Description

This invention is directed to improved antitussive swallowable liquid compositions for oral use. Oral cough preparations, such as syrups, solutions and suspensions, containing an effective antitussive agent have long been used for the symptomatic relief of coughs. The most popular of such preparations contain either dextromethorphan or its hydrobromide salt or codeine or its sulfate salt as the active antitussive agent.

Phenol is a known topical anesthetic, which has been used to treat minor sore mouth and sore throat pain. The mode of action, fast acting but not long lasting, is that it desensitizes sensory nerve receptors present in the mucous membranes of the throat and oral cavity to exert its local anesthetic effect. Previous dosage forms of administration have included aqueous solutions of 1.4% phenol for use as a mouthwash, rinse or gargle, which is expelled from the oral cavity after use, and as a throat spray. Such forms provide topical application of an effective dose of phenol directly to the mucous membranes or mouth tissues. The ensuing anesthesia/analgesia lasts so long as an effective concentration of the phenol is supplied to the site of action. As the phenol is washed away, e.g., by saliva, the anesthetic/analgesia action recedes.

Solid lozenge forms of the antitussive agent, dextromethorphan hydrobromide (10 mg), and phenol (32.5 mg) are known to be commercially available in Canada for the respective systemic treatment of coughs and local treatment of accompanying irritated throat. Also in GB-A-1,144,915, medicinal two-phase solid pastille forms containing (among others) dextromethorphan and phenol in the separate phases are disclosed for the respective treatment of cough and sore throat relief. Such solid lozenge and pastille forms require the action of saliva over an extended period of time for dissolution of the solid form, thereby effectuating release of the respective active ingredients and prolonged contact of phenol at the mucosal membrane throat site.

To date, however, applicants herein are unaware of any combination of an effective oral antitussive drug and phenol in a liquid composition for administration by immediate swallowing.

It has now been found that the combined use of phenol and an oral antitussive drug in a swallowable liquid provides improved relief to an individual afflicted with cough or cough and associated sore throat, without the aforementioned need for prolonged contact with mucosal membranes of the throat and oral cavity.

More specifically, the subject invention provides a liquid pharmaceutical composition of matter for the treatment of cough or cough and associated sore throat in a human afflicted with same. Said composition comprises, per dose of 5-30 milliliters, an aqueous-based orally acceptable pharmaceutical carrier, from 10 to 30 mg of dextromethorphan hydrobromide, and from 10 to 150 mg and preferably from 50 to 150 mg, of phenol, said composition having a pH of 6-9.

As used herein, the term "oral antitussive drug" means a drug that is taken by mouth and acts systemically to relieve cough (see Federal Register, Vol. 52, No. 155, 12 August 1987, page 30055).

The highly advantageous properties of the compositions of this invention are demonstrated by their improved anti-cough effectiveness, for example, by the method of E.W. Packman and S.J. London described in Current Therapeutic Research, Vol. 21, No. 6, June 1977, page 855. The methodology involves the quantitative measurement of the effect of an antitussive preparation on cough artificially induced in normal healthy subjects by a citric acid aerosol at various intervals.

The subject compositions surprisingly provide marked anti-cough effectiveness and also provide fast-acting and effective relief of accompanying irritated or sore throat even though the subject composition is swallowed in the normal fashion, as opposed to the heretofore usage of phenol locally over a period of time, for example, by means of a spray, gargle, or lozenge. It is surprisingly found that, by the simple act of completely swallowing the subject composition, which provides minimal contact time with the mucosal membranes of the throat and oral cavity, the therapeutic anesthetic effect of phenol is still exerted promptly.

In preparing the pharmaceutical compositions of the present invention, the oral antitussive drug and phenol components are incorporated into an aqueous-based orally acceptable pharmaceutical carrier consistent with conventional pharmaceutical practices. An "aqueous-based orally acceptable pharmaceutical carrier" is one wherein the entire or predominant solvent content is water. Typical carriers include simple aqueous solutions, syrups, dispersions and suspensions, and aqueous based emulsions such as the oil-in-water type. The most preferred carrier is the commonly used syrup form, an aqueous solution of high sugar content. While the amount of water in the compositions of this invention can vary over quite a wide range depending upon the total weight and volume of the two essential active ingredients and other optional non-active ingredients, the total water content, based on the weight of the final composition, will generally range from 20 to 75%, and, preferably, from 20 to 40%, by weight/volume.

The cough formulations herein also contain a co-solvent, for example, ethyl alcohol, propylene glycol or

glycerin, to assist solubilization and incorporation of water insoluble ingredients and flavoring oils into the composition. In general, the compositions of this invention contain from 5 to 25 volume/volume percent and, preferably, from 10 to 20 volume/volume percent, of the co-solvent.

To provide and maintain the subject compositions at a pH of from 5 to 9 and preferably from 6 to 7, buffers consistent with conventional pharmaceutical practices are generally utilized such as, for example, sodium citrate buffer and sodium phosphate buffer.

The compositions of this invention may optionally contain one or more other known therapeutic agents, particularly those commonly utilized in cough/cold preparations, such as, for example, a decongestant such as pseudoephedrine hydrochloride, phenylephedrine hydrochloride and ephedrine hydrochloride; an analgesic such as acetaminophen and ibuprofen; an expectorant such as glyceryl guaiacolate, terpin hydrate and ammonium chloride; and an antihistamine such as chlorpheniramine maleate, doxylamine succinate, brompheniramine maleate and diphenhydramine hydrochloride.

Other optional ingredients well known to the pharmacist's art may also be included in amounts generally known for these ingredients, for example, natural or artificial sweeteners, flavoring agents and colorants to provide a palatable and pleasant looking final product; antioxidants, for example, butylated hydroxy anisole or butylated hydroxy toluene, and preservatives, for example, methyl or propyl paraben or sodium benzoate to prolong and enhance shelf life.

The following examples illustrate embodiments of the subject invention wherein both essential and optional ingredients are combined.

EXAMPLE 1	
Ingredients	Amount/10 ml Dose
Invert syrup, medium	8.5 g
Sodium citrate, hydrous	200.0 mg
Sodium benzoate	10.0 mg
Absolute alcohol	1.00 ml
Propylene glycol	1.16 g
Phenol	75.0 mg
Dextromethorphan HBr	30.0 mg
Chlorpheniramine maleate	4.0 mg
Colorant	207.0 mg
Flavorants	60.55 mg
Purified water, q.s. ad (pH = 6.6)	10.00 ml

EXAMPLE 2	
Ingredients	Amount/15 ml Dose
Liquid sugar (66% sucrose in water)	12.0 g
Sodium benzoate	15.0 mg
Sodium citrate, hydrous	300.0 mg
Citric acid, anhydrous	4.11 mg
Sodium saccharin	30.00 mg
Propylene glycol	2.25 g
Dextromethorphan HBr	30.00 mg
Pseudoephedrine HCl	60.00 mg
Absolute alcohol	1.50 ml
Phenol	112.50 mg
Guaifenesin	200.00 mg
Menthol	22.50 mg
Colorant	5.1 mg
Flavorants	82.55 mg
Purified water (pH = 7.0)	15.00 ml

EXAMPLE 3	
Ingredients	Amount/15 ml Dose
Liquid sugar	12.00 g
Sodium benzoate	15.00 mg
Sodium citrate, hydrous	300.00 mg
Citric acid, anhydrous	4.11 mg
Sodium saccharin	30.00 mg
Propylene glycol	2.25 mg
Dextromethorphan HBr	30.00 mg
Absolute alcohol	1.50 ml
Phenol	150.00 mg
Colorant	0.045 ml
Flavorant	0.015 ml
Purified water q.s. ad (pH) - 7.0	15.00 ml

Claims

1. A liquid pharmaceutical composition of matter for use in the treatment of coughs and associated sore throat, by direct swallowing, comprising, per 5-30 ml dose:
   (a) an aqueous-based orally accceptable pharmaceutical carrier;
   (b) from 10 to 30 mg of dextromethorphan hydrobromide;
   (c) from 10 to 150 mg of phenol; and
   (d) from 5 to 25 volume/volume percent of co-solvent; said composition having a pH of from 5 to 9.

2. The composition of Claim 1 wherein said co-solvent in (d) is selected from ethyl alcohol, glycerin and propylene glycol.

3. A liquid pharmaceutical composition of matter for use in the treatment of coughs and associated sore throat, by direct swallowing, comprising, per 5-30 ml dose:
   (a) from 20 to 75% of water by weight/volume;
   (b) from 10 to 30 mg of dextromethorphan hydrobromide;
   (c) from 50 to 150 mg of phenol; and
   (d) from 10 to 20 volume/volume percent of ethyl alcohol;
   said composition having a pH of from 6 to 7.

4. The composition of Claim 3 wherein (a) is from 20 to 40% by weight/volume of water.

Revendications

1. Composition pharmaceutique liquide de matière pour utilisation dans le traitement de la toux et du mal de gorge associé , par absorption directe, comprenant, par dose de 5-30 ml:
   (a) un véhicule pharmaceutique à base aqueuse, acceptable par voie orale;
   (b) de 10 à 30 mg de dextrométhorphane (bromhydrate);
   (c) de 10 à 150 mg de phénol; et
   (d) de 5 à 25 % v/v de co-solvant;
   ladite composition ayant un pH de 5 à 9.

2. Composition selon la revendication 1, dans laquelle ledit co-solvant en (d) est choisi parmi l'alcool éthylique, le glycérol et le propylèneglycol.

3. Composition pharmaceutique liquide de matière pour utilisation dans le traitement de la toux et de mal de gorge associé, par absorption directe, comprenant, par dose de 5-30 ml:
   (a) de 20 à 75 % en poids par volume d'eau;
   (b) de 10 à 30 mg de dextrométhorphane (bromhydrate);
   (c) de 50 à 150 mg de phénol; et

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Sodium benzoate	15.00 mg
Sodium citrate, hydrous	300.00 mg
Citric acid, anhydrous	4.11 mg
Sodium saccharin	30.00 mg
Propylene glycol	2.25 mg
Dextromethorphan HBr	30.00 mg
Absolute alcohol	1.50 ml
Phenol	150.00 mg
Colorant	0.045 ml
Flavorant	0.015 ml
Purified water q.s. ad (pH) - 7.0	15.00 ml

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   said composition having a pH of from 6 to 7.

4. The composition of Claim 3 wherein (a) is from 20 to 40% by weight/volume of water.

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3. Composition pharmaceutique liquide de matière pour utilisation dans le traitement de la toux et de mal de gorge associé, par absorption directe, comprenant, par dose de 5-30 ml:
   (a) de 20 à 75 % en poids par volume d'eau;
   (b) de 10 à 30 mg de dextrométhorphane (bromhydrate);
   (c) de 50 à 150 mg de phénol; et

(d) de 10 à 20 % en volume par volume d'alcool éthylique;
ladite composition ayant un pH de 6 à 7.

4. Composition selon la revendication 3, dans laquelle (a) consiste en 20-40 % en poids/volume d'eau.

Patentansprüche

1. Flüssige pharmazeutische Zusammensetzung zur Verwendung in der Behandlung von Husten und damit verbundener Halsentzündung durch direktes Verschlucken, umfassend, je 5-30 ml-Dosis:
   (a) einen oral annehmbaren pharmazeutischen Träger auf wäßriger Basis;
   (b) von 10 bis 30 mg Dextromethorphanhydrobromid;
   (c) von 10 bis 150 mg Phenol; und
   (d) von 5 bis 25 % Volumen/Volumen Co-Lösungsmittel;
   wobei diese Zusammensetzung einen pH-Wert von 5 bis 9 aufweist.

2. Zusammensetzung nach Anspruch 1, worin das Co-Lösungsmittel in (d) unter Ethylalkohol, Glycerin und Propylenglykol ausgewählt ist.

3. Flüssige pharmazeutische Zusammensetzung zur Verwendung in der Behandlung von Husten und damit verbundener Halsentzündung durch direktes Verschlucken, umfassend, je 5-30 ml-Dosis:
   (a) von 20 bis 75 % Gewicht/Volumen an Wasser;
   (b) von 10 bis 30 mg Dextromethorphanhydrobromid;
   (c) von 50 bis 150 mg Phenol; und
   (d) von 10 bis 20 % Volumen/Volumen an Ethylalkohol;
   wobei diese Zusammensetzung einen pH-Wert von 6 bis 7 aufweist.

4. Zusammensetzung nach Anspruch 3, worin (a) aus 20 bis 40 % Gewicht/Volumen Wasser besteht.