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(54) Title: COMPOSITIONS HAVING IMPROVED STABILITY

(57) Abstract: The present invention pertains to improved stability of compositions that deliver pharmaceutical active ingredients. These compositions have exceptional stability when used in various product forms including 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.

COMPOSITIONS HAVING IMPROVED STABILITY

TECHNICAL FIELD

5 The present invention pertains to improved stability of compositions that deliver pharmaceutical active ingredients. These compositions have exceptional stability when used in various product forms including 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
10 associated with respiratory illnesses.

BACKGROUND OF THE INVENTION

Routes for delivering pharmaceutical actives include delivering actives by intranasal, pulmonary, buccal, sublingual, transdermal, vaginal and rectal and ocular administration. However, most common are compositions that are swallowed. When these compositions are
15 swallowed, they enter the gastrointestinal tract 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
20 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.

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
25 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
30 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 guaifenesin, 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.

US Patent 4,839,176, Pankhania et al. to Boots Company, issued June 13, 1989, discloses the use of bisulfites in making tablets comprising CMC that avoid degradation. US Patent 4,474,985, Keel et al., September 25, 1993 to Monsanto, discloses a process for increasing the color-free shelf life of a crude N-aminophenol. The process comprises dissolving the crude N-acetyl aminophenol in a solvent containing a reducing agent, such as metabisulfite US Patent 4,478,822, issued Oct. 23, 1984 and US Patent 4,474,752, issued Oct. 2, 1984 both to Haslam et al, and assigned to Merck & Co. claim gel compositions comprising polymers that provide gelling of the liquid when entering the body cavity. Disclosed is a group of microbiological preservatives including sodium bisulfite and sodium thiosulfate. The art known to the applicants does not demonstrate a specific chemical stabilization benefit by the inclusion of solution or liquid-based product forms.

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, certain combining chelating agents and reducing agents in liquid compositions comprising pharmaceutical actives improves the active's stability in such compositions.

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

What has not been realized until now is that after careful and diligent research into pharmaceutical, 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.
10 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.

It would be desirable 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 environment 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. 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 would further be desirable 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 sites 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

The present invention provides an oral liquid composition having improved stability comprising a pharmaceutical active, solvent to solubilize said active and a chelating agent present in a phase of the composition other than the phase of the composition containing said active.

The present invention further provides an oral liquid composition having improved stability comprising a pharmaceutical active, solvent to solubilize said active, chelating agent and reducing agent having Electrode Potential value E° greater than about -0.119V.

The present invention yet further provides an oral liquid composition having improved stability comprising a pharmaceutical active, solvent to solubilize said active, chelating agent present in a phase of the composition other than that containing said active and reducing agent having Electrode Potential value E° greater than about -0.119V.

The present invention still further provides a method of treating respiratory illness by orally administering the composition described herein against any mucosal membrane of the mouth.

The present invention yet further provides a method of treating a respiratory illness by oral administration of compositions as described herein, said composition has a total dosage volume of no more than 3.0 mls.

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; see US Patent 5,196,436, Smith, issued May 23, 1993; incorporated herein by reference. In the present invention, when actives are combined with certain materials in formulations for delivery of the active, utilizing particular materials to enhance long term stability of the formulation is an important benefit. In a stable formulation the actives are efficiently delivered to produce a positive impact.

The composition comprises a pharmaceutical active and a stabilizing material along with other commonly known ingredients to make a composition for delivery of said actives. In a particularly preferred embodiment the composition comprises a solvent that 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.

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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
5 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-
10 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
15 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
20 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 its 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
25 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, dextrophan, diphenhydramine, hydrocodone, noscapine, oxycodone, pentoxyverine, morphine, pholcodeine and mixtures thereof. Of these antitussives,
30 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-1,3,4,9,10a-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.

- 5 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, pheniramine, phenyltoloxamine, promethazine, pyrilamine, tripelemamine, triprolidine and mixtures thereof. Non-sedating antihistamines useful in the
- 10 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
- 15 ammonium chloride, guaifenesin, ipecac fluid extract, potassium iodide and mixtures thereof. Mucolytics useful in the present invention include, but, are not restricted to the group consisting of acetylcysteine, 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
- 20 thereof. Local anesthetics useful in the present invention include, but, are not restricted to the group consisting of lidocaine, benzocaine, phenol, dyclonine, benzonotatate and mixtures thereof.

Solvents

- The un-ionized form of the pharmaceutical active is maintained using a selected group of
- 25 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 solvent of the present invention is normally liquid at ambient or room temperatures. It is water-soluble or water-miscible. Solvents of the present invention are preferably selected
- 30 from the group consisting of propylene glycol, ethanol, poly(ethylene glycol) or PEG, propylene carbonate, diethylene glycol monoethyl ether, poloxamer, glycofurol, glycerol, polyvinylpyrrolidone (PVP), Transcutol™ (2-(2 ethoxyethoxy) ethanol), Lauroglycol 90™ (fatty acid esters and propylene glycol), Labrasol™ (glyceryl and polyethylene glycol esters), Capryol 90™ (propylene glycol monocaprylate and mixtures thereof all available from

Gattefosse SA. Company of 69804 Saint Priest Cedex, France. Propylene glycol and ethanol 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.

Chelating Agents

10 The addition of chelating agents have been found to have a beneficial chemical stabilizing effect on the actives comprising the present invention. This phenomena surprisingly takes place where the chelating agent is present in a phase of the composition other than the phase of the composition containing the active. For example, where the active is soluble in a non-polar environment or phase of the composition, the chelating agent selected could be a polar phase, 15 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 chelating agent are co-soluble in the solvent. Therefore, the chelating agents useful in the composition depend on the active selected and its solubility.

Chelating agents useful in the present invention include those that chelate transition 20 metal ions such as iron, copper, zinc and other such metals. Not to be bound by theory, it is reasonable to postulate that metal cations play major role in the formation of oxidizing species. The free radical producing reactions involve the transfer of electrons by redox cycling between two different valence stages. Trace amount of heavy metal ions often catalyze auto-oxidation reaction. In fact as little as 0.05 ppm metal ions may be sufficient to initiate the oxidation and 25 enhance the rate of propagation of the chain reaction. See W. Lund, The Pharmaceutical CODEX, 12th Edition, p.287 & 290 The Pharmaceutical Press, 1994, incorporated herein by reference

Chelating agents have been shown to reduce the facileness of the electron transfer reactions between these valance stages. This characteristic of chelating agents dampens auto-oxidation reactions. This could explain why chelating agents are effective in protecting 30 pharmaceutical actives. The rate and extent of oxidation is known to be greater at alkaline pH than acidic pH values. This may be due in part to what appears to be a greater tendency of the divalent cations to catalyze oxidation reactions in alkaline medium. See Townsend M.W. and Byron P.R. "The Effect of Formulation Additives on Degradation of Freeze-Dried Ribonuclease

A", Pharmaceutical Research Vol. 7, No. 10, pp.1086-1091 (1990). Several other drug compounds having nitrogen in their side chain have been shown to be stabilized by EDTA; see Fog A.G. & Summan A.M. EDTA was shown to be effective in stabilizing acetamido groups in Drug and food coloring compounds from degradation by light when in presence of ascorbic acid; 5 "Journal of Clinical Pharmacology and Therapeutics", Vol. 17, pp. 107-109 (1992).

The chelating agents useful in present invention are stable and effective in non-aqueous and aqueous medium and in pH range between 5 to 12. Preferred chelating agents are selected from the group consisting of disodium and calcium salts of Ethylene diamine tetraacetic acid (EDTA), tetrasodium EDTA, sodium hexametaphosphate (SHMP), citric acid, phosphoric acid, 10 Di(hydroxyethyl)glycine, 8-hydroxyquinoline and mixtures thereof.

The level of chelating agents useful in the present invention depends on the load of metal ions likely to be introduced into the formulation by way of contamination of the ingredients. In the present invention, the chelating agents are used at levels from about 0.005% to 1.000%, preferably from about 0.150% to about 0.050%, and most preferably from about 0.300% to about 15 0.010% by weight of the composition.

Reducing Agents

It has also been observed that when a reducing agent is in the presence of the chelating agent of the present invention as described above, the reducing agent has significantly increased shelf life. This is the case even where the chelating agent is at low levels, as little as 0.001%, in 20 the formulation. The extended shelf life translates to an improvement in terms of the reducing agent's effectiveness as antioxidant over prolonged period. Not to be bound by theory, it's believed that the reaction of reduction (oxidation of reducing agent) takes a different course when a chelating agent is present. In presence of chelating agent, the initiative process should depend upon the generation of superoxide radicals whereas in absence of chelating agent radicals other 25 than $O_2^{\cdot -}$ (oxidizing species) will be involved as initiating species. Chelating agents, therefore, are capable of playing a dual role in the aerobic oxidation of reducing agents. It complexes trace metals which could catalyze spontaneous oxidation and thus change the mechanism of initiation. It can also act as chain breaker by scavenging the oxidizing radicals which propagate the reaction chain. Therefore, the reducing agent's chemical stabilizing effect on the actives comprising the 30 present invention is dramatically increased. 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 environment or phase of the composition, the reducing agent selected should be soluble in 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 an Electrode Potential value E^0 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 0.050% to about 0.500%, and most preferably from about 0.010% to 0.200% by weight of the composition.

The reducing agent protects the pharmaceutical active in the invention from degrading by acting as a donor-oxidizing compound that sacrifices itself to oxidation rather than the active itself. Chelators also afford some practical protection by chelating the metal ions present in formulation ingredients including flavorings, coolants and sweeteners as well as the potential migration of metal ions from packaging materials. In the absence of such metal ions, there is little or no generation of oxy and peroxy radicals generated by metal catalysis. This results in stabilizing the pharmaceutical actives.

While the additive effect of using any reducing agent and chelating agents together may not be surprising, the benefits found by using these particular reducing agents is surprising. Furthermore, the benefits observed by using levels of chelators in excess of that required to chelate all the metal ions in a system not continuously generating metal ions is also surprising. While not wishing to be bound by theory, it is believed that in the presence of an excessive level of a chelating agent such as EDTA, the degradation of a reducing agent such as metabisulfite is

surprisingly retarded. Sustaining the presence of the reducing agent in the composition of the present invention serves to preserve higher levels of pharmaceutical actives in that composition.

Optional Ingredients

Water may be used in compositions of the present invention. 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.

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, 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 to 10.

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 to 10.

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™ (Thaumatococcus) and its diluted products, such as Talin GA90, (sold by the Talin Food Company, Birkenhead, England); and Acesulfame K, and mixtures thereof. Since the products made with sweeteners are orally consumed it is preferable that products such as lozenges utilize sweeteners that are sugar free, or non-cariogenic. This means that the sweetener will not be metabolized by cariogenic bacteria in the oral cavity and hence they cannot generate an acidic environment. If this is not possible, then the products may be formulated to contain an alkaline buffer with a pKa of greater than 7, preferably 8 for preconditioning the oral cavity.

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.

5 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.

10 Preferred coolants are the paramenthan carboxamide 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 carboxamide agents such as N-ethyl-p-menthan-3-carboxamide. Another preferred paramenthan carboxamide agent is N,2,3-trimethyl-2-
15 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
20 thereof.

Additional cooling agents include cyclic sulphones and sulfoxides 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 levorotatory
25 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.

30 METHOD OF USE

The delivery of drugs into the bloodstream by placing a dosage form into the mouth can be classified into two major subclasses dependent upon the desired action. In one case where the drug is delivered into the blood absorption after swallowing (i.e. from the stomach, small intestine or colon) and in the other case where absorption, or a significant percentage of the absorbance

occurs through the membranes of the oral cavity either immediately or via over extended time periods due to retention of the drug by mucoadhesive materials. This route is generally referred to as "Buccal" or "oral mucosal" absorption' versus the former which is classically called the peroral route. The Peroral route of drug delivery is by far the most commonly used in all of
5 medicine, has been well studied, and is explained in detail in: Mayerson, M., Principles of Drug Absorption; Chapter 2 in "Modern Pharmaceutics", 2nd ed., G.S. Banker and C.T. Rhodes, editors, Marcel Dekker Inc., New York. 1990.

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
10 rapid therapeutic effect; see D. Harris and J.R. Robinson, Drug Delivery via the Mucous 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
15 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
20 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 or poured into the mouth, the entire vial containing exactly one therapeutic dose. Typical dosage
25 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,
30 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	Propylene Glycol	80.664
2	Ethanol (100 %)	9.000
3	Purified Water	5.000
4	Disodium Ethylene diamine tetraacetate (Disodium EDTA)	0.050
5	Sodium Saccharin	0.650
6	Peppermint Flavorant	2.000
7	Acesulfame K ¹	0.450
8	Takasago 10 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
13	Sodium Metabisulfite	0.10
Total		100.000

5 ¹ Acesulfame K available 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 glycyrrhizinate) and continuously mix at low heat (30°C). To this vessel add the Propylene Glycol and liquid sweeteners (Pro-sweet Liquid K). Combine the
 10 the chelating agent (disodium EDTA), reducing agent (sodium metabisulfite) and water together and mix until uniform. Add the mixture to the vessel and mix for 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 10 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 1.5 grams of the elixir dropped onto the tongue and then swallowed.

Dextromethorphan is rapidly absorbed into the blood.

Example II

5 Liquid Elixir

Item #	Material	% Comp. (w/w)
1	Dextromethorphan Base	2.055
2	Ethanol (100 %)	10.000
3	Propylene Glycol	63.075
4	Di sodium Ethylene diamine tetra acetate (EDTA)	0.1%
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
11	Guaiphenesin	20.00
12	Sodium Metabisulfite	0.200

Total 100.000

- Add a portion of Ethanol to the active (Dextromethorphan base) and solid sweetening agents (Sucralose, Monoammonium glycyrrhizinate) 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). Add the disodium EDTA, sodium metabisulfite and water to gather
- 10 and mix until clear. Add mixture to the vessel, add guaiphenesin and continue mixing for about 2 hrs. 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 10 minutes. Mix until a homogenous solution is obtained, and filter through a US # 100 mesh
- 15 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	Sodium hexametaphosphate (SHMP)	0.050
3	Propylene Glycol	95.355
5	Sucralose	0.300
6	Pro-Sweet Liquid K	0.700
7	Monoammonium Glycyrrhizinate	0.050
8	Flavorant	0.015
9	Colorant ¹	0.005
10	Sodium Thiosulphate	0.100

Total 100.000

1. Green Shade CSL-15689 obtained from the Warner Jenkins Co., St. Louis, MO, USA.

- 5 Add a portion of propylene glycol 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 propylene glycol and liquid sweeteners (Pro-sweet Liquid K). Dissolve sodium hexametaphosphate (SHMP) and sodium thiosulphate in water and mix until clear. Add mix to vessel and mix until all materials are in solution, about 2 hours time.
- 10 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 10 minutes. 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
- 15 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

20 there.

Example IV

Liquid Spray

Item #	Material	% Comp. (w/w)
1	Dextromethorphan Base	3.425
2	Ethanol (100 %)	5.350
3	Propylene Glycol	41.315
4	Propylene Carbonate	40.000
5	Triethanolamine	3.740
6	Disodium Editic Acid (Disodium EDTA)	0.050
7	Sucralose	0.300
8	Pro-Sweet Liquid K	0.700
9	Monoammonium Glycyrhizinate	0.050
10	Flavorant	0.015
11	Purified Water	5.000
12	Potassium Metabisulfite	0.050
13	Colorant	0.005

Total 100.000

- Add a portion of Ethanol to the active (Dextromethorphan base) and solid sweetening agents (sucralose, monoammonium glycyrrhizinate) and continuously mixed at low heat (30°C). To this vessel add the additional Propylene Carbonate and Propylene Glycol, liquid sweeteners
- 5 (Pro-sweet Liquid K) reducing agent and buffer (Triethanolamine, a liquid). Mix until all materials are in solution, about 2 hours time. Allow the composition to reside in the mixing vessel, open to the atmosphere for about 10 minutes. 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
- 10 (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	Propylene Glycol	89.775
5	Disodium Ethylenediaminetetraacetate	0.050
6	Sucralose	0.300
7	Pro-Sweet Liquid K	0.700
8	Monoammonium Glycyrhizinate	0.050
9	Flavorant	0.015
10	Colorant	0.005
11.	Sodium Metabisulfite	0.050

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).

- 5 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. Mix until a homogenous solution is obtained. Prepare a premix of flavorants and colorants in the remaining portion of ethanol, disodium EDTA, sodium metabisulfite and water, and add to the vessel containing the nearly completed solution. Allow the composition to reside in the mixing vessel, open to the atmosphere for about 10
- 10 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
- 15 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	Propylene Glycol	79.725
5	Disodium ethylenediaminetetraacetate (EDTA)	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
11	Fatty acid esters and propylene glycol ¹	10.00
12	Sodium Metabisulfite	0.100

Total 100.000

1. Lauroglycol 90 available from Gattefosse SA. Company
of 69804 Saint Priest Cedex, France

- Add a portion of Ethanol to the active (Dextromethorphan Base) and solid sweetening agents (sucralose, monoammonium glycyrrhizinate) and continuously mixed at low heat (30°C). To this vessel add the propylene glycol, fatty acid esters and propylene glycol and liquid sweeteners (Pro-sweet Liquid K). Prepare an aqueous premix of disodium EDTA, sodium metabisulfite 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. Allow the composition to reside in the mixing vessel, open to the atmosphere for about 10 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

- 15 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	Guaifenesine	20.00
3	Ethanol (100%)	10.000
4	Propylene Glycol	53.135
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
11	Disodium Ethylene diamine tetra acetate (Disodium EDTA)	0.050
12	2-(2 ethoxyethoxy) ethanol ¹	10.00
13	Sodium Metabisulfite	0.100
Total		100.000

1. Transcutol P available Gattefosse SA. Company of 69804 Saint Priest Cedex, France

- Add a portion of Ethanol to the active (Dextromethorphan base) and solid sweetening agents (Sucralose, Monoammonium glycyrrhizinate) and continuously mixed at low heat (30°C). To this vessel add the bulk of the propylene glycol, 2-(2 ethoxyethoxy) ethanol, Guaifenesine and 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 portions of water and ethanol as well as the disodium EDTA and sodium metabisulfite 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	Chlorpheniramine Base	0.263
2	Pseudoephedrine Base	4.593
3	Ethanol (100%)	10.000
4	Propylene Glycol	83.974
5	Sucralose	0.150
6	Pro-Sweet Liquid K	0.700
7	Monoammonium Glycyrrhizinate	0.050
8	Flavorant	0.015
9	Colorant	0.005
10	Di(Hydroxyethyl)glycine	0.050
11	Disodium EDTA	0.10
12.	Sodium Metabisulfite	0.10
Total		100.000

Add a portion of Ethanol to the actives (Chlorpheniramine base & Pseudoephedrine base) and solid sweetening agents (Sucralose, Monoammonium glycyrrizinate) and continuously mixed at low heat (30°C). To this vessel add the bulk of the propylene glycol, liquid sweeteners (Pro-sweet Liquid K), di(hydroxyethyl)glycine 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, disodium EDTA, sodium metabisulfite 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.

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

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	Propylene Glycol	51.885
5	Polyvinyl pyrrolidone ¹	2.170
6	Triethanolamine	3.740
7	Sucralose	0.150
8	Pro-Sweet Liquid K	0.700
9	Monoammonium Glycyrhizinate	0.050
10	Flavorant	0.015
11	Colorant	0.005
12	Sodium Metabisulfite	0.050
13	Disodium EDTA	0.200
Total		100.000

¹ PVP-K17PF available from BASF Corp.

- 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 Acetoaminophen 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. 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 disodium EDTA and sodium metabisulfite 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 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

Liquid Elixir

Items #	Material	% Comp. (w/w)

1	Ethanol (100%)	88.334
2	Water	10.00
3	Dextromethorphan Base	1.466
4	Ethylene diamine tetra acetic acid (EDTA)	0.10
5.	Sodium Metabisulfite	0.10
Total		100.000

Dissolve Dextromethorphan Base in portion of alcohol to make a premix. In separate container add disodium EDTA and sodium metabisulfite to water and mix until uniform. Add this mixture to the Dextromethorphan Base premix.

- 5 Mix until all materials are in solution. Add remaining portion of alcohol. 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 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 XI

Liquid Elixir

Items #	Material	% Comp.
		(w/w)
1	Ethanol (100%)	84.434
2	Water	10.00
3	Dextromethorphan Base	1.466
4	Ethylene diamine tetra acetic acid (EDTA)	0.05
5	Aesthetics package ¹	4.000
6.	Sodium Metabisulfite	0.05
Total		100.000

¹ see above examples

- 10 Dissolve Dextromethorphan Base in portion of alcohol to make a premix. In separate container dissolve EDTA and sodium metabisulphite in water. 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 alcohol, EDTA 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 in a amber glass bottles, and
- 5 cap with an integrated cap/ calibrated medicine dropper assembly. About 1.5 grams of the elixir is dropped onto the tongue and then swallowed.

Example XII

chewable soft gelatin capsules

Items #	Material	% Comp.
		(w/w)
1	Propylene Glycol	25.572
2	Glycerine	10.000
3	Dextromethorphan Base	1.100
4	Acetoaminophen Base	32.500
5	Pseudoephedrine Base	2.458
6	Polyvinyl pyrrolidone	4.170
7	Aesthetics package ¹	4.000
8	Water	10.000
9	Disodium calcium Ethylenediaminetetraacetate (EDTA)	0.050
10.	Glyceryl and polyethylene glycol esters ²	10.00
11.	Sodium Metabisulfite	0.15
Total		100.000

1 see above examples

2 Labrasol available Gattefosse SA. Company of 69804 Saint Priest Cedex, France

- Dissolve Dextromethorphan Base in portion of alcohol to make a premix. In separate
- 10 container heat water and disodium calcium EDTA to about 70°C. Add acetoaminophen 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 Mix until uniform and cool to room temperature. Mix until all materials are in solution. Add the remaining

- portion of alcohol, polyvinyl pyrrolidone, sodium metabisulfite, glyceryl and polyethylene glycol esters 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 gelatin capsules
- 5 using the above formulation. Said gelatin capsules are available from the trade by companies such as R. P. Scherer, of St. Petersburg, Florida. About 1.84 grams of the elixir is delivered to the mouth by mastication of the capsule(s) and then swallowed.

Example XIII

chewable soft gelatin capsules

Items #	Material	% Comp.
		(w/w)
1	Propylene Glycol	74.750
2	Glycerine	10.000
3	Dextromethorphan Base	1.100
4	Aesthetics package ¹	4.000
5	Water	10.000
6	Disodium calcium ethylenediaminetetraacetate (EDTA)	0.050
7	Sodium Metabisulfite	0.10
Total		100.000

¹ see above examples

- Dissolve Dextromethorphan Base in portion of alcohol to make a premix. In separate
- 10 container mix water, sodium metabisulfite and disodium calcium EDTA. until 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
- 15 until homogeneous and filter through a US #100 mesh sieve. Fill chewable soft gelatin capsules using the above formulation. Said gelatin capsules are available from the trade by companies such as R. P. Scherer, of St. Petersburg, Florida. About 1.84 grams of the elixir is delivered to the mouth by mastication of the capsule(s) and then swallowed.

Example XIV

Liquid Elixir

Items #	Material	% Comp.
		(w/w)
1	Dextromethorphan Base	0.714
2	Propylene glycol	20.2
3	Ethanol (95%)	24.3
4	Polyethylene glycol ¹	22.6
5	Disodium EDTA	0.100
6	Flavorants	0.340
7	Color	0.034
8	Phenol	2.14
9	Sodium Saccharin	0.150
10	Purified Water	28.922
11	Sodium Metabisulfite	0.50
Total		100.000

¹ Carbowax 400 available from Union Carbide

- Add the dextromethorphan and phenol to the propylene glycol with stirring. Add incrementally with stirring the polyethylene glycol, alcohol, flavorants, and sodium saccharin. Add the monobasic sodium phosphate as a 10% solution in purified water with stirring. Add the colorant as a water solution with stirring. Dissolve sodium metabisulfite to remaining quantity of water and add, with stirring to the final volume.

Example XV

Liquid Elixir

Items #	Material	% Comp.
		(w/w)
1	Dextromethorphan Base	0.286
2	Propylene glycol	20.45
3	Ethanol (95%)	16.3
4	Polyethylene glycol ¹	22.6
5	Monobasic sodium phosphate	0.240
6	Flavorants	0.004
7	Color	0.034

8	Sodium Saccharin	0.200
9	Disodium EDTA	0.1
10	Purified Water	39.586
11.	Sodium Metabisulfite	0.20
Total		100.000

¹ Carbowax 400 available from Union Carbide.

- Add the dextromethorphan to the propylene glycol with stirring. The polyethylene glycol, alcohol, flavorants, and sodium saccharin are added incrementally with stirring. Add with stirring the monobasic sodium phosphate as a 10% solution in purified water. The colorant is added as a water solution with stirring. Dissolve sodium metabisulfite to remaining quantity of water and add, with stirring to the final volume.

Example XVI:

Liquid for Oral Application

Items #	Material	% Comp (w/w)
1.	Dextromethorphan Base	1.47
2.	Poloxamer ¹	33.56
3.	Ethanol	10.51
4	Sodium Saccharin	0.3
5.	Monoammonium Glycerizinate	0.05
6.	Flavors	1.40
7.	Water	13.42
8.	Sodium Metabisulfite	0.1
9.	Disodium EDTA	0.1
10.	Propylene glycol	39.09

Total 100

1. Poloxamer (Pluronic F127) available from BASF Specialty Chemicals, Mount Olive, N.J.

10 Preparation:

Add propylene glycol and poloxamer to a clean vessel (main mix). While stirring, heat the mixture as appropriate to sufficiently melt the poloxamer. Once a uniform solution is obtained remove from heat source and continue mixing. In a separate vessel (alcohol pre-mix) add alcohol, dextromethorphan base and monoammonium glycerizinate and mix until uniform.

- 15 In another vessel (water pre-mix), add water, EDTA, sodium saccharin, acesulfame and sodium

metabisulfite. Mix until all materials are dissolved.

- Add the alcohol containing premix to the main mixing vessel containing the poloxamer. Mix until uniform. While stirring, add the water containing premix to the main vessel and continue to mix until uniform. Subsequently, add desired flavor component and mix until uniform. About 1.5gm of liquid is delivered to the mouth with a suitable device.

Example XVII:

Liquid for Treatment of Cough

Items #	Component	% Comp (w/w)
1.	Dextromethorphan Base	1.465
2.	Guaifenesine	20.00
3.	Sodium Metabisulfite	0.10
4.	Disodium EDTA	0.10
5.	Sodium Saccharin	0.40
6.	Monoammonium Glyzeriizinate	0.15
7.	Acesulfame	0.50
8.	Ethanol	10.51
9.	Water	24.61
10.	Propylene Glycol	10.95
11.	Poloxamer	29.08
12.	Flavor	1.40

Total

100

1. Pluronic F127 (BASF Specialty Chemicals, Mount Olive, N.J.)

Preparation:

- 10 Add propylene glycol and poloxamer to a clean vessel (main mix). While stirring, heat the mixture as appropriate to sufficiently melt the poloxamer. Once a uniform solution is obtained remove from heat source and continue mixing. In a separate vessel (alcohol pre-mix) add alcohol, guaifenesin, dextromethorphan base and monoammonium glyzeriizinate and mix until uniform. In another vessel (water pre-mix), add water, EDTA, sodium saccharin, 15 acesulfame and sodium metabisulfite. Mix until all materials are dissolved.

Add the alcohol containing premix to the main mixing vessel containing the poloxamer. Mix until uniform. While stirring, add the water containing premix to the main vessel and continue to mix until uniform. Subsequently, add desired flavor component and mix until

uniform. About 1 gm liquid is delivered to the mouth by a suitable delivery device.

Example XVIII:

Liquid for Oral Administration

Items #	Component	% Comp (w/w)
1.	Dextromethorphan Base	2.20
2.	Sodium Metabisulfite	0.10
3.	Disodium EDTA	0.10
4.	Sodium Saccharin	0.40
5.	Monoammonium Glyzerizinate	0.15
6.	Acesulfame	0.50
7.	Flavor	1.40
8.	Pseudoephedrine Hydrochloride	6.00
9.	Poloxamer ¹	34.5
10.	Propylene Glycol	30.72
11.	Ethanol	10.51
12.	Water	13.42
Total		100

- 5 1. Pluronic F127 (BASF Specialty Chemicals, Mount Olive, N.J.)

Preparation:

Add propylene glycol and poloxamer to a clean vessel (main mix). While stirring, heat the mixture as appropriate to sufficiently melt the poloxamer. Once a uniform solution is obtained remove from heat source and continue mixing. In a separate vessel (alcohol pre-mix) add alcohol, dextromethorphan base and monoammonium glyzerizinate and mix until uniform. In another vessel (water pre-mix), add water, Pseudoephedrine HCl, EDTA, sodium saccharin, acesulfame and sodium metabisulfite. Mix until all materials are dissolved.

- 10 Add the alcohol containing premix to the main mixing vessel containing the poloxamer. Mix until uniform. While stirring, add the water containing premix to the main vessel and
15 continue to mix until uniform. Subsequently, add desired flavor component and mix until uniform. About 1 gm liquid is delivered to the mouth by a suitable delivery device.

Example XIX:

Liquid Elixir

Items #	Material	% Comp. (w/w)
1	Ethanol (100%)	88.334
2	Water	10.00
3	Dextromethorphan Base	1.466
4	Ethylene diamine tetra acetic acid (EDTA)	0.10
5.	Sodium Metabisulfite	0.10
Total		100.000

Dissolve Dextromethorphan Base in portion of alcohol to make a premix. In separate container add disodium EDTA and sodium metabisulfite to water and mix until uniform. Add this mixture to the Dextromethorphan Base premix.

- 5 Mix until all materials are in solution. Add remaining portion of alcohol. 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 in a amber glass bottles, and cap with an integrated cap/ calibrated medicine dropper assembly. About 1.00 grams of the elixir is dropped onto the tongue and then swallowed or dose appropriately by varying dose volume.

Throughout the description and claims of the specification the word "comprise" and variations of the word, such as "comprising" and "comprises", is not intended to exclude other additives, components, integers or steps.

The discussion of the background to the invention herein is included to explain the context of the invention. This is not to be taken as an admission that any of the material referred to was published, known or part of the common general knowledge in Australia as at the priority date of any of the claims.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. An oral liquid composition having improved stability comprising a pharmaceutical active, solvent to solubilize said active and a chelating agent present in a phase of the composition other than the phase of the composition containing said active.
2. An oral liquid composition having improved stability comprising a pharmaceutical active, solvent to solubilize said active, chelating agent and reducing agent having Electrode Potential value E° greater than about -0.119V.
3. The liquid composition according to claim 2 wherein said reducing agent has an Electrode Potential value E° from about -0.119V to +0.250V.
4. An oral liquid composition having improved stability comprising a pharmaceutical active, solvent to solubilize said active, chelating agent present in a phase of the composition other than that containing said active and reducing agent having Electrode Potential value E° greater than about -0.119V.
5. The liquid composition according to claim 4 wherein said reducing agent has an Electrode Potential value E° from about -0.119V to +0.250V.
6. The composition according to any one of the preceding claims wherein chelating agent and reducing agent are active in pH range between 5 to 12 and in aqueous and non-aqueous solvent compositions.
7. The composition according to any one of the preceding claims wherein the chelating agent is selected from the group consisting of the salts of disodium and calcium salts of ethylene diamine tetraacetic acid (EDTA), tetrasodium EDTA, Sodium hexametaphosphate (SHMP), citric acid, phosphoric acid, Di(hydroxyethyl)glycine, 8-hydroxyquinoline and mixtures thereof.
8. The composition according to any one of the preceding claims, wherein said chelating agent is a calcium or sodium salt of ethylene diamine tetraacetic acid (EDTA).
9. The composition according to any one of the preceding claims wherein the level of chelating agent is 0.005% to 1.000% by weight of the composition.

10. The composition according to any one of the preceding claims, wherein the level of chelating agent is from 0.050% to 0.150% by weight of the composition.
11. The composition according to any one of the preceding claims wherein the level of chelating agent is 0.300% to 0.010% by weight of the composition.
12. The composition according to claim 2 or claim 3 wherein the reducing agent is 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.
13. The composition according to any one of claims 2, 3 or 12 wherein the reducing agent is selected from the sodium and potassium salts of metabisulfite.
14. The composition according to claim 12 or claim 13 wherein the level of reducing agent is from 0.005% to 1.000% by weight of the composition.
15. The composition according to any one of claims 12, 13 or 14, wherein the level of reducing agent is from 0.050% to 0.500% by weight of the composition.
16. The composition according to any one of claims 12 to 15 wherein the level of reducing agent is from 0.010% to 0.200% by weight of the composition.
17. A composition according to any one of claims 1 to 16, comprising a pharmaceutical active in an 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 it free, un-ionized form as a monomolecular dispersion in the solvent and said water.
18. The composition according to any one of claims 1 to 17, wherein the pharmaceutical active has a molecular weight of less than 500 grams per mole, is capable of being ionised when in an aqueous solvent and has an octonal-water partition coefficient when in the un-ionized form of at least 100.
19. The composition according to any one of claims 1 to 18, wherein the pharmaceutical active is selected from the group consisting of antitussives, antihistamines, non-sedating

antihistamines, decongestants, expectorants, analgesic mucolytics, antipeyretic anti-inflammatory agents, local anesthetics and mixtures thereof.

20. The composition according to any one of claims 1 to 19, wherein the concentration of pharmaceutical active in the solvent is less than or equal to 125% of the percent solubility value of said active.

21. The composition according to any one of claims 1 to 20, wherein the pharmaceutical active is present in the solvent at a level from 0.075% to 25.0% by weight of the composition.

22. The composition according to any one of claims 1 to 21, wherein the pharmaceutical active is present in the solvent at a level from 0.28% to 10.0% by weight of the composition.

23. The composition according to any one of claims 1 to 22, wherein the solvent comprises from 60% to 99.975% by weight of the composition.

24. The composition according to anyone of claims 1 to 23, wherein the solvent comprises from 70% to 99% by weight of the composition.

25. The composition according to anyone of claims 1 to 24, wherein the solvent comprises from 85% to 98% by weight of the composition.

26. The composition according to any one of claims 1 to 25, wherein the solvent is hydrophilic, water-miscible, and anhydrous selected from the group consisting of propylene glycol, ethanol, poly(ethylene glycol) or PEG, propylene carbonate, diethylene glycol monoethyl ether, poloxamer, glycofurol, glycerol, polvinylpyrrolidone (PVP), 2-(2 ethoxyethoxy) ethanol, fatty acid esters and propylene glycol, glyceryl and polyethylene glycol esters, propylene glycol monocaprylate and mixtures thereof.

27. A method of treating respiratory illness by orally administering the composition of any one of claims 1 to 6 against any mucosal membrane of the mouth.

28. The method according to claim 27 wherein said composition has a total dosage volume of no more than 3.0 mls

29. An oral liquid composition according to claim 1, substantially as hereinbefore described with reference to any one of the Examples.

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30. An oral liquid composition according to claim 2, substantially as hereinbefore described with reference to any one of the Examples.

5 31. An oral liquid composition according to claim 4, substantially as hereinbefore described with reference to any one of the Examples.

32. A method according to claim 27, substantially as hereinbefore described with reference to any one of the Examples.

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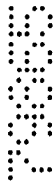
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