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[57] (see abstract next page)

ABSTRACT OF THE DISCLOSURE

Disclosed are oral pharmaceutical compositions for the treatment of cough adapted for unit dosage oral administration comprising: (a) a safe and effective amount of tryptophan; and (b) a safe and effective amount of an oral antitussive drug. Also provided are methods for the treatment of cough in humans or animals which comprises orally administering to said human or animal a safe and effective amount of a pharmaceutical composition comprising tryptophan and an oral antitussive drug. Preferably, the oral antitussive drug is selected from the group consisting of dextromethorphan, chlophedianol, carbetapentane, caramiphen, noscapine, diphenhydramine, codeine, hydrocodone, hydromorphone, fominoben, pharmaceutically acceptable salts thereof, and mixtures thereof.

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ANTITUSSIVE ORAL COMPOSITIONS

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TECHNICAL FIELD

The present invention relates to antitussive oral pharmaceutical compositions containing tryptophan along with an oral antitussive drug.

BACKGROUND OF THE INVENTION

The cough reflex is an important mechanism whereby secretions from the lungs and airways are removed. Generally, such secretions are removed by the muscociliary escalator. However, when this mechanism is defective, or becomes overwhelmed by, for example, excessive secretions, cough then becomes a principal means of secretion removal.

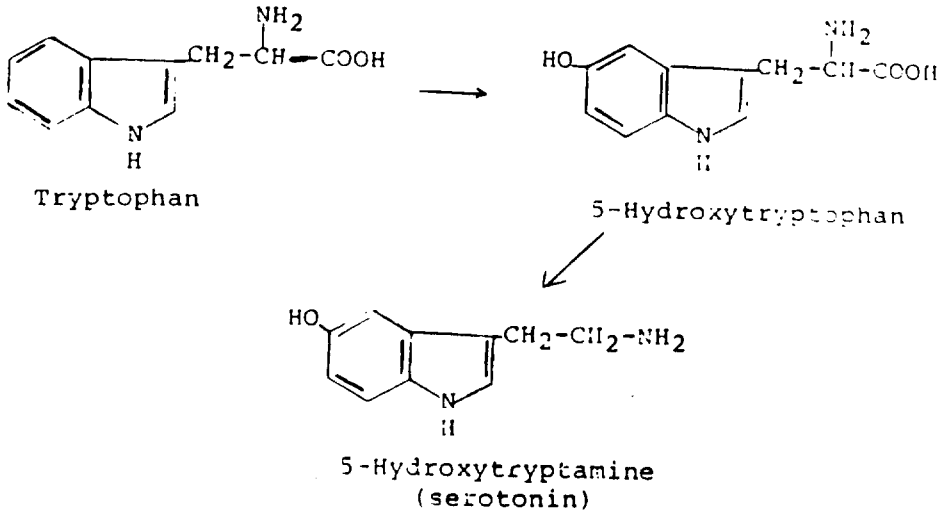
The cough reflex is initiated by stimulation of mechanical receptors and is controlled by afferent pathways within the vagus (X), glossopharyngeal (IX), and superior laryngeal nerves to the cough center in the brainstem. Cough can be caused by, for example, foreign bodies, dust, mucus, debris, gases and smoke in the lower respiratory tract. Irritation of various sensory nerves in the nose, sinuses, pharynx, ears, stomach, pericardium or diaphragm can also produce coughing. In many of these conditions, chronic or paroxysmal cough, however, can be exhausting and debilitating, particularly when it interferes with sleep.

Oral cough preparations, such as tablets, lozenges, syrups, solutions, suspensions and the like, 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. These treatments, among many others, are fully described in Drug Evaluations, 6th Ed., Chapter 21 (The American Medical Association, 1986).

It has now been discovered that tryptophan has antitussive activity in humans and lower animals. Further, it has been found that tryptophan in combination with oral antitussive drugs provides improved antitussive efficacy in humans and animals.

While the usefulness of tryptophan in cough has never been reported, tryptophan has been found to be an effective sleep inducer alone (see e.g., Spinweber, Psychopharm Bulletin, 17:81, 1981 and Smith and Prockup, New England Journal of Medicine, 267:1338, 1982) or in combination with other agents such as calcium (U.S. Patent 4,419,345 to Wyatt, issued December 6, 1983, and carbohydrates (European Patent Application 088,621, Wurtman, published September 14, 1983); appetite supressant (see U.S. Patent 4,210,637 to Wurtman et al., issued July 1, 1980); antidepressant; and analgesic (see Martindale The Extra Pharmacopeia 28th Ed., 61-2 The Pharmaceutical Press, 1982.

The usefulness of tryptophan in the disorders described above is thought to be related to increased brain serotonin levels since serotonin is synthesized from tryptophan via the following metabolic pathway:



Tryptophan

Kamei et al. suggest that the serotonergic system may play a role in modulating the cough reflex ("Effects of Methylsergide on the Cough Reflex", Japan J. Pharmacol., 42:450, 1986). In another study, Kamei et al. demonstrated that the immediate precursor of serotonin, 5-hydroxytryptophan (5-HTP), does not significantly inhibit the cough reflex ("Involvement of Central Serotonergic mechanisms in the Cough Reflex", Japan J. Pharmacol., 42:531, 1986) despite the fact that 5-HTP administration results in significant increases in brain serotonin content and activity (Trulson and Jacobs, "Dose-Response Relationships between Systemically administered L-tryptophan or Oral L-5-Hydroxytryptophan and Raphe Unit Activity in the Rat", Neuropharmacol., 15:339, 1976). Thus, it is unexpected that tryptophan, but not 5-HTP, significantly inhibits the cough reflex.

It is therefore an object of the present invention to provide oral pharmaceutical compositions containing tryptophan which are highly efficacious in the treatment of cough. It is still a further object of the present invention to provide pharmaceutical compositions containing tryptophan along with an oral antitussive drug which provide improved antitussive efficacy. It is still a further object of the present invention to provide a method of using these pharmaceutical compositions in the treatment of cough in humans or animals.

SUMMARY OF THE INVENTION

The present invention relates to an oral pharmaceutical composition for the treatment of cough adapted for unit dosage oral administration comprising: (a) a safe and effective amount of tryptophan; and (b) a safe and effective amount of an oral antitussive drug.

Also provided are methods for the treatment of cough in humans or animals which comprises orally administering to said human or animal a safe and effective amount of a pharmaceutical composition comprising tryptophan and an oral antitussive drug.

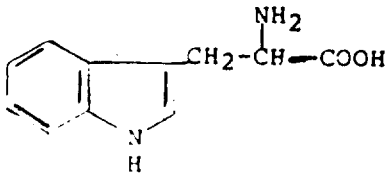
All percentages and ratios used herein are by weight unless otherwise indicated.

Preferably, the oral antitussive drug is selected from the group consisting of dextromethorphan, chlophedianol, carbetapentane, caramiphen, noscapine, diphenhydramine, codeine, hydrocodone, hydromorphone, fominoben, pharmaceutically acceptable salts thereof, and mixtures thereof.

DETAILED DESCRIPTION OF THE DEVELOPMENT

More specifically, the present invention provides oral antitussive pharmaceutical compositions and methods for the treatment of cough in humans or animals afflicted with the same. The compositions of the present invention comprise an oral pharmaceutical composition for the treatment of cough adapted for unit dosage oral administration comprising: (a) a safe and effective amount of tryptophan; and (b) a safe and effective amount of an oral antitussive drug. By safe and effective amount is meant that amount which provides antitussive efficacy thereby alleviating or preventing cough at a reasonable benefit/risk ratio, as is attendant with any medical treatment. Obviously, the amount of the antitussive pharmaceutical composition which is administered will vary with such factors as the particular condition that is being treated, the severity of the condition that is being treated, the duration of the treatment, the physical condition of the patient, the nature of concurrent therapy (if any), the specific formulation and carrier employed, and the solubility and concentration of the antitussive used.

Tryptophan has the following general formula:



Tryptophan

It is generally believed that the biologically active isomer of tryptophan is the L-isomer. Tryptophan is commercially available from, for example, Ajinimoto, Inc. (Tokyo, Japan)

A number of agents have been shown to increase plasma and/or brain tryptophan concentrations and these maybe added to the formulation as desired. Examples of these compounds include lithium, sodium salicylate, aminophylline and clofibrate and are described in: Curzon, G. and Knott, P.J., "Environmental, Toxicological and Related Aspects of Tryptophan Metabolism with Particular Reference to the Central Nervous System", CRC Critical Reviews in Toxicology, 5:187, 1977; Gessa, G.L. and Tagliamonte, A., "Serum Free Tryptophan: Control of Brain Concentrations of Tryptophan and of Synthesis of 5-Hydroxytryptophan", Aromatic Amino Acids In The Brain, 1974, Ciba Foundation Symposium, Elsevier; Gessa, G.L. and Tagliamonte, A., "Possible Role of Free Serum Tryptophan in the Control of Brain Tryptophan Level and Serotonin Synthesis", Adv. Biochem. Psychopharmacol., 11:119, 1974. All of the above are incorporated by reference herein.

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).

Useful recognized oral antitussive drugs include, but are not limited to, for example, the non-narcotic types such as dextromethorphan and its acid salts, preferably the hydrobromide, chlophedianol hydrochloride, carbetapentane citrate, caramiphen edisylate, diphenhydramine and its hydrochloride salt, fominoben, and the like, and the narcotic type such as codeine and its sulfate or phosphate salts, noscapine hydrochloride, hydrocodone and its bitartrate salt, hydromorphone hydrochloride, and the like. The usual adult dosages for

such antitussives, which may also be utilized per dose in the subject compositions, are indicated in Table I.

TABLE I

Oral Antitussive Drug	Usual Adult Dose (mg)
Dextromethorphan HBr	10-30
Chlophedianol HCl	15-25
Carbetapentane citrate	15-30
Caramiphen edisylate	15-20
Noscapine HCl	15-30
Diphenhydramine HCl	15-25
Codeine sulfate	10-20
Hydrocodone bitartrate	5-10
Hydromorphone HCl	2
Fominoben	80-160

Preferred oral antitussive agents are dextromethorphan, codeine and diphenhydramine and pharmaceutically acceptable salts thereof and mixtures thereof. Even more preferred are dextromethorphan and codeine, pharmaceutically acceptable salts thereof and mixtures thereof. Most preferred is dextromethorphan and its pharmaceutically acceptable salts.

The tryptophan and oral antitussive drug are combined in a ratio of tryptophan to oral antitussive drug of from about 2:1 to about 5000:1 more preferably from about 3:1 to about 5000:1, even more preferably from about 8:1 to about 400:1 and most preferably from about 16:1 to about 100:1.

Various oral dosage forms can be used, including such solid forms as tablets, capsules, granules, lozenges and bulk powders and liquid forms such as syrups, suspensions and solutions. These oral forms comprise a safe and effective amount, usually at least about 0.1% of the active component. Solid oral dosage forms preferably contain from about 5% to about 95%, more preferably from about 10% to about 95%, and most preferably from about 25% to about 95% of the active component. Liquid oral

dosage forms preferably contain from about 1% to about 50% and more preferably from about 1% to about 25% and most preferably from about 3% to about 10% of the active component.

Tablets can be compressed, tablet triturates, enteric-coated, sugar-coated, film-coated or multiple compressed, containing suitable binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, preservatives and flow-inducing agents.

Liquid oral dosage forms include aqueous and non-aqueous solutions, emulsions, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules, containing suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, agents, coloring agents, and flavoring agents. Preferred carriers for oral administration include gelatin, propylene glycol, ethyl oleate, cottonseed oil and sesame oil. Specific examples of pharmaceutically acceptable carriers and excipients that may be used to formulate oral dosage forms, are described in U.S. Patent 3,903,297, Robert, issued September 2, 1975, incorporated by reference herein. Techniques and compositions for making solid oral dosage forms are described in Marshall, "Solid Oral Dosage Forms," Modern Pharmaceutics, Vol. 7, (Banker and Rhodes, editors), 359-427 (1979), incorporated by reference herein. Techniques and compositions for making tablets (compressed, formulas and molded), capsules (hard and soft gelatin) and pills are described in Remington's Pharmaceutical Sciences (Arthur Osol, editor), 1553-1593 (1980), incorporated herein by reference.

Since many of the oral antitussive drugs are generally used in the form of a water-soluble salt, they can be readily incorporated into conventional aqueous-based cough syrups and solution formulations. Water-insoluble or poorly soluble antitussives, generally in base form, may also be incorporated into aqueous-based orally acceptable pharmaceutical carriers such as dispersions,

suspensions, oil-in-water emulsions and the like by means of suitable dispersing, suspending or emulsifying agents, respectively, which are readily apparent to those skilled in the art of pharmaceutical formulations.

In preparing the pharmaceutical compositions of the present invention, the oral antitussive drug and tryptophan 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 a suspension of the pharmaceutical composition in an aqueous vehicle containing a suitable suspending agent. Suitable suspending agents include Avicel RC-591 (a microcrystalline cellulose/sodium carboxymethyl cellulose mixture available from FMC), guar gum and the like. Such suspending agents are well known to those skilled in the art. 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 about 20 to about 75%, and, preferably, from about 20 to about 40%, by weight/volume.

Although water itself may make up the entire carrier, typical cough formulations preferably contain a co-solvent, for example, propylene glycol, glycerin, sorbitol solution and the like, to assist solubilization and incorporation of water-insoluble ingredient, flavoring oils and the like into the composition. In general, therefore, the compositions of this invention preferably contain from about 5 to about 25 volume/volume percent and, most preferably, from about 10 to about 20 volume/volume percent, of the co-solvent.

To provide and maintain the subject compositions at a pH of from about 3 to about 9 and preferably from about 4 to about 7, buffers consistent with conventional pharmaceutical practices are generally utilized such as, for example, sodium citrate buffer, sodium phosphate buffer, and the like. 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, phenylpropanolamine HCl, phenylephrine hydrochloride and ephedrine hydrochloride; an analgesic such as acetaminophen and ibuprofen; an expectorant or mucolytic such as glyceryl guaiacolate, guaiacolate, terpin hydrate, ammonium chloride, N-acetylcysteine and ambroxol; and an antihistamine such as chlorpheniramine maleate, doxylamine succinate, brompheniramine maleate and diphenhydramine hydrochloride: all of which are described in U.S. Patent 4,619,934 to Sunshine et al., issued October 28, 1986, which is incorporated by reference herein. Also useful are bronchodilators such as theophylline and albuterol.

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, colorants and the like 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.

METHOD OF TREATMENT

The present invention also encompasses methods of treating cough in humans or lower animals through administering, to the human or lower animal in need of such treatment, a safe and effective amount of a pharmaceutical composition comprising tryptophan along with an oral antitussive drug. The amount of the pharmaceutical

composition administered depends upon the percent of active ingredients within its formula, which is a function of the amount of the tryptophan and oral antitussive drug required per dose, stability, release characteristics and other pharmaceutical parameters. Usually from about 2 mg/kg to about 3000 mg/kg per day, preferably from about 6 mg/kg to about 360 mg/kg per day and most preferably from about 14 mg/kg per day to about 180 mg/kg per day of the pharmaceutical composition is administered as described herein. This amount can be given in a single dose or, preferably, in multiple (two to six) doses repeatedly or sustained release dosages over the course of treatment. Generally, each individual dosage of the pharmaceutical compositions of the present invention range from about 1.0 mg/kg to about 500 mg/kg, preferably from about 3 mg/kg to about 60 mg/kg and most preferably from about 7 mg/kg to about 30 mg/kg. While dosages higher than the foregoing are effective to prevent cough, care must be taken, as with any drug, in some individuals to prevent adverse side effects.

The compositions and methods described herein are used in an art recognized manner to provide antitussive activity.

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

EXAMPLE I

A suspension for oral administration is prepared by combining the following ingredients:

Ingredient	Amount	
L-tryptophan	2000.0	mg
Dextromethorphan HBr	30.0	mg
Microcrystalline cellulose and sodium carboxy methyl cellulose	375.0	mg
Sucrose	13.5	g
Glycerin	600.0	mg
Sorbitol solution (70%)	1.5	g
Potassium sorbate	30.0	mg
Sodium saccharin	60.0	mg
Glucose acid	75.0	mg
Flavorant	45.0	mg
Colorant	5.0	mg
Purified water, q.s. ad	30.0	ml

The above ingredients are combined to produce a suspension with a pH of 4.3, and packaged under aseptic conditions in 6 oz. bottles. 30 ml of this formulation are administered to an adult human in need of treatment, thereby reducing cough.

Substantially similar results are obtained when the dextromethorphan is replaced with a therapeutically equivalent level of chlophedianol, carbetapentane, caramiphen, noscapine, diphenhydramine, codeine, hydrocodone, hydromorphone, fominoben, their pharmaceutically-acceptable salts, and mixtures thereof.

EXAMPLE II

A syrup for oral administration is prepared by combining the following ingredients:

Ingredient	Amount	
L-Tryptophan	1000.0	mg
Dextromethorphan HBr	30.0	mg
Citric Acid	5.7	mg
Glycerin	12.0	mg
Sorbitol Solution (70%) q.s. ad	30.0	ml
Color and Flavor	qs	

The citric acid is dissolved in the glycerin at a temperature of from about 40°C-60°C. While stirring, the

L-tryptophan is added to this mixture. The resultant mixture is cooled to room temperature and the flavor and color are added. The sorbitol solution is then added thereby producing a thick syrupy liquid. 30 ml of this liquid is administered to an adult human in need of treatment, thereby reducing cough.

Substantially similar results are obtained when the dextromethorphan is replaced with a therapeutically equivalent level of chlophedianol, carbetapentane, caramiphen, noscapine, diphenhydramine, codeine, hydrocodone, hydromorphone, fominoben, their pharmaceutically-acceptable salts, and mixtures thereof.

EXAMPLE III

A hard capsule for oral administration is prepared as follows: 500 mg of L-tryptophan and 15 mg dextromethorphan HBr as dry powder are encapsulated into a number 0 hard shell capsule using techniques as are known in the art. One to two capsules are administered to a human in need of treatment, thereby reducing cough.

Substantially similar results are obtained when the dextromethorphan is replaced with a therapeutically equivalent level of chlophedianol, carbetapentane, caramiphen, noscapine, diphenhydramine, codeine, hydrocodone, hydromorphone, fominoben, their pharmaceutically acceptable salts, and mixtures thereof.

EXAMPLE IV

A soft gelatin capsule composition for oral administration is prepared by combining the following ingredients:

Ingredient	Amount
L-tryptophan	250.0 mg
Dextromethorphan HBr	15.0 mg
Sesame oil	735.0 mg

L-tryptophan and dextromethorphan are combined with the sesame oil and are packaged in soft gelatin capsules using methods known in the art. One to two of the resulting capsules, each containing 1000 mg of the

composition, are administered to an adult human, in need of treatment, thereby reducing cough.

Substantially similar results are obtained when the dextromethorphan is replaced with a therapeutically equivalent level of chlophedianol, carbetapentane, caramiphen, noscapine, diphenhydramine, codeine, hydrocodone, hydromorphone, fominoben, their pharmaceutically-acceptable salts, and mixtures thereof.

EXAMPLE V

A tablet for oral administration is produced by combining the following ingredients:

Ingredient	Amount
L-tryptophan	500 mg
Dextromethorphan HBr	15 mg
Maltodextrin	50 mg
Croscarmelose	25 mg
Magnesium Stearate	5 mg

L-tryptophan and dextromethorphan are granulated with a 10% w/w solution maltodextrin (available from Corn Products as Maltrin M-100). The resulting granule is dried at a temperature of about 45°C overnight. The dry granule is milled and blended with the Croscarmelose (available from GAF Corporation as AC-DI-SOL) and the magnesium stearate. The resulting powder blend is compressed into 580 mg tablets as is conventional in the art. One to two of the resulting tablets are administered to a human in need of treatment, thereby reducing cough.

Substantially similar results are obtained when the dextromethorphan is replaced with a therapeutically equivalent level of chlophedianol, carbetapentane, caramiphen, noscapine, diphenhydramine, codeine, hydrocodone, hydromorphone, fominoben, their pharmaceutically-acceptable salts, and mixtures thereof.

EXAMPLE VI

A chewable tablet for oral administration is produced by combining the following ingredients:

Ingredient	Amount
L-tryptophan	500 mg
Dextromethorphan HBr adsorbate (10%)	150 mg
Maltodextrin	50 mg
Crystalline Sorbitol	500 mg
Magnesium Stearate	1 mg
Color and Flavor	q.s.

The L-tryptophan and dextromethorphan adsorbate are is granulated with a 10% w/w solution of maltodextrin. The resulting granule is dried at a temperature of about 45 C overnight. The dry granule is milled and blended with the remaining components. The resulting powder blend is compressed into 1.05 g tablet as is conventional in the art. One to two tablets are administered to a human in need of treatment, thereby reducing cough.

Substantially similar results are obtained when the dextromethorphan is replaced with a therapeutically equivalent level of chlophedianol, carbetapentane, caramiphen, noscapine, diphenhydramine, codeine, hydrocodone, hydromorphone, fominoben, their pharmaceutically-acceptable salts, and mixtures thereof.

WHAT IS CLAIMED IS:

1. An oral pharmaceutical composition for the treatment of cough adapted for unit dosage oral administration comprising:
   (a) a safe and effective amount of tryptophan; and
   (b) a safe and effective amount of an oral antitussive drug;

2. The pharmaceutical composition of claim 1 wherein the ratio of tryptophan to the oral antitussive drug ranges from about 2:1 to about 5000:1.

3. The pharmaceutical composition of claim 2 wherein said oral antitussive drug is selected from the group consisting of dextromethorphan, chlophedianol, carbetapentane, caramiphen, noscapine, diphenhydramine, codeine, hydrocodone, hydromorphone, fominoben, their pharmaceutically-acceptable salts, and mixtures thereof.

4. The pharmaceutical composition of Claim 3 wherein the ratio of tryptophan to oral antitussive drug ranges from about 3:1 to about 5000:1.

5. The pharmaceutical composition of Claim 4 wherein the ratio of tryptophan to oral antitussive drug ranges from about 8:1 to about 400:1.

6. A pharmaceutical composition according to Claim 5 wherein said oral antitussive drug is selected from the group consisting of dextromethorphan, codeine, diphenhydramine, pharmaceutically-acceptable salts thereof and mixtures thereof.

7. A pharmaceutical composition according to Claim 6 wherein the ratio of tryptophan to oral antitussive drug ranges from about 16:1 to about 100:1.

8. A pharmaceutical composition according to Claim 7 wherein said oral antitussive drug is selected from the group consisting of dextromethorphan, codeine, pharmaceutically acceptable salts thereof and mixtures thereof.

9. A pharmaceutical composition according to Claim 1 in the form of a syrup, emulsion, suspension or solution.

10. A pharmaceutical composition according to Claim 7 in the form of a syrup, emulsion, suspension or solution.

11. A pharmaceutical composition according to Claim 1 in the form of a tablet, lozenge, capsule, granule or bulk powder.

12. A pharmaceutical composition according to Claim 7 in the form of a tablet, lozenge, capsule, granule or bulk powder.

13. A method for the treatment of cough in humans or animals which comprises administering to a human or animal in need of such treatment the pharmaceutical composition of Claim 1.

14. A method for the treatment of cough in humans or animals which comprises administering to a human or animal in need of such treatment the pharmaceutical composition of Claim 3.

15. A method for the treatment of cough in humans or animals which comprises administering to a human or animal in need of such treatment the pharmaceutical composition of Claim 5.

16. A method for the treatment of cough in humans or animals which comprises administering to a human or animal in need of such treatment the pharmaceutical composition of Claim 8.

17. A method for the treatment of cough in humans or animals which comprises administering to a human or animal in need of such treatment the pharmaceutical composition of Claim 10.

18. A method for the treatment of cough in humans or animals which comprises administering to a human or animal in need of such treatment the pharmaceutical composition of Claim 12.