el caso, las medicinas más comúnmente empleadas tratan los síntomas incómodos y problemáticos de estas dolencias respiratorias. Estos síntomas incluyen narices tapadas o llorosas, dolor e inflamación de la nariz y

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garganta, accesos de tos, dolores generales en el cuerpo, fiebre y dolor de cabeza. De estos síntomas, la tos en accesos incontrolables es considerada por muchos el más problemático e incómodo. La tos interrumpe la respiración normal, llevando a dolor de cabeza aumentado y dolor de garganta, así como a la pérdida de sueño de quien la sufre y de quienes viven con quien la sufre.

Las composiciones usadas para tratar los síntomas antes mencionados generalmente caen en una de las siguientes clasificaciones farmacológicas: antihistaminas; descongestionantes; antitusivos; expectorantes; mucolíticos; analgésicos, antipiréticos y agentes antiinflamatorios. Las composiciones son elaboradas en un número de formas de producto, siendo la más común jarabes y elíxires líquidos para ser deglutidos, gotas bucales y pastillas así como inhaladores y cremas tópicas o lociones que liberan agentes volátiles que son inhalados a través de la nariz en el tracto respiratorio. Las composiciones son típicamente deglutidas inmediatamente o lentamente disueltas en la boca. Típicamente contienen activos tales como guafenesin, que ayuda al cuerpo en la remoción de exceso de moco respiratorio o flema, defenhidramina, que disminuye los efectos negativos incluyendo la tos y otros síntomas debidos a la histamina producida en el cuerpo en respuesta a la infección viral y dextrometorfan, que actúa dentro de la parte del cerebro humano controlando el reflejo de la tos. Entre estos activos el dextrometorfan es el activo más comúnmente usado en el mundo para el alivio de la tos.

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El dextrometorfan en virtud de sus propiedades de absorción fisicoquímica y biodisponibilidad, es un muy buen candidato para aumentar la biodisponibilidad a través de métodos de administración distintos de la deglución. Por ejemplo se ha reportado en patentes y literatura farmacéutica que aumentos sustanciales en la biodisponibilidad pueden ser logrados usando formulaciones intranasales; ver Nasal Delivery of 14-C dextrometorfan in Rats (Suministro Nasal de 14-C dextrometorfan en Ratas) de H Char y otros en el *Journal of Pharmaceutical Sciences* 81:750,1992.

RESUMEN DEL INVENTO

Lo que hasta ahora no se ha considerado es que compuestos activos que están combinados con solventes tradicionales, pueden ser impactados positivamente cuando agentes particulares son adicionados a las composiciones. Sorprendentemente, adicionando agua a una composición, particularmente una que contenga activos de baja solubilidad en agua, mejora la estabilidad del activo en tales composiciones.

Las composiciones del presente invento proveen excelente suministro de activos a las superficies orales, particularmente cuando es un producto peroral. Estas composiciones también demuestran excelente duración en el almacenamiento cuando son incorporadas en una variedad de formas de producto incluyendo tabletas, pastillas rellenos de líquido, dispositivos de dosificación líquida medida, atomizadores y

cápsulas comestibles liberadoras de líquido. Tales composiciones son particularmente útiles para tratar síntomas asociados con enfermedades respiratorias.

Lo que hasta ahora no se ha considerado es que después de una investigación cuidadosa y diligente en las propiedades farmacéuticas, terapéuticas y efectos secundarios de compuestos activos, las composiciones pueden ser elaboradas para mejorar positivamente el efecto terapéutico sin aumentar los efectos secundarios o la toxicidad. Estos compuestos tienen estabilidad mejorada en la forma de producto seleccionada para suministrar tales composiciones. Este beneficio es logrado por medio de adicionar a la formulación que contiene activos, agentes que promueven la estabilidad del activo en la formulación. Estos agentes son efectivos para reducir y aún eliminar la inestabilidad debida al curso de degradación por oxidación del activo, para de esta forma aumentar la duración en el almacenamiento de las composiciones.

Un objetivo por lo tanto, del presente invento es proveer composiciones mejoradas para tratar los síntomas asociados con dolencias respiratorias, particularmente minimizando los accesos de tos. Una composición particularmente preferida es en forma de líquidos anhídridos hidrófilos en un ambiente muy estable para suministro rápido de activos incluyendo antitusivos; antihistaminas (incluyendo antihistaminas no sedantes); descongestionantes; expectorantes; mucolíticos; analgésicos, antipiréticos y agentes antiinflamatorios y anestésicos locales para tratar los síntomas de

dolencias respiratorias (esto es generalmente verdad para este invento). Las composiciones pueden ser dosificadas usando una variedad de formas de producto y u opciones de empaques suministradores. Las composiciones del presente invento proveen actividad deseada al tiempo que minimizan los efectos secundarios potenciales de los compuestos activos. También es un objetivo de la materia del invento, proveer métodos para lograr suministro rápido transmucoso de las composiciones anteriormente mencionadas.

Definiciones y Términos

Las siguientes son definiciones de términos encontrados en la presente especificación:

1. suministro transmucoso

Se refiere a la aplicación de drogas a las membranas mucosas de la cavidad oral, incluyendo la boca (mejillas), labios, encías, paladar y lengua, con la meta de pasar la droga través de la piel que cubre estos lugares y entrarla en la corriente sanguínea.

2. dosis terapéutica

Se refiere a la cantidad de la sustancia que cuando es administrada a una persona en la forma apropiada, producirá el efecto deseado dentro del cuerpo con mínimos efectos secundarios no deseados.

3. activo farmacéutico/activo

Se refiere a la molécula química la cual ejerce el efecto deseado en el cuerpo, cuando es administrada en la cantidad y forma apropiada.

4. metabolitos activos

Se refiere a especies químicas del activo farmacéutico las cuales son formadas al experimentar el activo el metabolismo.

5. dispersión monomolecular

Se refiere al hecho que las moléculas del activo están libres y no impedidas de difusión por asociación en formas sólidas cristalinas o amorfas o asociación poli molecular.

6. valor de solubilidad porcentual

Se refiere al límite de equilibrio de solubilidad o máxima solubilidad de una molécula en un solvente a temperatura de habitación usual, expresado como un porcentaje en peso de la molécula en la composición.

7. solvente anhídrido

Se refiere a solventes que contienen menos que 5% de agua.

DESCRIPCION DETALLADA DEL INVENTO

Activos Farmacéuticos

Las composiciones del presente invento contienen activos farmacéuticas también denominados aquí como "activos" para tratar enfermedades, particularmente síntomas asociados con dolencias respiratorias tales como resfriados, influenza, así como alergia. Estos activos incluyen aquellos frecuentemente usados para tratar los síntomas más problemáticos incluyendo narices tapadas y llorosas, dolor e inflamación de la nariz y garganta, accesos de tos, dolores generales en el cuerpo, fiebre y dolor de cabeza. En el presente invento, cuando los activos están combinados con solventes, los activos obtienen suministro transmucoso a la sangre mejorado. En el caso que metabolitos de activos contribuyan en el efecto terapéutico deseado, este suministro mejorado es logrado sin disminución apreciable del nivel de los metabolitos activos correspondientes. Adicionalmente, el nivel de activo en la sangre es mantenido a un nivel que evita efectos secundarios no deseados, producidos por niveles muy altos de activo en la sangre.

La composición contiene un activo farmacéutico y un solvente. En una ejecución particularmente preferida, el solvente es hidrófilo, miscible en agua, anhídrido donde el activo farmacéutico en su forma no ionizada tiene un valor porcentual de solubilidad en el solvente a temperatura ambiente, que es igual o mayor que 0.075% y el activo

farmacéutico es en su forma libre no ionizada como una dispersión monomolecular en el solvente.

Los activos farmacéuticos preferibles del presente invento tienen peso molecular de menos que 500 grs por mol, son capaces de ser ionizados cuando están en un solvente acuoso y tienen un coeficiente de partición octanol-agua cuando están en la forma no ionizada de al menos 100. El coeficiente de partición octanol-agua está revelado en Physical Pharmacy (Farmacia Física) de A, Martin, P. Bustamente y A.H.C. Chun, cuarta edición, Lea and Febiger editores, Philadelphia, 1993, página 237; incorporada aquí como referencia.

Los activos que constituyen las composiciones del presente invento incluyen activos que caen en al menos una de las siguientes clasificaciones farmacológicas: antihistaminas; descongestionantes; expectorantes; mucolíticos; analgésicos, antipiréticos y agentes antiinflamatorios, anestésicos locales y mezclas de ellos. Referencias que describen el uso de tales activos incluyen The Pharmacologic Basis of Therapeutics (Las Bases Farmacológicas de las Terapéuticas) de J.G. Hardman, novena edición, McGraw-Hill, Nueva York, 1995. Entre los activos que caen en esta clasificación farmacológica están aquellos que son apropiados para absorción a través de los tejidos mucosos. Estos activos pueden ser usados solos o en combinación con otros activos no necesariamente absorbidos de esta manera y pueden ser formulados dentro de técnicas de formulación existentes.

Cuando se usan activos que se pretende sean absorbidos por las mucosas, la concentración de activos en la porción solvente de la composición es preferiblemente menor o igual que 125% del valor porcentual de solubilidad, más preferiblemente menor o igual que el valor porcentual de solubilidad del activo farmacéutico. Para maximizar el beneficio de las composiciones del presente invento, el activo es preferiblemente una solución como dispersión monomolecular. Los activos absorbidos útiles en el presente invento están presentes en el sistema solvente a un nivel desde 0.075% hasta 25.0%, preferiblemente desde 0.28% hasta 10.0% en peso de la composición. Es preferido que dicho activo esté en su forma libre no ionizada como una dispersión monomolecular en dicho sistema solvente. En los casos donde tanto las formas salinas o formas ionizadas de droga activa existan, se prefiere usar la forma libre no cargada (no sal) de la droga en el presente invento.

Los antitusivos son activos de uso particularmente para accesos de tos incontrolados. Los antitusivos útiles en el presente invento incluyen, pero no restringidos al grupo consistente de codeína, dextrometorfan, dextrorfan, difenhidramina, hidrocodona, noscapina, oxicodona, pentoxiverina y mezclas de ellos. De estos antitusivos el dextrometorfan es el preferido. El dextrometorfan se sabe que tiene actividad farmacológica como una agente antitusivo y está descrito en la U.S. Patent No. 5,196,436, expedida a Smith; incorporada aquí como referencia. Como se usa aquí "dextrometorfan" significa racemetorfan, 3-metoxi-17-metilmorfinan (dl-cis-1,3,4,9,10a-hexahidro-6-metoxi-11-metil-2H-10,4a-iminoetanofenantreno y sales

farmacéuticamente aceptables de ellos. Las composiciones presentes que contienen dextrometorfan preferiblemente contienen desde 0.1% hasta 9.3%, más preferiblemente desde 0.26% hasta 6.2% y mucho más preferiblemente desde 1.16% hasta 4.6% de dextrometorfan. Otras cantidades seguras y efectivas de otras drogas activas para resfriado/tos pueden ser incluidas en tales composiciones que contienen dextrometorfan.

Las antihistaminas útiles en el presente invento incluyen pero no restringidas al grupo consistente de acrivastina, azatadina, bomfeniramina, clorofeniramina, clemastina, ciproheptadina, dexbromfeniramina, dimenhidrinato, difenhidramina, doxilamina, hidroxizina, meclisina, feninamina, feniltoloxamina, prometazina, pirilamina, tripelennamina, triprolidina y mezclas de ellos. Las antihistaminas no sedantes útiles en el presente invento incluyen pero no están restringidas al grupo consistente de astemizol, cetirizina, ebastina, fexofenadina, loratidina, terfenadina y mezclas de ellos. Los descongestionantes útiles en el presente invento incluyen pero no están restringidos al grupo consistente de fenilpropanolamina, pseudoefedrina, efedrina, fenilefedrina, oximetazolina y mezclas de ellos. Los expectorantes útiles en el presente invento incluyen pero no están restringidos al grupo consistente de cloruro de amonio, guafenesin, extracto fluido de ipecacuana, yoduro potásico y mezclas de ellos. Los mucolíticos útiles en el presente invento incluyen pero no están restringidos al grupo consistente de acetilcisteína, ambroxol, bromhexina y mezclas de ellos. Los analgésicos, antipiréticos y agentes antiinflamatorios útiles en el presente invento incluyen pero no

están restringidos al grupo consistente de acetaminofen, aspirina, diclofenaco, diflunisal, etodolaco, fenoprofen, flurbiprofen, ibuprofen, ketoprofen, ketorolac, nebumetone, naxopren, piroxicam, cafeína y mezclas de ellos. Los anestésicos locales útiles en el presente invento incluyen pero no están restringidos al grupo consistente de lidocaina, benzocaina, fenol, diclonine, benzonotato y mezclas de ellos.

Solventes

La forma no ionizada de un activo farmacéutico es mantenida usando un grupo seleccionado de solventes. La porción solvente de las composiciones del presente invento comprenden desde 60% hasta 99.75%, preferiblemente desde 70% hasta 99% y mucho más preferiblemente desde 85% hasta 98% en peso de la composición.

Los solventes del presente invento son normalmente líquidos a temperatura ambiente o de habitación. Son solubles en agua o miscibles en agua. Los solventes para el presente invento son preferiblemente seleccionados del grupo consistente de glicol propileno, etanol, poli(glicol etileno) o PEG, carbonato de propileno, éter monoetilo glicol dietileno, poloxamer, glicofurol, glicerina y mezclas de ellos. El glicol propileno es particularmente preferido. Hay mezclas de estos solventes que son particularmente preferidas para ciertas formas de producto del presente invento. Por ejemplo, si la forma de producto es un elíxir, cápsula líquida o pastilla que contiene líquido, el solvente es una combinación de glicol propileno, etanol y PEG. Si la forma de producto es un rociado, el solvente es una

combinación de glicol propileno, etanol, PEG y usualmente carbonato de propileno. El nivel de cada solvente que constituye estas mezclas es dependiente parcialmente de beneficios estéticos vistos por el formulador. Las más preferidas son las formas anhídridas de los solventes anteriores.

Agua

El agua provee un beneficio estabilizante sorprendente a las composiciones del presente invento. Mientras no se quiere estar limitado por un mecanismo particular, se cree que en el presente invento ekl agua actúa como un agente extinguidor para los radicales oxi y peroxi que crean o facilitan la degradación del activo antes del uso de dicha composición. Esto promueve el mejoramiento de la duración en el almacenamiento de la composición así como la eficacia de la composición cuando el producto es almacenado por períodos normalmente asociados con productos comerciales. En el presente invento el nivel máximo de agua es 10%, preferiblemente desde 1% hasta 10%, más preferiblemente desde 5% hasta 10% y mucho más preferiblemente desde 5% hasta 8% en peso de la composición.

donde dicha composición tiene una reducción significativa de degradación de activo antes del uso (define "antes del uso" en la especificación).

Ingredientes Opcionales

Los ingredientes normalmente asociados con las medicinas del tratamiento para el resfriado y la influenza, pueden ser usados con los activos farmacéuticos revelados aquí. Tales ingredientes están revelados en la U.S. Patent No. 5,196,436, incorporada aquí como referencia. Adicionalmente, los siguientes ingredientes pueden ser usados en el presente invento.

Agentes Reductores

La adición de agentes reductores se ha encontrado que tiene efecto químico estabilizante benéfico sobre los activos que constituyen el presente invento. Este fenómeno sorpresivamente tiene lugar donde el activo está en diferente fase que el agente reductor. Por ejemplo, donde el activo es soluble en un ambiento no polar o fase de la composición, el agente reductor seleccionado debe ser una fase polar como el agua. Por lo tanto, a pesar de estar en fases separadas, la estabilidad química del activo es todavía positivamente impactada. El mismo beneficio de estabilidad no se observa cuando el activo y el agente reductor son cosolubles en el solvente. Por lo tanto, los agentes reductores útiles en la composición dependen del activo seleccionado y de su solubilidad.

Los agentes reductores son sustancias que tienen un menor potencial redox que la droga o el adyuvante que ellos pretenden proteger contra la oxidación. Así los agentes reductores son más fácilmente oxidados

que la droga o el adyuvante y son efectivos en presencia de agente oxidantes. Ver The Pharmaceutical DODEX de W. Lund, 12 edición, página 290, The Pharmaceutical Press, 1994, incorporada aquí como referencia. Los agentes reductores presentes tienen un valor de potencial de electrodo. Este esta definido por la ecuación de Nernst usando prácticamente celdas electromecánicas estándar de referencia. Los valores resultantes son por lo tanto llamados Potencial de Electrodo Estandar, de E^0 medico en voltios de (V). Al comparar los potenciales estándar de electrodo para diferentes sustancias puede ser usado para comprobar la efectividad de diferentes agentes reductores; ver Pharmaceutical Preformulation (Preformulación Farmacéutica) de Wells, Ellis Horwood Limited Publishing, 1988, páginas 168-172; incorporada aquí como referencia.

Los reductores útiles en el presente invento tienen valor mayor que -0.119 V, preferiblemente desde -0.119V hasta +0.250V. Los agentes reductores preferidos son seleccionados del grupo consistente de sales de meta bisulfito y bisulfito, incluyendo sus sales de sodio y potasio, ditiotreitol, tiourea, tiosulfato sódico, ácido tioglicólico, terbuti hidroquinona (TBHQ), acetilo de cisteína, hidroquinona y mezclas de ellos.

El nivel de agentes reductores útiles en el presente invento es desde 0.005% hasta 1.000%, preferiblemente desde 0.500% hasta 0.050% y mucho más preferiblemente desde 0.100% hasta 0.010% en peso de la composición. Amortiguantes y mezclas de agentes amortiguantes, incluyendo amortiguantes básicos como componentes simples con

pKa de desde 8 hasta 11, incluyen trietanolamina, trometamina, sales de amino ácidos, incluyendo sales alcalinas de glicina, glicilglicina, glutamina u otros amino ácidos, sales alcalinas de fosfato, carbonato y mezclas de ellas. Los amortiguantes proveen resistencia composicional a cambios de pH a la dilución de la composición con la saliva dentro del rango de 8 hasta 10.

Los edulcorantes incluyendo aspartame, sacarina y sus sales, Sucralose™ (vendido por McNeil Specialty Products Co., New Brunswich, NJ); Prosweet™ (vendido por Virginia Dare Extract Co., New York, NY); Magnasweet™ (vendido por MAFCO Worldwide Corp., Licorice Division, Camdem, NJ); glicirrizinato de amonio, sus sales, Talin™ (Taumatin) y sus productos diluidos, como Talin GA90 (vendido por Talin Food Company, Birknhead, Inglaterra); y Acesulfame K y mezclas de ellos.

Los saborantes incluyen anís, aceite de menta piperita, aceite de clavo, eucalipto, limón, lima, limón miel, fruta roja, menta, toronja, naranja, cereza cola y mezclas de ellos.

Agentes sensorios. También útiles aquí son los agentes sensorios seleccionados del grupo consistente de refrescantes, agentes salivantes, agentes cálidos. Preferiblemente estos agentes están presentes en las composiciones a un nivel de desde 0.001% hasta 10%, preferiblemente desde 0.1% hasta 1% en peso de la composición.

Los agentes refrescantes y cálidos apropiados incluyen carboxamidas, mentoles, timol, alcanfor, pimiento, fenol, aceite de eucalipto, alcohol de bencilo, alcohol de salicilo, etanol, aceite de botón de clavo y hexilresorcinol, acetales, dioles y mezclas de ellos. Los agentes cálidos preferidos incluyen timol, alcanfor, pimiento, fenol, alcohol de bencilo, alcohol de salicilo, etanol, aceite de botón de clavo y hexilresorcinol, ésteres nicotinato tales como nicotinato de bencilo, acetales, dioles y mezclas de ellos.

Los refrescantes preferidos son los agentes paramentan carboxamida tales como N-etil-p-mentan-3-carboxamida (WS-3 suministrado por Sterling Organics), enseñado por la U.S. Patent No. 4,136,163 expedida el 23 de enero de 1979 a Watson y otros, la cual se incorpora aquí como referencia en su totalidad. Los refrescantes preferidos son los agentes paramentan carboxamida tales como N-etil-p-mentan-3-carboxamida. Otro agente paramentan carboxamida preferido es N,2,3-trimetil-2-isopropilbutanamida, conocido como "WS-23" y mezclas de WS-3 y WS-23.Refrescantes adicionales preferidos son seleccionados del grupo consistente de mentol, 3-1-mentoxipropano-1,2-diol, conocido como TK-10 suministrado por Takasago Perfumery Co., Ltd, Tokio, Japón, acetal de glicerina de mentona, conocido como MGA, fabricado por Haarmann y Reimer, lactato de mentilo conocido como Frescolat® elaborado por Haarmann y Reimer y mezclas de ellos.

Agentes refrescantes adicionales incluyen sulfonas y sulfóxidos cíclicos y otros todos los cuales están descritos en la U.S. Patent No.

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4,032,661 expedida el 28 de junio de 1977 a Rowsell y otros l cual se incorpora aquí como referencia.

Los términos "mentol" y "mentilo" como se usan aquí incluyen isómeros dextro y levogiros de estos compuestos y mezclas racémicas de ellos.

El TK-10 esta descrito en detalle en la U.S. Patent No. 4,459,425 expedida el 10 de julio de 1984 a Amano y otros y se incorpora aquí como referencia.

Los agentes salivantes del presente invento incluyen Jambu® elaborado por Takasago Perfumery Co., Tokio, Japón.

METODO DE USO

En términos de los métodos de suministro del activo, es generalmente aceptado que el suministro oral mucoso dentro de la boca debe ser dirigido hacia la región sublingual con el fin de lograr un muy rápido efecto terapéutico; ver Drug Delivery Via the Mucus Membranes of the Oral Cavity (Suministro de Droga a Través de las Membranas Mucosas de la Cavidad Oral) de D. Harris y J.R Robinson, en Journal of Pharmaceutical Sciences 81:1,1992. Tales formas de dosificación están diseñadas para colocar bajo la lengua, sobre el piso de la boca y mantenerlas allí por algún tiempo prolongado. Los inventores han encontrado sin embargo, que un gran aumento de la biodisponibilidad

con una muy rápida absorción pueden ser logrados cuando las composiciones de la materia son colocadas contra cualquiera de las mes mucosas de la boca, aún sobre la lengua y deglutidas. La forma del invento es un elíxir en solución líquida. Se pretende que se aplique a cualquiera de las membranas mucosas dentro de la boca. Esto puede ser logrado usando un gotero medicinal que esté calibrado para indicar la cantidad apropiada a ser administrada y soltar el elíxir sobre la lengua antes de deglutirlo. Puede estar encapsulado en una suerte de cubierta la cual lo haga portable y conveniente de transportar y administrar sin tener que medir la cantidad de elíxir líquido. Ejemplos de cubierta de encapsulamiento incluyen caramelos duros que son usados como pastillas, cubiertas basadas en gelatina o almidón. El elíxir puede ser empacado en pequeños frascos desechables los cuales pueden ser fácilmente abiertos y liberado el elíxir dentro de la boca, el contenido total del frasco correspondiente a una dosis terapéutica exactamente. Las formas de dosificación típicas de la composición del presente invento contienen no más de 3 ml, preferiblemente desde 0.2 ml hasta 3 ml.

Una forma preferida es encapsular el líquido en una cubierta dura de caramelo o gelatina. La cubierta que contiene sustancias para pretratar la mucosa y de esta forma mejorar la absorción del activo del centro líquido. El pretratamiento ocurre por medio de chupar o masticar el material de la cubierta y la ventaja se obtiene por medio de separar en el tiempo el tratamiento de la mucosa, lo cual ocurre primero, seguido por la presentación del activo a ser absorbido. Ejemplos de sustancias para pretratamiento de las membranas

mucosas son mejoradores de penetración de las membranas que son comúnmente conocidos en la técnica, ejemplos incluyendo mentol, aceite de menta piperita, surfactantes como polisorbato 80 o poloxamer. Otro ejemplo de un pretratamiento para la membrana mucosa son los amortiguantes como los listados anteriormente, los cuales preacondicionan el pH del micro ambiente salivar en un rango de 8 a 11.

EJEMPLOS

Ejemplo I

Elíxir Líquido

Item #	**Material**	**% Comp. (peso/peso)**
1	Base Dextrometorfan	1.466
2	Etanol (100%)	9.000
3	6-metil-1,2,3-oxatiazina-4(3H)-ona-2,2- Dióxido; Sal de Potasio[1]	0.450
4	Glicol Propileno	80.814
5	Sacarina Sódica	0.650
6	3-Metoxipropan-1,2-diol[2]	0.100
7	Glicirrizinato de Monoamonio	0.150
8	Saborante de Menta Piperita	2.000
9	Etilo Metano Carboxamida	0.070
10	Agua Purificada	5.000
11	Acetal Mentona Glicerina	0.300
	Total	100.000

1 Acetasulfame K producido por Nutrinova Inc. Company de Somerset, NJ-08873, USA

2 TK 10 producido por Takasago Company de Rockleigh, NJ-07657, USA

Adicionar una porción de etanol al activo (Dextrometorfan base) y los agentes edulcorantes sólidos (Sucralose, glicirrizinato de monoamonio) y mezclar continuamente a baja temperatura (30°C). A este recipiente adicionar los solventes adicionales (Glicol propileno, glicol polietileno 600) y los edulcorantes líquidos (Pro-sweet Liquid K). Mezclar hasta que todos los materiales estén en solución, por cerca de 2 horas. Preparar una premezcla de saborantes y colorantes en la porción restante de etanol y adicionarla al recipiente que contiene la solución cercana a estar completa. Mezclar hasta que se obtenga una solución homogénea y filtrar a través de un tamiz US# 100 (densidad del producto 1.07 gr/ml). Llenar frascos de vidrio ámbar y taparlos con un conjunto de tapa integral/gotero calibrado para medicinas.

Cerca de 1.5 gramos del elíxir goteado sobre la lengua y luego deglutido. El dextrometorfan es rápidamente absorbido en la sangre.

Ejemplo II

Elíxir Líquido

Item #	Material	% Comp. (peso/peso)
1	Base Dextrometorfan	2.055
2	Etanol (100%)	10.000
3	Glicol Propileno	78.285
4	Agua Purificada	5.000
5	Trietanolamina	3.740
6	Sucralose	0.150
7	Pro-Sweet Líquido K	0.700
8	Glicirrizinato de Monoamonio	0.050
9	Saborante	0.015
10	Colorante	0.005
	Total	100.000

Adicionar una porción de etanol al activo (Dextrometorfan base) y los agentes edulcorantes sólidos (Sucralose, glicirrizinato de monoamonio) y mezclar continuamente a baja temperatura (30°C). A este recipiente adicionar el Glicol propileno, los edulcorantes líquidos (Pro-sweet Liquid K) y el amortiguante (Trietanolamina líquida). Mezclar hasta que todos los materiales estén en solución, por cerca de 2 horas. Preparar una premezcla de saborantes y colorantes en la porción restante de etanol y adicionarla al recipiente que contiene la solución cercana a estar completa. Mezclar hasta que se obtenga una solución homogénea y filtrar a través de un tamiz US# 100 (densidad

del producto 1.07 gr/ml). Llenar frascos de vidrio ámbar y taparlos con un conjunto de tapa integral/gotero calibrado para medicinas.

Cerca de 1.0 ml del elíxir goteado sobre la lengua y luego deglutido. El dextrometorfan es rápidamente absorbido en la sangre.

Ejemplo III

Elíxir Líquido

Item #	**Material**	**% Comp. (peso/peso)**
1	Glicol Propileno	80.764
2	Etanol (100%)	9.000
3	Agua Purificada	5.000
4	Metabisulfito Sódico	0.050
5	Sacarina Sódica	0.650
6	Saborante de Menta Piperita	2.000
7	6-metil-1,2,3-oxatiazina-4(3H)-ona-2,2- Dióxido; Sal de Potasio[1]	0.450
8	3-Metoxipropan-1,2-diol[2]	0.100
9	Acetal Mentona Glicerina	0.300
10	Etilo Metano Carboxamida	0.070
11	Glicirrizinato de Monoamonio	0.150
12	Base Dextrometorfan	1.466
	Total	100.000

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1 Acetasulfame K producido por Nutrinova Inc. Company de Somerset, NJ-08873, USA

2 TK 10 producido por Takasago Company de Rockleigh, NJ-07657, USA

Adicionar una porción de etanol al activo (Dextrometorfan base) y los agentes edulcorantes sólidos (Sucralose, glicirrizinato de monoamonio) y mezclar continuamente a baja temperatura (30°C). A este recipiente adicionar el Glicol propileno y los edulcorantes líquidos (Pro-sweet Liquid K). Adicionar el metabisulfito sódico y mezclar hasta que todos los materiales estén en solución, por cerca de 2 horas. Adicionar una premezcla de saborantes y colorantes en la porción restante de etanol y adicionarla al recipiente que contiene la solución cercana a estar completa. Mezclar hasta que se obtenga una solución homogénea. Dejar que la solución resida en el recipiente de mezcla, abrirlo a la atmósfera por cerca de 30 minutos. Filtrar la composición a través de un tamiz US# 100 (densidad del producto 1.07 gr/ml). Llenar frascos de vidrio ámbar y taparlos con un conjunto de tapa integral/gotero calibrado para medicinas.

Cerca de 1.0 ml del elíxir goteado sobre la lengua y luego deglutido. El dextrometorfan es rápidamente absorbido en la sangre.

Ejemplo IV

Pastilla de Centro Líquido

Item #	Material	% Comp. (peso/peso)
1	Base Dextrometorfan	2.055
2	Etanol (100%)	2.000
3	Agua Purificada	5.000
4	Glicol Propileno	84.825
5	Tioglicerina	0.050
6	Sucralose	0.300
7	Edulcorante Pro-Sweet Líquido K	0.700
8	Glicirrizinato de Monoamonio	0.050
9	Saborante	0.015
10	Colorante	0.005
	Total	100.000

Adicionar una porción de etanol al activo (Dextrometorfan base) y los agentes edulcorantes sólidos (Sucralose, glicirrizinato de monoamonio) y mezclar continuamente a baja temperatura (30°C). A este recipiente adicionar el glicol propileno y los edulcorantes líquidos (Pro-sweet Liquid K). Mezclar hasta que todos los materiales estén en solución, por cerca de 2 horas. Adicionar la tioglicerina y mezclar todos los materiales estén en solución por cerca de 2 horas. Adicionar una premezcla de saborantes y colorantes en la porción restante de etanol y adicionarla al recipiente que contiene la solución cercana a estar completa. Mezclar hasta que se obtenga una solución homogénea. Dejar que la composición resida en el recipiente de

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mezcla, abrir a la atmósfera por cerca de 30 minutos. Mezclar hasta que se obtenga una solución homogénea y filtrar a través de un tamiz US# 100 (densidad del producto 0 1.07 gr/ml). Elaborar pastillas rellenas individuales que contengan cerca de 1.0 ml de líquido por pastilla, por medio de un método comúnmente usado, tal como extrusión.

Una persona coloca una pastilla llena de líquido en la boca y chupa la pastilla hasta que el relleno líquido sea liberado. Algún alivio para la tos es obtenido por la acción de chupar la cubierta de la pastilla. Cuando el centro líquido es liberado, el dextrometorfan es rápidamente absorbido en la sangre.

Ejemplo V

Pastilla de Centro Líquido

Item #	**Material**	**% Comp. (peso/peso)**
1	Base Dextrometorfan	2.055
2	Etanol (100%)	2.000
3	Agua Purificada	5.000
4	Glicol Propileno	5.000
5	Glicinato Sódico	5.000
6	Sucralose	0.300
7	Pro-Sweet Líquido K	0.700
8	Glicirrizinato de Monoamonio	0.050
9	Saborante	0.015

10	Colorante	0.005
	Total	100.000

Adicionar una porción de etanol al activo (Dextrometorfan base) y los agentes edulcorantes sólidos (Sucralose, glicirrizinato de monoamonio) y mezclar continuamente a baja temperatura (30°C). A este recipiente adicionar el glicol propileno y los edulcorantes líquidos (Pro-sweet Liquid K). Preparar una premezcla acuosa de amortiguante (Glicinato sódico) y adicionarla al recipiente. Mezclar hasta que todos los materiales estén en solución, por cerca de 2 horas. Preparar una premezcla de saborantes y colorantes en la porción restante de etanol y adicionarla al recipiente que contiene la solución cercana a estar completa. Mezclar hasta que se obtenga una solución homogénea. y filtrar a través de un tamiz US# 100 (densidad del producto 0 1.07 gr/ml). Elaborar pastillas rellenas individuales que contengan cerca de 1.0 ml de líquido por pastilla, por medio de un método comúnmente usado, tal como extrusión.

Una persona coloca una pastilla llena de líquido en la boca y chupa la pastilla hasta que el relleno líquido sea liberado. Algún alivio para la tos es obtenido por la acción de chupar la cubierta de la pastilla. Cuando el centro líquido es liberado, el dextrometorfan es rápidamente absorbido en la sangre y el alivio de la tos se obtiene dentro de los 10 minutos de tiempo.

Ejemplo VI

Elíxir Líquido

Item #	Material	% Comp. (peso/peso)
1	Dextrometorfan Base	2.055
2	Pseudoefedrina Base	4.593
3	Etanol (100%)	10.000
4	Glicol Propileno	78.892
5	Trietanolamina	3.740
6	Sucralose	0.150
7	Pro-Sweet Líquido K	0.700
8	Glicirrizinato de Monoamonio	0.050
9	Saborante	0.015
10	Colorante	0.005
	Total	100.000

Adicionar una porción de etanol a la Dextrometorfan base, la Pseudoefedrina base y los agentes edulcorantes sólidos (Sucralose, glicirrizinato de monoamonio) y mezclar continuamente a baja temperatura (30°C). A este recipiente adicionar el Glicol propileno, los edulcorantes líquidos (Pro-Sweet Liquid K) y el amortiguante (trietanolamina líquida). Mezclar hasta que todos los materiales estén en solución, por cerca de 2 horas. Preparar una premezcla de saborantes y colorantes en el glicol propileno y la porción restante de etanol y adicionarla al recipiente que contiene la solución cercana a estar completa. Mezclar hasta que se obtenga una solución homogénea y filtrar la composición a través de un tamiz US# 100

(densidad del producto 1.07 gr/ml). Llenar frascos de vidrio ámbar y taparlos con un conjunto de tapa integral/gotero calibrado para medicinas.

Cerca de 1.0 ml del elíxir goteado sobre la lengua y luego deglutido. El dextrometorfan y la pseudoefedrina son rápidamente absorbidos en la sangre.

Ejemplo VII

Elíxir Líquido

Item #	**Material**	**% Comp. (peso/peso)**
1	Clorfeniramina Base	0.263
2	Pseudoefedrina Base	4.593
3	Etanol (100%)	10.000
4	Glicol Propileno	79.124
5	Agua	5.000
6	Sucralose	0.150
7	Pro-Sweet Líquido K	0.700
8	Glicirrizinato de Monoamonio	0.050
9	Saborante	0.015
10	Colorante	0.005
11	Sulfito Sódico	0.100
	Total	100.000

Adicionar una porción de etanol a la Clorfeniramina base, la Pseudoefedrina base y los agentes edulcorantes sólidos (Sucralose, glicirrizinato de monoamonio) y mezclar continuamente a baja temperatura (30°C). A este recipiente adicionar el Glicol polietileno 600, los edulcorantes líquidos (Pro-sweet Liquid K), el sulfito sódico y el amortiguante (trietanolamina líquida). Mezclar hasta que todos los materiales estén en solución, por cerca de 2 horas. Preparar una premezcla de saborantes y colorantes en el glicol propileno y la porción restante de etanol y adicionarla al recipiente que contiene la solución cercana a estar completa. Mezclar hasta que se obtenga una solución homogénea y filtrar a través de un tamiz US# 100 (densidad del producto 1.07 gr/ml). Llenar frascos de vidrio ámbar y taparlos con un conjunto de tapa integral/gotero calibrado para medicinas.

Cerca de 1.0 ml del elíxir goteado sobre la lengua y luego deglutido.

Ejemplo VIII

Elíxir Líquido

Item #	**Material**	**% Comp. (peso/peso)**
1	Acetaminofen	27.169
2	Dextrometorfan Base	1.195
3	Pseudoefedrina Base	2.671
4	Etanol (100%)	10.000
5	Glicol Propileno	47.069
6	Polivil Pirrolidona	2.170

6	Polivil Pirrolidona	2.170
7	Trietanolamina	3.740
8	Sucralose	0.150
9	Pro-Sweet Líquido K	0.700
10	Glicirrizinato de Monoamonio	0.050
11	Saborante	0.015
12	Agua Purificada	5.000
13	Colorante	0.005
	Total	100.000

1 P-K17PF producido por BASF

Disolver la Dextrometorfan base y la Pseudoefedrina base en una porción de alcohol para hacer una premezcla. En un recipiente separado calentar glicol propileno a cerca de 70°C. Una vez todo el material esté fundido y en forma líquida clara, adicionar el acetaminofen y continuar calentando hasta 110-120°C con mezclado continuo. Retirar el calor una vez el líquido esté claro. Enfriar a temperatura de habitación. Adicionar la mezcla a la premezcla de dextrometorfan y pseudoefedrina. También adicionar el edulcorante líquido (Pro-Sweet Liquid K) y el amortiguante (trietanolamina).

Mezclar hasta que todos los materiales estén en solución. Preparar una premezcla de saborantes y colorantes en la porción restante de alcohol y adicionarla al recipiente que contiene la solución cercana a estar completa. Mezclar hasta que se obtenga una solución homogénea y filtrar a través de un tamiz US# 100. Llenar un frasco de

vidrio ámbar y taparlo con un conjunto de tapa integral/gotero calibrado para medicinas.

Cerca de 1.84 gramos del elíxir es goteado sobre la lengua y luego deglutido.

Ejemplo IX

Elíxir Líquido

Item #	**Material**	**% Comp. (peso/peso)**
1	Etanol (100%)	88.534
2	Agua	10.000
3	Dextrometorfan Base	1.466
	Total	100.000

Disolver la Dextrometorfan base en una porción de alcohol para hacer una premezcla. En un recipiente separado calentar agua y meta bisulfito a cerca de 70°C. Mezclar hasta que esté uniforme y enfriar a temperatura de habitación. Adicionar esta mezcla al Dextrometorfan base.

Mezclar hasta que todos los materiales estén en solución. Adicionar la porción restante del recipiente que contiene la solución cercana a estar completa. Mezclar hasta que esté homogénea y filtrar a través de un tamiz US# 100. Llenar un frasco de vidrio ámbar y taparlo con un conjunto de tapa integral/gotero calibrado para medicinas. Cerca de 1.84 gramos del elíxir es goteado sobre la lengua y luego deglutido.

Ejemplo X

Cápsulas de gelatina suave masticables

Item #	Material	% Comp. (peso/peso)
1	Glicol Polietileno	35.159
2	Glicerina	10.000
3	Dextrometorfan Base	1.100
4	Acetaminofen	32.500
5	Pseudoefedrina Base	2.671
6	Polivil Pirrolidona	4.170
7	Empaque Estético[1]	4.000
8	Agua	10.000
12	Agua Purificada	5.000
13	Colorante	0.005
	Total	100.000

1 ver los ejemplos anteriores

Disolver el Dextrometorfan base en una porción de alcohol para hacer una premezcla. En un recipiente separado calentar el meta bisulfito a cerca de 70°C. Adicionar el acetaminofen y continuar calentando hasta 110-120°C con mezclado continuo. Retirar el calor una vez el líquido esté claro. Enfriar a temperatura de habitación. Mezclar hasta que esté uniforme y enfriar a temperatura de habitación. Mezclar hasta que todos los materiales estén en solución. Adicionar la porción restante de alcohol, polivinil pirrolidona y el empaque estético al recipiente que contiene la solución cercana a estar completa. Mezclar

hasta que esté homogénea y filtrar a través de un tamiz US# 100. Llenar cápsulas de gelatina blanda masticables usando la formulación anterior. Dichas cápsulas de gelatina se consiguen en el mercado de compañías como R.P Scherer de San Petersburgo, Florida. Cerca de 1.84 gramos del elíxir es suministrado a la boca por medio de masticar las cápsulas y luego deglutirlas.

Ejemplo XI

Elíxir Líquido

Item #	**Material**	**% Comp. (peso/peso)**
1	Glicol Propileno	75.000
2	Glicerina	10.000
3	Dex Base	1.100
4	Empaque Estético	4.000
5	Agua	10.000
	Total	100.000

1 ver los ejemplos anteriores

Disolver la Dextrometorfan base en una porción de alcohol para hacer una premezcla. En un recipiente separado calentar agua a cerca de 70°C. Retirar el calor una vez el líquido esté claro. Enfriar a temperatura de habitación. Adicionar la mezcla al dextrometorfan. Mezclar hasta que esté uniforme y enfriar a temperatura de habitación. Mezclar hasta que todos los materiales estén en solución. Adicionar la porción restante de alcohol y el empaque estético al recipiente que

contiene la solución cercana a estar completa. Dejar que la composición resida en el recipiente de mezcla, abrirlo a la atmósfera por cerca de 10 minutos. Mezclar hasta que esté homogénea y filtrar a través de un tamiz US# 100. Llenar cápsulas de gelatina blanda masticables usando la formulación anterior. Dichas cápsulas de gelatina se consiguen en el mercado de compañías como R.P Scherer de San Petersburgo, Florida. Cerca de 1.84 gramos del elíxir es suministrado a la boca por medio de masticar las cápsulas y luego deglutirlas.

EXTRACTO

COMPOSICIONES QUE TIENEN SUMINISTRO DE ACTIVOS MEJORADO

El presente invento pertenece a composiciones que tienen suministro de activos farmacéuticos mejorado. Estas composiciones contienen activos farmacéuticos en un solvente. Estas composiciones pueden tomar la forma de elíxires líquidos puestos en la boca y eventualmente deglutidos o pueden ser suministrados a través de perlas rellenas de líquido, dispositivos de dosificación líquida medida, atomizadores y cápsulas comestibles liberadoras de líquido.

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APPLICATION NUMBER: ***60/156,539***
FILING DATE: ***September 29, 1999***

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COMMISSIONER OF PATENTS AND TRADEMARKS

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John M. Howell — 33,713
Attorney mailing application — Reg No

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PROVISIONAL PATENT APPLICATION COVER SHEET

APPROV

This is a request for filing a PROVISIONAL PATENT APPLICATION under 37 CFR §1.53(b)(2).

Docket Number	7805P	Type a plus sign (+) inside this box ⇒	+

INVENTOR(s) / APPLICANT(s)

LAST NAME	FIRST NAME	MIDDLE INITIAL	RESIDENCE (CITY AND EITHER STATE OR FOREIGN COUNTRY)
Drobrozsi	Douglas	J.	Loveland, OH

TITLE OF THE INVENTION (280 characters max)

COMPOSITIONS HAVING IMPROVED STABILITY

CORRESPONDENCE ADDRESS

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ENCLOSED APPLICATION PARTS *(check all that apply)*

X Specification — Number of Pages: 18 + Abstract — Small Entity Statement

_ Drawing(s) — Number of Sheets: _ — Other (specify) _

METHOD OF PAYMENT *(check one)*

_	A check or money order is enclosed to cover the Provisional filing fees	PROVISIONAL FILING FEE AMOUNT(S)	$150.00
X	The Commissioner is hereby authorized to charge filing fees specified under 37 CFR §1.19(f) and credit Deposit Account Number: 16-2480		

The invention was made by an agency of the United States Government or under a contract with an agency of United States Government.

X No

_ Yes, the name of the U. S. Government agency and the Government contract number are: _____

Respectfully submitted,

SIGNATURE John M Howell Date Sept 29, 1999

TYPED or PRINTED NAME John M. Howell REGISTRATION NO. 33,713 (*if appropriate*)

_ Additional inventors are being named on separately numbered sheets attached hereto

PROVISIONAL PATENT APPLICATION FILING ONLY

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09/28/99 U.S. PTO 60/156139
09/28/99 U.S. PTO

Case 7805P

COMPOSITIONS HAVING IMPROVED STABILITY

Douglas J. Dobrozsi

TECHNICAL FIELD

The present invention pertains to improved stability of compositions that deliver pharmaceutical active ingredients, particularly those having low water-solubility. These compositions have exceptional stability when used in various product forms including tablets, liquid elixirs placed into the mouth and eventually swallowed, or can be delivered via liquid-filled lozenges, metered liquid dosing devices, atomizers and liquid-releasing, edible capsules. Such compositions are particularly useful for treating symptoms associated with respiratory illnesses.

BACKGROUND OF THE INVENTION

Routes for delivering pharmaceutical actives include delivering actives by intranasal, pulmonary, buccal, sublingual, transdermal, and rectal administration. These routes tend to be used for avoiding first-pass metabolism of drugs that are swallowed. "First past metabolism" refers to the arrangement and order of placement of the metabolizing enzymes within the body of a human, with respect to the path followed by substances that enter the gastrointestinal tract by swallowing, and are absorbed into the general blood circulation. Items swallowed by humans, including food, drink, and medicines, enter the stomach and from there flow into the intestine. Many of the chemicals associated with the food, drink, or medicine pass through the mucosal membranes in the gastrointestinal tract and into the blood in the mesenteric veins draining from the intestine. The blood flow from the mesenteric veins passes into the liver. Metabolizing enzymes in the mucosal membranes of the intestine and in the liver can chemically alter the nature of substances passing from the intestine, through the liver, and into the common blood circulation of the body. Since all swallowed medicines are subject to the metabolizing capacity of the intestinal mucosal membranes and the liver before entering the general blood circulation of the body, frequently only a small fraction of those substances go unmetabolized, and reach the general blood circulation

Avoiding first pass metabolism can increase the bioavailability, or blood concentrations of the administered compound. Metabolic formation of metabolites of the administered compound, however, can at the same time decrease. Where formation of metabolites from the first pass metabolism is desirable, avoiding the first pass metabolism is not preferred since it logically leads to lower amounts of the metabolite in the blood. Furthermore, the blood concentrations of the active substance can increase, leading to

potential toxicity or side effects attributable to the active per se. Reducing the amount of active in the dose for avoiding toxicity, concomitantly decreases the circulating blood levels of the active metabolite. This results in loss of therapeutic affect and ultimately, benefit to the patient. In order to provide a medication that is effective and avoids unwanted side effects, the composition and its means of delivery must be modified.

Respiratory illnesses covers a broad range of ailments, including viral infections and allergic reaction to inhaled allergens. Viral infections in the upper respiratory tract of humans leads to illness usually referred to as colds, or influenza. Such an illness is quite common in the general population and can be the cause of significant discomfort and suffering. Allergen inhalation also negatively impacts a fair number in the population at the same or even at a greater degree than those having a viral infection.

There are no generally regarded effective and convenient methods for preventing viral infections or allergies. In the case of viral infections, the body's natural defense mechanisms fight the infection for a period of time normally ranging from 3 days to 2 weeks. This being the case, the most commonly employed medicines treat the uncomfortable, problematic symptoms of these respiratory ailments. These symptoms include stuffy and runny noses, soreness and inflammation in the nose and throat, fits of coughing, general aches in the body, fever, and headache. Of these symptoms, coughing in uncontrollable fits is considered by many to be the most problematic and uncomfortable. Coughing disrupts normal respiration, leading to increased headache and sore throat as well as loss of sleep to the sufferer and others living with the sufferer

The compositions used to treat the above mentioned symptoms generally fall into one of the following pharmacological classifications: antihistamines; decongestants; antitussives; expectorants; mucolytics; analgesics, antipyretic and anti-inflammatory agents. The compositions are manufactured in a number of product forms, the most common being liquid syrups and elixirs for swallowing, mouth drops and lozenges as well as inhalants and topical creams or lotions that release volatile agents that are inhaled through the nose into respiratory tract. The compositions are typically swallowed immediately, or slowly dissolved in the mouth. They typically contain actives such as guafenesin, that aids the body in the removal of excess respiratory mucus or phlegm, diphenhydramine, that lessens the negative effects including coughing and other symptoms due to histamine produced in the body in response to the viral infection, and dextromethorphan, that acts within the part of the human brain controlling the coughing reflex. Among these actives, dextromethorphan is the most commonly used active in the world for relief of cough.

Dextromethorphan, by virtue of it's physicochemical, absorption, and bioavailability properties, is a very good candidate for increasing bioavailability via

methods of administration other than swallowing. For example it has been reported in patents and pharmaceutical literature that substantial increases in bioavailability can be achieved using intranasal formulations; see H. Char *et al*, Nasal Delivery of 14-C dextromethorphan in Rats, Journal of Pharmaceutical Sciences 81:750, 1992.

SUMMARY OF THE INVENTION

What has not been realized until now is that active compounds that are combined with traditional solvents can be positively impacted when particular agents are added to the compositions. Surprisingly, adding water to a composition, particualrly one comprising low water-soluble actives improves the active's stability in such compositions.

The compositions of the present invention provide excellent delivery of actives to oral surfaces, particularly when as a peroral product. These compositions also demonstrate excellent shelf-life when incorporated into a variety of product forms including tablets, liquid-filled lozenges, metered liquid dosing devices, atomizers and liquid-releasing, edible capsules. Such compositions are particularly useful for treating symptoms associated with respiratory illnesses.

What has not been realized until now is that after careful and diligent research into pharmaceutic, therapeutic, and side effect properties of active compounds, compositions can be made to positively improve the therapeutic effect without increased side effects or toxicity. These compounds have improved stability in the product form selected to deliver such compositions. This benefit is achieved by adding to the active containing formulation agents that promote stability of the active in the formulation. These agents are effective in reducing and even eliminating instability due to the active's oxidation degradation pathway, thereby extending the shelf life of the compositions.

One object, therefore, of the present invention is to provide improved compositions for treating the symptoms associated with respiratory ailments, particularly minimizing fits of coughing. One particularly preferred composition is in the form of an anhydrous, hydrophilic liquids in a very stable enviroment for rapid delivery of actives including antitussives; antihistamines (including non-sedating antihistamines); decongestants; expectorants; mucolytics; analgesic, antipyretic and anti-inflammatory agents and local anesthetics for treating the symptoms of respiratory illnesses (is this generally true for this invention). The compositions can be dosed using a variety of product forms and, or package delivery options. The compositions of the present invention provide desired activity while minimizing potential side effects of the active compounds. It is also an objective of the subject invention to provide methods for achieving rapid transmucosal delivery of the aforementioned compositions.

Definitions and Terms

The following are definitions of terms found in the present specification:

1. transmucosal delivery:

Refers to application of drugs to the mucosal membranes of the oral cavity, including buccal (cheek), lips, gums, palates, and tongue, with the goal of the drug passing through the skin covering these places and entering the bloodstream.

2. therapeutic dose

Refers to the amount of the substance that when administered to a person in the proper form, will produce the desired effect within the body with minimal undesired side effects.

3. pharmaceutical active/active:

Refers to the chemical molecule which exerts the desired effect on the body, when administered in the proper amount and form

4. active metabolites

Refers to the chemical species of the pharmaceutical active which is formed upon the active undergoing metabolism.

5. monomolecular dispersion

Refers to the fact that molecules of the active are free and unencumbered from diffusion by association in crystalline or amorphous solid forms, or poly molecular association.

6. percent solubility value

Refers to the equilibrium solubility limit or maximum solubility of a molecule in a solvent at usual room temperature, expressed as the weight percent of the molecule in the composition.

7. anhydrous solvent

Refers to solvents containing less than about 5 % water.

DETAILED DESCRIPTION OF THE INVENTION

Pharmaceutical Actives

The compositions of the present invention comprise pharmaceutical actives also referred to herein as "actives" for treating illnesses, particularly symptoms associated with respiratory ailments such as colds, influenza as well as allergy. These actives include those frequently used for treating the most problematic symptoms including a stuffy and runny nose, soreness and inflammation in the nose and throat, fits of coughing, general aches in the body, fever, and headache. In the present invention, when actives are combined with solvents, the actives obtain enhanced transmucosal delivery into the blood In the case that active metabolites contribute to the desired therapeutic effect, this enhanced delivery is achieved without appreciably lowering the level of the corresponding active metabolites.

Furthermore, the level of active in the blood is maintained at a level that avoids unwanted side effects brought on by too high of levels of active in the blood.

The composition comprises a pharmaceutical active and a solvent. In a particularly preferred embodiment the solvent is a hydrophilic, water-miscible, anhydrous solvent wherein the pharmaceutical active in its un-ionized form has a percent solubility value in the solvent at ambient temperature that is equal to or greater than 0.075% and the pharmaceutical active is in its free, un-ionized form as a monomolecular dispersion in the solvent.

The preferable pharmaceutical actives of the present invention have molecular weight of less than 500 grams per mole, is capable of being ionized when in an aqueous solvent and has an octanol-water partition coefficient when in the un-ionized form of at least 100. The octanol-water partition coefficient is disclosed in A. Martin, P. Bustamante, and A.H.C. Chun, Physical Pharmacy, Fourth Edition, Lea and Febiger publishers, Philadelphia, 1993, page 237; herein incorporated by reference.

The actives that comprise compositions of the present invention include actives that fall into at least one of the following pharmacological classifications: antitussives; antihistamines; non-sedating antihistamines; decongestants; expectorants; mucolytics, analgesic, antipyretic anti-inflammatory agents, local anesthetics and mixtures thereof. References that describe the use of such actives include J. G. Hardman, The Pharmacologic Basis of Therapeutics, Ninth Edition, McGraw-Hill, New York, 1995. Among the actives that fall in these pharmacological classifications are those that are suited for absorption through mucosal tissues. These actives can be used alone or in combination with other actives not necessarily absorbed in this manner and may be formulated within existing formulation techniques.

When using actives intended for mucosal absorption, the concentration of actives in the solvent portion of the composition is preferably less than or equal to 125% of the percent solubility value, more preferably less than or equal to the percent solubility value of the pharmaceutical active. To maximize the benefits of the compositions of the present invention, the active is preferably in solution as monomolecular dispersion. The absorbed actives useful in the present invention are present in the solvent system at a level from about 0.075% to about 25.0%, preferably from about 0.28% to 10.0% by weight of the composition. It is preferred that said active is in it free, un-ionized form as a monomolecular dispersion in said solvent system. In the cases where either the salt forms or ionized forms of the drug active exist, it is preferred to use the uncharged free (non salt) form of the drug in the present invention.

Antitussives are actives of particularly use for arresting uncontrollable fits coughing. Antitussives useful in the present invention include, but, are not restricted to the

group consisting of codeine, dextromethorphan, dextrorphan, diphenhydramine, hydrocodone, noscapine, oxycodone, pentoxyverine and mixtures thereof. Of these antitussives, dextromethorphan is preferred. Dextromethorphan is known to have pharmacological activity as an antitussive agent and is described in US Patent 5,196,436, Smith; incorporated herein by reference. As used herein, "dextromethorphan" means racemethorphan, 3-methoxy-17-methylmorphinan (dl-cis-1,3,4,9,10,10a-hexahydro-6-methoxy-11-methyl-2H-10,4a-iminoethanophenanthrene and pharmaceutically-acceptable salts thereof. Compositions of the present comprising dextromethorphan preferably comprise from about 0.1% to about 9.3%, more preferably from about 0.26% to about 6.2% and most preferably from about 1.16% to about 4.6% dextromethorphan. Other safe and effective amounts of other cough/cold drug actives may be included in such dextromethorphan-containing compositions.

Antihistamines useful in the present invention include, but, are not restricted to the group consisting of acrivastine, azatadine, brompheniramine, chlorpheniramine, clemastine, cyproheptadine, dexbrompheniramine, dimenhydrinate, diphenhydramine, doxylamine, hydroxyzine, meclizine, pheninamine, phenyltoloxamine, promethazine, pyrilamine, tripelennamine, triprolidine and mixtures thereof. Non-sedating antihistamines useful in the present invention include, but, are not restricted to the group consisting of astemizole, cetirizine, ebastine, fexofenadine, loratidine, terfenadine, and mixtures thereof. Decongestants useful in the present invention include, but, are not restricted to the group consisting of phenylpropanolamine, pseudoephedrine, ephedrine, phenylephrine, oxymetazoline, and mixtures thereof Expectorants useful in the present invention include, but, are not restricted to the group consisting of ammonium chloride, guafenesin, ipecac fluid extract, potassium iodide and mixtures thereof. Mucolytics useful in the present invention include, but, are not restricted to the group consisting of acetylcycsteine, ambroxol, bromhexine and mixtures thereof. Analgesic, antipyretic and anti-inflammatory agents useful in the present invention include, but, are not restricted to the group consisting of acetaminophen, aspirin, diclofenac, diflunisal, etodolac, fenoprofen, flurbiprofen, ibuprofen, ketoprofen, ketorolac, nabumetone, naproxen, piroxicam, caffeine and mixtures thereof. Local anesthetics useful in the present invention include, but, are not restricted to the group consisting of lidocaine, benzocaine, phenol, dyclonine, benzonotate and mixtures thereof.

Solvents

The un-ionized form of the pharmaceutical active is maintained using a selected group of solvents. The solvent portion of compositions of the present invention comprises from about 60% to about 99.975%, preferably from 70% to about 99% and most preferably from about 85% to about 98% by weight of the composition.

The solvents of the present invention is normally liquid at ambient or room temperatures. They are water-soluble or water-miscible. Solvents of the present invention are preferably selected from the group consisting of propylene glycol, ethanol, poly(ethylene glycol) or PEG, propylene carbonate, diethylene glycol monoethyl ether, poloxamer, glycofurol, glycerol, and mixtures thereof. Propylene glycol is particularly preferred. There are mixtures of these solvents that are particularly preferred for certain product forms of the present invention. For example, if the product form is an elixir, liquid capsule or liquid containing lozenge, the solvent is a combination of propylene glycol, ethanol, and PEG. If the product form is a spray, the solvents is a combination of propylene glycol, ethanol, PEG and usually propylene carbonate. The level of each solvent that makes up these mixtures is partially dependent on aesthetic benefits sought by the formulator. Most preferable are anhydrous forms of the above solvents.

Water

Water provides a surprising stabilizing benefit to the compositions of the present invention. While not wishing to be limited by a particular mechanism, it is believed that in the present invention water acts as a quenching agent for oxy- and peroxy- radicals that create or facilitate the active's degradation prior to use of said composition. This promotes improved shelf-life of the composition as well as improved compositional efficacy when the product is stored over periods normally associated with commercial products. In the present invention the maximum level of water is about 10%, preferably from about 1% to about 10% more preferably from 5% to about 10% and most preferably from about 5% to about 8% by weight of the composition.

wherein said composition has a significant reduction of active degradation prior to use (define "prior to use" in specification).

Optional Ingredients

Ingredients normally associated with cold and influenza treatment medicines can be used with the pharmaceutical actives disclosed herein. Such ingredients are disclosed in US Patent 5,196,436, incorporated herein by reference. Additionally, the following ingredients may be used in the present invention:

Reducing Agents

The addition of reducing agents has been found to have a beneficial chemical stabilizing effect on the actives comprising the present invention. This phenomena surprisingly takes place where the active is in different phase than the reducing agent. For example, where the active is soluble in a non-polar enviroment or phase of the composition, the reducing agent selected should be a polar phase, such as water. Therefore, despite being in separate phases, the chemical stability of the active is still positively impacted. The same stability benefit is not observed when the active and the reducing agent are co-

soluble in the solvent. Therefore, the reducing agents useful in the composition depend on the active selected and its solubility.

Reducing agents are substances that have a lower redox potential than the drug or adjuvant that they are intended to protect against oxidation. Thus reducing agents are more readily oxidized than the drug or adjuvant and are effective in the presence of oxidizing agents. See W. Lund The Pharmaceutical DODEX, 12th Edition, p.290, The Pharmaceutical Press, 1994, incorporated herein by reference. Reducing agents of the present have a electrode potential value. This is defined by the Nernst equation and measured using practically standard electrochemical reference cells. The resulting values are therefore called the Standard Electrode Potential, of E^0 as measured in volts of (V). Comparing standard electrode potentials for different substances can be used to assess the effectiveness of different reducing agents; see Wells, Pharmaceutical Preformulation, Ellis Horwood Limited Publishing, 1988, pp. 168-172; incorporated herein by reference.

The reducing useful in the present invention have value greater than about -0.119V, preferably from about -0.119V to +0.250V. Preferred reducing agents are selected from the group consisting of the salts of meta bisulfite and bisulfite, including their sodium and potassium salts, dithiothreitol, thiourea, sodium thiosulphate, thioglycolic acid, terbuty hydroquinone (TBHQ), acetyl cysteine, hydroquinone and mixtures thereof.

The level of reducing agents useful in the present invention is from about 0.005% to 1.000%, preferably from about 0.500% to about 0.050%, and most preferably from about 0.100% to about 0.010% by weight of the composition. Buffers and mixtures of buffering agents, including basic buffers as single components with pKa of from 8 to 11, include triethanolamine, tromethamine, salts of amino acids, including alkaline salts of glycine, glycylglycine, glutamine or other amino acids, alkaline salts of phosphate, carbonate and mixtures thereof. The buffers provide compositional resistance to pH changes upon dilution of the composition with saliva within the range of 8 to10.

Sweeteners, including aspartame, saccharin and its salts, Sucralose™ (sold by the McNeil Specialty Products Co., New Brunswick, NJ); Prosweet™ (sold by the Virginia Dare Extract Co., New York, NY); Magnasweet™ (sold by MAFCO Worldwide Corp., Licorice Division, Camden, NJ); ammonium glycyrrhizinate, its salts, Talin™ (Thaumatin) and its diluted products, such as Talin GA90, (sold by the Talin Food Company, Birkenhead, England); and Acesulfame K, and mixtures thereof.

Flavorants, include anise, oil of peppermint, oil of clove, eucalyptus, lemon, lime, honey lemon, red fruit, mint, grapefruit, orange, cherry cola and mixtures thereof.

Sensory agents. Also useful herein are sensory agents selected from the group consisting of coolants, salivating agents, warming agents. Preferably these agents are

present in the compositions at a level of from about 0.001% to about 10 %, preferably from about 0.1% to about 1%, by weight of the composition.

Suitable cooling agents and warming agents include carboxamides, menthols, thymol, camphor, capsicum, phenol, eucalyptus oil, benzyl alcohol, salicyl alcohol, ethanol, clove bud oil, and hexylresorcinol, ketals, diols, and mixtures thereof. Preferred warming agents include thymol, camphor, capsicum, phenol, benzyl alcohol, salicyl alcohol, ethanol, clove bud oil, and hexylresorcinol, nicotinate esters such as benzyl nicotinate, ketals, diols, and mixtures thereof.

Preferred coolants are the paramenthan carboxyamide agents such as N-ethyl-p-menthan-3-carboxamide (WS-3 supplied by Sterling Organics), taught by U.S. Patent 4,136,163, issued January 23, 1979, to Watson et al., which is incorporated herein by reference in its entirety. Preferred coolants are the paramenthan carboxyamide agents such as N-ethyl-p-menthan-3-carboxamide. Another preferred paramenthan carboxyamide agent is N,2,3-trimethyl-2-isopropylbutanamide, known as "WS-23", and mixtures of WS-3 and WS-23.

Additional preferred coolants are selected from the group consisting of menthol, 3-1-menthoxypropane-1,2-diol, known as TK-10 supplied by Takasago Perfumery Co., Ltd., Tokyo, Japan, menthone glycerol acetal known as MGA, manufactured by Haarmann and Reimer, menthyl lactate known as Frescolat® manufactured by Haarmann and Reimer, and mixtures thereof.

Additonal cooling agents include cyclic sulphones and sulphoxides and others, all of which are described in U.S. Patent 4,032,661, issued June 28, 1977, to Rowsell et al., which is herein incorporated by reference.

The terms "menthol" and "menthyl" as used herein include dextro- and levoratotory isomers of these compounds and racemic mixtures thereof.

TK-10 is described in detail in U.S. Patent 4,459,425, issued July 10, 1984 to Amano et al. and incorporated herein by reference.

Salivating agents of the present invention include Jambu® manufactured by Takasago Perfumery Co., Ltd., Tokyo, Japan.

METHOD OF USE

In terms of the methods of delivery of the active, it is generally accepted that oral mucosal delivery inside the mouth must be targeted to the sub-lingual region in order to achieve a very rapid therapeutic effect; see D. Harris and J.R. Robinson, Drug Delivery via the Mucus Membranes of the Oral Cavity, Journal of Pharmaceutical Sciences 81: 1, 1992. Such dosage forms are designed to be placed under the tongue, on the floor of the mouth, and held there for some extended time. The inventors have found, however, that a large increase in bioavailability with very rapid absorption can be achieved when the subject

compositions are placed against any of the mucosal membranes of the mouth, even onto the tongue and swallowed. The form of the invention is a liquid elixir solution. It is intended to be applied to any of the mucosal membranes within the mouth. This can be achieved using a medicine dropper that is calibrated to indicate the proper amount to be administered, and squirting the elixir onto the tongue prior to swallowing. The elixir can be atomized into mouth and throat and then swallowed. It can be encapsulated into some sort of shell which makes it portable and convenient to transport and administer without having to measure the quantity of liquid elixir. Examples of encapsulation shell includes hard candies as are used for lozenges, gelatin, or starch-based shells. The elixir may be packaged into a small, disposable vial which can readily be opened and squirted into the mouth, the entire vial containing exactly one therapeutic dose. Typical dosage forms of the composition of the present invention contain no more than about 3 ml., preferable from about 0.2 ml. to about 3ml.

One preferred form is to encapsulate the liquid into a shell of hard candy or gelatin. The shell containing substances to pretreat the mucosa and thereby enhance the absorption of the active from the liquid center. The pretreatment occurs by sucking or chewing the shell material, and the advantage is gained by separating in time the treatment of the mucosa, which occurs first, followed by the presentation of the active to be absorbed. Examples of substances for pretreatment of the mucosal membranes are membrane penetration enhancers that are commonly known in the art, examples including menthol, peppermint oil, surfactants such as polysorbate 80 or poloxamer. Another example of a mucosal membrane pretreatment are buffers as listed above, which would precondition salivary micro environment pH in the range of 8 to 11.

EXAMPLES

Example I

Liquid Elixir

Item #	Material	% Comp. (w/w)
1	Dextromethorphan Base	1.466
2	Ethanol (100 %)	9.000
3	6-methyl-1,2,3-oxathiazine-4(3H)-one-2,2 Dioxide; Potasium Salt [1]	0.450
4	Propylene Glycol	80.814
5	Sodium Saccharin	0.650
6	3-Methoxypropan-1,2-diol [2]	0.100
7	Monoammonium Glycyrrhizinate	0.150

8	Peppermint Flavorant	2.000
9	Ethyl Methane Carboxamide	0.070
10	Purified Water	5.000
11	Methone Glycerine Acetal	0.300
	Total	100.000

1 Acesulfame K available from Nutrinova Inc Company of Somerset,NJ-08873,USA

2 TK 10 available from Takasago Company of Rockleigh, NJ-07657,USA

Add a portion of Ethanol to the active (Dextromethorphan base) and solid sweetening agents (Sucralose, Monoammonium glycyrrizinate) and continuously mix at low heat (30°C). To this vessel add the additional solvents (Propylene Glycol, Polyethylene Glycol 600) and liquid sweeteners (Pro-sweet Liquid K). Mix until all materials are in solution, about 2 hours time. Prepare a premix of flavorants and colorants in the remaining portion of ethanol, and add to the vessel containing the nearly completed solution. Mix until a homogenous solution is obtained, and filter through a US # 100 mesh sieve (product density = 1.07 g/ml.). Fill into amber glass bottles, and cap with an integrated cap / calibrated medicine dropper assembly.

About 1.5 grams of the elixir dropped onto the tongue and then swallowed. Dextromethorphan is rapidly absorbed into the blood.

Example II

Liquid Elixir

Item #	Material	% Comp. (w/w)
1	Dextromethorphan Base	2.055
2	Ethanol (100 %)	10.000
3	Propylene Glycol	78.285
4	Purified Water	5.000
5	Triethanolamine	3.740
6	Sucralose	0.150
7	Pro-Sweet Liquid K	0.700
8	Monoammonium Glycyrrhizinate	0.050
9	Flavorant	0.015
10	Colorant	0.005
	Total	100.000

Add a portion of Ethanol to the active (Dextromethorphan base) and solid sweetening agents (Sucralose, Monoammonium glycyrrizinate) and continuously mixed at low heat (30°C). To this vessel add the Propylene Glycol, liquid sweeteners (Pro-sweet

Liquid K), and buffer (Triethanolamine, a liquid). Mix until all materials are in solution, about 2 hours time. Prepare a premix of flavorants and colorants in the remaining portion of ethanol and water, and add to the vessel containing the nearly completed solution. Mix until a homogenous solution is obtained, and filter through a US # 100 mesh sieve (product density = 1.07 g/ml.). Fill into amber glass bottles, and cap with an integrated cap / calibrated medicine dropper assembly.

About 1.0 ml. of the elixir dropped onto the tongue and then swallowed. Dextromethorphan is rapidly absorbed into the blood.

Example III

Liquid Elixir

Item #	Material	% Comp. (w/w)
1	Propylene Glycol	80.764
2	Ethanol (100 %)	9.000
3	Purified Water	5.000
4	Sodium Metabisulfite	0.050
5	Sodium Saccharin	0.650
6	Peppermint Flavorant	2.000
7	6-methyl-1,2,3-oxathiazine-4(3H)-one-2,2 Dioxide; Potasium Salt [1]	0.450
8	3-Methoxypropan-1,2-diol [2]	0.100
9	Methone Glycerine Acetal	0.300
10	Ethyl Methane Carboxamide	0.070
11	Monoammonium Glycyrrhizinate	0.150
12	Dextromethorphan Base	1.466
	Total	100.000

1 Acesulfame K available from Nutrinova Inc Company of Somerset,NJ-08873,USA

2 TK 10 available from Takasago Company of Rockleigh, NJ-07657,USA.

Add a portion of Ethanol to the active (Dextromethorphan base) and solid sweetening agents (Sucralose, Monoammonium glycyrrizinate) and continuously mix at low heat (30°C). To this vessel add the Propylene Glycol and liquid sweeteners (Pro-sweet Liquid K). Add the sodium metabisulfide and mix until all materials are in solution, about 2 hours time. Add a premix of flavorants and colorants in the remaining portion of ethanol, and add to the vessel containing the nearly completed solution. Mix until a homogenous solution is obtained. Allow the composition to reside in the mixing vessel, open to the atmosphere for about 30 minutes. Filter the composition through a US # 100 mesh sieve

(product density = 1.07 g/ml.). Fill into amber glass bottles, and cap with an integrated cap / calibrated medicine dropper assembly.

About 1.0 ml. of the elixir dropped onto the tongue and then swallowed. Dextromethorphan is rapidly absorbed into the blood.

Example IV

Liquid Centered Lozenge

Item #	Material	% Comp. (w/w)
1	Dextromethorphan Base	2.055
2	Ethanol (100 %)	2.000
3	Purified Water	5.000
4	Propylene Glycol	84.825
5	Thioglycerol	0.050
6	Sucralose	0.300
7	Pro-Sweet Liquid K	0.700
8	Monoammonium Glycyrrhizinate	0.050
9	Flavorant	0.015
10	Colorant	0.005
	Total	100.000

Add a portion of Ethanol to the active (Dextromethorphan base) and solid sweetening agents (Sucralose, Monoammonium glycyrrizinate) and continuously mixed at low heat (30°C). To this vessel add the Propylene Glycol and liquid sweeteners (Pro-sweet Liquid K). Mix until all materials are in solution, about 2 hours time. Add the thioglycerol and mix until all materials are in solution, about 2 hours time. Add a premix of flavorants and colorants in the remaining portion of ethanol, and add to the vessel containing the nearly completed solution. Mix until a homogenous solution is obtained. Allow the composition to reside in the mixing vessel, open to the atmosphere for about 30 minutes. Mix until a homogenous solution is obtained, and filter through a US # 100 mesh sieve (product density = 1.07 g/ml.). Make individual filled lozenges containing about 1.0 ml. of liquid per lozenge by a commonly used method such as extrusion

A person places a liquid filled lozenge into the mouth and sucks on the lozenge until the liquid fill is released. Some cough relief is obtained through the action of sucking on the shell of the lozenge. When the liquid center is released, dextromethorphan is rapidly absorbed into the blood.

Example V

Liquid Centered Lozenge

Item #	Material	% Comp. (w/w)
1	Dextromethorphan Base	2.055
2	Ethanol (100 %)	2.000
3	Purified Water	5.000
4	Propylene Glycol	5.000
5	Sodium Glycinate	5.000
6	Sucralose	0.300
7	Pro-Sweet Liquid K	0.700
8	Monoammonium Glycyrrhizinate	0.050
9	Flavorant	0.015
10	Colorant	0.005
	Total	100.000

Add a portion of Ethanol to the active (Dextromethorphan base) and solid sweetening agents (Sucralose, Monoammonium glycyrrizinate) and continuously mixed at low heat (30°C). To this vessel add Propylene Glycol and liquid sweeteners (Pro-sweet Liquid K). Prepare an aqueous premix of buffer (Sodium Glycinate) and add to the vessel. Mix until all materials are in solution, about 2 hours time. Prepare a premix of flavorants and colorants in the remaining portion of ethanol, and add to the vessel containing the nearly completed solution. Mix until a homogenous solution is obtained, and filter through a US # 100 mesh sieve (product density = 1.07 g/ml.). Make individual filled lozenges containing about 1.0 ml. of liquid per lozenge by a commonly used method such as extrusion

A person places a liquid filled lozenge into the mouth and sucks until the liquid fill is released. Some cough relief is obtained through the action of sucking on the shell of the lozenge. When the liquid center is released, dextromethorphan is rapidly absorbed into the blood, and relief from coughing is obtained within 10 minutes time.

Example VI

Liquid Elixir

Items #	Material	% Comp. (w/w)
1	Dextromethorphan Base	2.055
2	Pseudoephedrine base	4.593

3	Ethanol (100%)	10.000
6	Propylene Glycol	78.892
7	Triethanolamine	3.740
8	Sucralose	0.150
9	Pro-Sweet Liquid K	0.700
10	Monoammonium Glycyrrhizinate	0.050
11	Flavorant	0.015
12	Colorant	0.005
	Total	100.000

Add a portion of Ethanol to the Dextromethorphan Base, Pseudoephedrine Base and solid sweetening agents (Sucralose, Monoammonium glycyrrizinate) and continuously mixed at low heat (about 30°C). To this vessel add the Propylene Glycol, liquid sweeteners (Pro-sweet Liquid K), and buffer (Triethanolamine, a liquid). Mix until all materials are in solution, about 2 hours time. Prepare a premix of flavorants and colorants in the propylene glycol and remaining portion of ethanol, and add to the vessel containing the nearly completed solution. Mix until a homogenous solution is obtained, and filter through a US # 100 mesh sieve (product density = 1.07 g/ml.). Fill into amber glass bottles, and cap with an integrated cap / calibrated medicine dropper assembly.

About 1.0 ml. of the elixir dropped onto the tongue and then swallowed. Dextromethorphan & pseudoephedrine is rapidly absorbed into the blood.

Example VII

Liquid Elixir

Items #	Material	% Comp. W/W
1	Chlorpheniramine base	0.263
2	Pseudoephedrine base	4.593
3	Ethanol (100%)	10.000
4	Propylene Glycol	79.124
5	Water	5.000
6	Sucralose	0.150
7	Pro-Sweet Liquid K	0.700
8	Monoammonium Glycyrrhizinate	0.050
9	Flavorant	0.015
10	Colorant	0.005
11.	Sodium sulfite	0.100

Total	100.00

Add a portion of Ethanol to the Chlorpheniramine Base, Pseudoephedrine Base and solid sweetening agents (Sucralose, Monoammonium glycyrrizinate) and continuously mixed at low heat (30°C). To this vessel add the Polyethylene Glycol 600, liquid sweeteners (Pro-sweet Liquid K), sodium sulfite and buffer (Triethanolamine, a liquid). Mix until all materials are in solution, about 2 hours time. Prepare a premix of flavorants and colorants in the propylene glycol and remaining portion of ethanol, and add to the vessel containing the nearly completed solution. Mix until a homogenous solution is obtained, and filter through a US # 100 mesh sieve (product density = 1.07 g/ml.). Fill into amber glass bottles, and cap with an integrated cap / calibrated medicine dropper assembly.

About 1.0 ml. of the elixir dropped onto the tongue and then swallowed.

Example VIII

Liquid Elixir

Items #	Material	% Comp. (w/w)
1	Acetoaminophen	27.169
2	Dextromethorphan Base	1.195
3	Pseudoephedrine Base	2.671
4	Ethanol (100%)	10.000
5	Propylene Glycol	47.069
6	Polyvinyl Pyrrolidone[1]	2.170
7	Triethanolamine	3.740
8	Sucralose	0.150
9	Pro-Sweet Liquid K	0.700
10	Monoammonium Glycyrrhizinate	0.050
11	Flavorant	0.015
12	Purified Water	5.000
13	Colorant	0.005
	Total	100.00

1 P-K17PF available from BASF.

Dissolve Dextromethorphan Base and Pseudoephedrine Base in portion of alcohol to make a premix. In separate container heat propylene glycol to about 70°C. Once all material is melted and in clear liquid form add Acetoamonophen and continue to heat to 110-120 °C with continuous mixing. Remove heat once liquid is clear. Cool it to room temperature. Add the mixture to the Dextromethorphan and Pseudoephedrine premix. Also add liquid sweetener (Pro-sweet Liquid K) and buffer (Triethanolamine).

Mix until all materials are in solution. Prepare a premix of flavorants and colorants in the remaining portion of alcohol, and add to the vessel containing the nearly completed solution. Mix until homogeneous and filter through a US #100 mesh sieve. Fill in a amber glass bottles, and cap with an integrated cap/ calibrated medicine dropper assembly. About 1.84 grams of the elixir is dropped onto the tongue and then swallowed.

Example IX

Liquid Elixir

Items #	Material	% Comp. (w/w)
1	Ethanol (100%)	88.534
2	Water	10.000
3	Dextromethorphan Base	1.466
	Total	100.00

Dissolve Dextromethorphan Base in portion of alcohol to make a premix. In separate container heat water and meta Bisulfite to about 70°C. Mix until uniform and cool to room temperature. Add this mixture to the Dextromethorphan Base.

Mix until all materials are in solution. Add the remaining portion of to the vessel containing the nearly completed solution. Mix until homogeneous and filter through a US #100 mesh sieve. Fill in a amber glass bottles, and cap with an integrated cap/ calibrated medicine dropper assembly. About 1.84 grams of the elixir is dropped onto the tongue and then swallowed.

Example X

chewable soft gellatin capsules

Items #	Material	% Comp. (w/w)
1	Polyethylene Glycol	35.159
2.	Glycerine	10.000
3	Dextromethorphan Base	1.100
4	Acetoaminophen	32.500
5	Pseudoephedrine Base	2.671
6	Polyvinyl Pyrrolidone	4.170
7	Aesthetics package[1]	4.000
8	Water	10.000
	Total	100.00

1. see above examples

Dissolve Dextromethorphan Base in portion of alcohol to make a premix. In separate container heat water and meta Bisulfite to about 70°C. Add acetoamonophen and continue to heat to 110-120 °C with continuous mixing. Remove heat once liquid is clear. Cool it to room temperature. Add the mixture to the Dextromethorphan and PseudoephedrineMix until uniform and cool to room temperature. Mix until all materials are in solution. Add the remaining portion of alcohol, polyvinyl pyrrolidone and the aesthetics package to the vessel containing the nearly completed solution. Mix until homogeneous and filter through a US #100 mesh sieve. Fill chewable soft gellatin capsules using the above formulation. Said gelatin capsules are available from the trade by companies such as R. P. Scherer, of St. Petersberg, Florida. About 1.84 grams of the elixir is delivered to the mouth by mastication of the capsule(s) and then swallowed

Example XI

Liquid Elixir

Items #	Material	% Comp. (w/w)
1	Propylene Glycol	75.000
2	Glycerine	10.000
3	Dex Base	1.100
4	Aesthetics package	4.000
5	Water	10.000
	Total	100.00

1. see above examples

Dissolve Dextromethorphan Base in portion of alcohol to make a premix. In separate container heat water to about 70°C. Remove heat once liquid is clear. Cool it to room temperature. Add the mixture to the Dextromethorphan. Mix until uniform and cool to room temperature. Mix until all materials are in solution. Add the remaining portion of alcohol and the aesthetics package to the vessel containing the nearly completed solution. Allow the composition to reside in the mixing vessel, open to the atmosphere for about 10 minutes. Mix until homogeneous and filter through a US #100 mesh sieve. Fill chewable soft gellatin capsules using the above formulation. Said gelatin capsules are available from the trade by companies such as R. P. Scherer, of St. Petersberg, Florida. About 1.84 grams of the elixir is delivered to the mouth by mastication of the capsule(s) and then swallowed.

WE CLAIM:

ABSTRACT

COMPOSITIONS HAVING IMPROVED DELIVERY OF ACTIVES

The present invention pertains to compositions having improved delivery of pharmaceutical actives. These compositions comprise pharmaceutical actives in an solvent. These compositions may take the form of liquid elixirs placed into the mouth and eventually swallowed, or can be delivered via liquid-filled drops, metered liquid dosing devices, atomizers and liquid-releasing, edible capsules.

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Date of Deposit September 29, 1999

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