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

Re: Expediente No. 00001049
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 el siguiente documento:

Copia certificada de la solicitud de Patente Número 60/115, 378 presentada en los Estados Unidos de América el día 11 de enero de 1999, con la debida traducción de lo pertinente, incluyendo el capítulo reivindicatorio.

Señor Superintendente,

JIMENA ESCOBAR URIBE
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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

Diciembre 02, 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: 60/115,378

Fecha de Presentación: Enero 11, 1999

Por la autoridad del
Comisionado de Patentes y Marcas

(fdo) H.L. JACKSON
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) ó 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 179806

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

December 02, 1999

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

H. L. Jackson

H. L. JACKSON
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

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

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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.

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.

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.

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:

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.

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.