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(54) Title: EFFERVESCENT COMPOSITION COMPRISING N- ACETYLCYSTEINE AND DOXOPHYLLINE OR THEOPHYLLINE

(57) Abstract: The present invention relates to pharmaceutical formulations prepared by combining a mucolytic agent N-Acetylcysteine with a xanthine derivative compound, their preparation method and use in treatment of respiratory tract diseases.

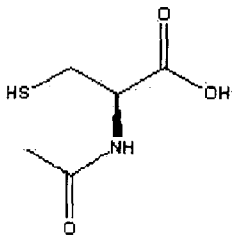
EFFERVESCENT COMPOSITION COMPRISING N-ACETYLCYSTEINE AND DOXOPHYLLINE OR THEOPHYLLINE

The present invention relates to pharmaceutical formulations prepared by combining a mucolytic agent N-Acetylcysteine with a xanthine derivative compound, their preparation method and use in treatment of respiratory tract diseases.

The respiratory tract diseases are one of the leading diseases threatening the human health. Chronic Obstructive Pulmonary Disease (COPD) is acknowledged as a serious health problem all around the world. COPD which narrows the airways and prevents the people it affects to breathe easily is a chronic pulmonary disease ranking 4th in mortality all over the world. Allergic rhinitis, on the other hand, is the allergy-induced inflammation of nasal mucosa. Allergic rhinitis is not a life-threatening disease but affects people's quality of life significantly. Thus, it must be easily diagnosed and an effective treatment must be administered.

The present invention relates to a pharmaceutical composition comprising N-acetylcysteine (hereinafter called "NAC") or a pharmaceutically acceptable salt thereof with a xanthine derivative compound or a pharmaceutically acceptable salt of it. The invention also relates to use of said pharmaceutical formulation for expectorating and decreasing phlegm in respiratory tract diseases; chronic obstructive pulmonary disease (COPD), allergic rhinitis, acute and chronic bronchitis, catarrh and cold, in the case that expectoration must be eased, in pulmonary diseases, bronchopulmonary diseases, bronchial secretion disorder.

NAC (*Formula I*) is an N-Acetylated derivative of L-Cysteine and used as a mucolytic agent.



(I)

N-Acetylcysteine

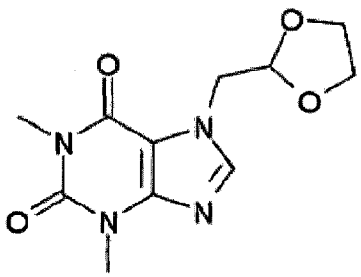
NAC breaks the disulphide bonds in mucoproteins in the bronchial secretions with the help of sulfhydryl group in its structure. Thus, the intensity of the mucus secretion in lungs decreases.

N-Acetylcysteine, chemical name of which is N-Acetyl-L-cysteine, is described in detail in the patent numbered US 3,184,505.

Xanthine compounds are in alkaloid group and also are purin bases. As for methyl xanthines, they are effective compounds used in treatment of Chronic Obstructive Pulmonary Disease (COPD) and other respiratory tract diseases.

Methylxanthine group comprises compounds such as theophylline and doxophylline, caffeine, acepiphylline, bamiphylline, bufylline, cafaminol, cafedrine, diprophylline, dihydroxypropyl theophylline, enprophylline, etamiphylline, ethophylline, proxyphylline, suxamidofylline, theobromine, furaphylline, 7-propyl-theophylline-dopamine, 3- isobutyl-1-methylxanthine, torbaphylline, pentoxiphylline, reproterol, denbufylline, arophylline and cymaphylline.

Doxophylline *(Formula II)*, which has the chemical name 7-(l,3-dioxolan-2-ylmethyl)-3,7-dihydro-l,3-dimethyl-lH-purine-2,6-dione is described in the patent numbered US 4,187,308.

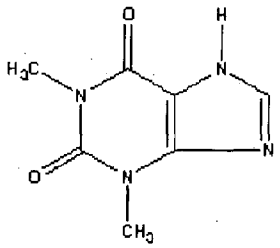


(II)

Doxophylline

Doxophylline is a methyl xanthine compound which is known with its bronchial and antitussive activity. In addition, it is effective on indications of bronchospasm, obstructive chronic bronchitis and spasmodic cough.

Theophylline *(Formula III)* is a methyl xanthine derivative. Theophylline, chemical name of which is 3,7-Dihydro-l,3-dimethyl-lH-purine-2,6-dione, is disclosed in *Traube, Ber. 33,3035* in 1900.



(III)

Theophylline

Theophylline is rather effective as a bronchodilator. In addition, it induces anti-inflammatory and immunomodulator effects. It causes loosening in bronchus smooth muscles and pulmonary blood vessels and relieves smooth muscle spasm.

It has been disclosed in the patent numbered US 4,187,308 that doxophylline shows bronchial and antitussive activity. Methyl xanthines compounds which are xanthine derivatives are indicated for diseases such as bronchopulmonary diseases, bronchospasm, obstructive chronic bronchitis and spasmodic cough. However, it may not be enough to use a xanthine compound alone for relieving the symptoms observed in respiratory tract diseases such as acute and chronic bronchopulmonary, COPD, allergic rhinitis and bronchitis.

When the prior art is taken into consideration, there is need for new pharmaceutical compounds which will be used in treatment of respiratory tract diseases and yield more effective and precise results in comparison with existing therapies.

The inventors have surprisingly obtained a better mucolytic effect by combining NAC and xanthine derivative compounds and found that the treatment in which the combination of the present invention is administered induces greater therapeutic benefit in comparison with the treatment in which said active ingredients are administered separately.

In another aspect, the inventors have found the use of xanthine derivative compounds in combination with N-Acetylcysteine that is a mucolytic agent both for the treatment of said diseases; expectoration and reduction of phlegm caused by these diseases and easing expectoration provides the desired positive therapeutic effect.

In another aspect; use of NAC and xanthine derivative compounds in combination both constitutes an alternative and effective method in the treatment of bronchopulmonary diseases; and provides reduction and expectoration of phlegm observed as a consequence of bronchopulmonary diseases and easing expectoration. Furthermore, it removes the difficulty of taking more than one drug for people who are diagnosed with said diseases.

The present invention relates to use of N-Acetylcysteine (NAC) in combination with xanthine derivative compounds.

The present invention further comprises the use of NAC in combination with methylxanthine compounds.

In another aspect, pharmaceutically acceptable excipients can optionally be used in the composition of the present invention.

According to the present invention, methylxanthine derivative compounds used in the pharmaceutical composition can be selected from theophylline and doxophylline, caffeine, acepiphylline, bamiphylline, bufylline, cafaminol, cafedrine, diprophylline, dihydroxypropyl theophylline, enprophylline, etamiphylline, ethophylline, proxyphylline, suxamidofylline, theobromine, furaphylline, 7-propyl-meophyllme-dopamine, 3-isobutyl-1-methylxanthine, torbaphylline, pentoxiphylline, reproterol, denbufylline, arophylline and cymaphylline.

In another aspect, the inventors have found that use of theophylline or doxophylline as xanthine derivative compounds in the pharmaceutical formulations of the present invention is more effective in the treatment of the above mentioned diseases.

Throughout the invention, the term "xanthine derivative compound" refers to theophylline or doxophylline.

In the present invention, the active agents of the said combination can be in free form or in the form of pharmaceutically acceptable salts, enantiomers, racemates, solvates, hydrates, different polymorphic forms and amorphous form of the related active agents.

In another aspect, the composition of the present invention can be used simultaneously, sequentially or separately for reducing the symptoms of respiratory tract diseases or slowing the progression of the disease.

According to the present invention; the combination of NAC and the xanthine derivative compounds can be used for expectoration and reduction of phlegm caused by respiratory tract diseases; chronic obstructive pulmonary disease (COPD), allergic rhinitis, acute or chronic bronchitis, catarrh and cold, in the cases requiring easing expectoration, and in treatment of pulmonary diseases, bronchopulmonary diseases, disorders of bronchial secretion.

In another aspect, the compositions of the invention can be prepared as a drug composition for administration on mammals including humans for expectoration and reduction of phlegm caused

by respiratory tract diseases; chronic obstructive pulmonary disease (COPD), allergic rhinitis, acute or chronic bronchitis, catarrh and cold, in the cases requiring easing expectoration, and in treatment of pulmonary diseases, bronchopulmonary diseases, disorders of bronchial secretion.

In another aspect, the present invention relates to a pharmaceutical composition which will be used in production of an effective medicament so as to be utilized in treatment of respiratory tract diseases wherein said composition is characterized by comprising NAC and a xanthine derivative compound as active agent.

In another aspect, it is targeted to reduce symptoms of respiratory tract diseases, slow the progression of the disease and treat the disease by means of pharmaceutical compositions in which effective amounts of NAC and effective amounts of xanthine derivative compounds and sufficient amounts of excipient/excipients are combined.

The term "reduction of the symptoms" refers to reducing the number of the symptoms observed in people who are diagnosed with said disease by administering the pharmaceutical composition comprising the combination of NAC – xanthine derivative compound to diagnosed people. The term "slowing the progression of the disease" refers to administration of the pharmaceutical composition comprising the combination of NAC – xanthine derivative compound to people who are in the first phase of said disease and/or diagnosed with said disease. The term "treatment of the disease" refers to removing present problems related to the disease by administering the pharmaceutical composition comprising the combination of NAC – xanthine derivative compound to people who are diagnosed with said disease and in any phases of the disease.

In another aspect, the composition of the present invention can be administered simultaneously, sequentially or separately so as to be used in the treatment of respiratory tract diseases.

In another aspect, the active agents in the composition of the present invention can be formulated separately in order to be used in a kit form in which they are placed together.

In the present invention, it has been observed that a more effective use is provided by formulating the combination comprising NAC and a xanthine derivative compound in the same dosage form.

In another aspect, the amount of the active agent in the composition of the present invention varies in the range of 0.5-95%, preferably in the range of 1-90% by weight in proportion to the total amount of the pharmaceutical composition. In addition, dosage of the active

ingredient/ingredients in the pharmaceutical composition can vary according to the route of application, the patient's age and state of health.

In another aspect, the pharmaceutical composition of the present invention can comprise NAC in the range of 1-50%, preferably in the range of 1-40%, more preferably in the range of 1-30%; and a xanthine derivative compound in the range of 1-40%, preferably in the range of 1-30% and more preferably in the range of 1-20%.

In another aspect, the pharmaceutical composition comprising the present invention can comprise NAC in the range of 0.1-2000 mg and a xanthine derivative compound in the range of 0.1-800 mg.

According to the invention, NAC which is one of the active agents in the composition pertaining to the present invention is preferably in doses of 200, 600, 900, 1200 mg and xanthine derivative compounds are preferably in doses of 200, 400 mg.

In another aspect; the ratio of NAC: xanthine derivative compounds in the composition of the present invention varies in the range of 8:1 to 0.2:1, preferably in the range of 6:1 to 0.5:1 by weight.

In another aspect, the pharmaceutical composition of the present invention can be prepared as applicable by the oral or inhalation route.

The pharmaceutical compositions of the present invention comprise pharmaceutical formulations comprising the active agents alone or together with pharmaceutically acceptable excipients; and oral dosage forms, inhalation dosage forms comprising these formulations.

According to the present invention; the oral dosage forms can be prepared in solid forms such as tablet; capsule; enterically coated or modified release tablet; prolonged release tablet; delayed release tablet; fast soluble tablet; effervescent tablet; effervescent granule; fast soluble powder mixture; granule; pellet; mini tablet; micro tablet; granule in capsule, pellet in capsule, mini tablet in capsule, micro tablet in capsule; dry powder mixture for syrups; dragee; orodispersible tablets; water-soluble powder, tablet or granule; film tablet or combinations thereof, and in liquid forms such as suspensions. Inhalation dosage forms can be prepared as dry powder formulation, aerosol, suspension and/or solution.

The pharmaceutically acceptable excipients can also be used in addition to the active agents used in oral formulations of the present invention. These excipients are agents such as at least one pharmaceutically acceptable sweetener and/or flavouring agent and optionally stabilizing agent,

diluent, binder, disintegrant, lubricant, effervescent acid-base couple, solvent or solvent mixtures, glidant and surfactant.

Pharmaceutically acceptable sweeteners can be selected from sucralose, sucrose, fructose, glucose, galactose, xylose, dextrose, laevulose, lactose, maltose, maltodextrin, mannitol, maltitol, maltol, sorbitol, xylitol, erythritol, lactitol, isomalt, corn syrup, saccharine, saccharine salts, acesulfame potassium, aspartame, D-tryptophane, monoammonium glycyrrhizinate, neohesperidin dihydrochalcone, thaumatine, neotame, alitame, stevioside and cyclamates. The amount of the sweetener used in the formulations is in the range of 0.1-10%, preferably in the range of 0.1-0.5% by weight.

Pharmaceutically acceptable flavouring agents can be selected from natural aroma oils (such as peppermint oil, wintergreen oil, clove bud oil, parsley oil, eucalyptus oil, lemon oil, orange oil), menthol, menthane, anethole, methyl salicylate, eucalyptol, cinnamon, 1 -methyl acetate, sage, eugenol, oxanone, alpha-irisone, marjoram, lemon, orange, propenyl guaethol acetyl, cinnamon, vanilla, thymol, linalool, cinnamaldehyde glycerol acetal, N-substituted p- menthane-3-carboxamide, 3,1-methoxy propane 1,2-diol. The amount of the flavouring agent used in the formulations is in the range of 0.1-10%, preferably in the range of 0.1-0.5% by weight.

Pharmaceutically acceptable stabilizing agent/agents can be selected from chelating agents and alkalinizing agents.

Pharmaceutically acceptable chelating agents can be selected from disodium EDTA, edetic acid, citric acid, sodium citrate, potassium citrate or combinations thereof.

Pharmaceutically acceptable alkalinizing agents can be selected from alkali metal salts such as sodium carbonate, sodium hydrogen carbonate, sodium hydroxide, sodium silicate, disodium hydrogen orthophosphate, sodium aluminate; alkaline earth metal salts such as calcium carbonate, calcium hydroxide, dibasic calcium phosphate, tribasic calcium phosphate, calcium sulphate, calcium acetate, calcium gluconate, calcium glycerophosphate, magnesium carbonate, magnesium hydroxide, magnesium sulphate, magnesium acetate, magnesium silicate, magnesium aluminate; and organic compounds such as primary, secondary and tertiary amines, cyclic amines, N,N'- dibenzylethylenediamine, diethanolamine, ethylenediamine, meglumine, monosodium glutamate, polacrilin sodium, sodium alginate.

Pharmaceutically acceptable diluents can be selected from lactose, microcrystalline cellulose, starch, pregelatinized starch, modified starch, calcium phosphate (dibasic and/or tribasic), calcium sulphate trihydrate, calcium sulphate dihydrate, calcium carbonate, kaolin, lactitol,

powder cellulose, dextrose, dextrates, dextrin, sucrose, maltose, fructose, mannitol, sorbitol and xylitol. The amount of diluents which can be used in the formulations is in the range of 0.1-80%, preferably in the range of 0.1-70% by weight.

Pharmaceutically acceptable binders can be selected from starches (such as potato starch, corn starch, wheat starch); sugars such as sucrose, glucose, dextrose, lactose, maltodextrin; natural and synthetic gums (such as acacia); gelatine; cellulose derivatives (such as microcrystalline cellulose, HPC, HEC, HPMC, carboxymethyl cellulose, methyl cellulose, ethyl cellulose); polyvinylpyrrolidone (PVP), polyethylene glycol (PEG); waxes; calcium carbonate; calcium phosphate; alcohols (such as sorbitol, xylitol, mannitol) and water. The amount of binder which can be used in the formulations is in the range of 0.1-30%, preferably in the range of 0.1-20% by weight.

Pharmaceutically acceptable effervescent bases can be selected from a group comprising sodium carbonate, sodium hydrogen carbonate, potassium carbonate, potassium hydrogen carbonate, calcium carbonate or combinations thereof. In the case that the formulation of the present invention is in effervescent form, the amount of effervescent base in the formulations is in the range of 10-80%, preferably in the range of 10-60%, more preferably in the range of 20-60% by weight.

Pharmaceutically acceptable effervescent acids can be selected from water soluble polybasic organic acids such as sodium hydrogen sulphate, potassium hydrogen sulphate, sodium dihydrogen phosphate, succinic acid, tartaric acid, adipic acid, citric acid, citric acid anhydrous or their salts, hydrates or anhydrous forms or combinations thereof. In the case that the formulation of the present invention is in effervescent form, the amount of effervescent acid in the formulations is in the range of 10-80%, preferably in the range of 10-60%, more preferably in the range of 20-50% by weight.

Pharmaceutically acceptable lubricants can be selected from metallic stearates (such as magnesium stearate, calcium stearate, aluminium stearate), fatty acid esters (such as sodium stearyl fumarate), fatty acids (such as stearic acid), fatty alcohols, glyceryl behenate, mineral oil, paraffins, hydrogenated vegetable oil, leucine, polyethylene glycols (PEG), metallic lauryl sulphates (such as sodium lauryl sulphate, magnesium lauryl sulphate), sodium chloride, sodium benzoate, sodium acetate and talc. The amount of the lubricant used in the formulations is in the range of 0.1-10%, preferably in the range of 0.1-5%.

Pharmaceutically acceptable glidants can be selected from silicon dioxide, magnesium trisilicate, cellulose powder, starch, talc, tribasic calcium phosphate, metallic stearates, calcium silicate and metallic lauryl sulphates.

Pharmaceutically acceptable surfactants can be selected from polyoxyethylene-sorbitan-fatty acid esters (polysorbates), sodium lauryl sulphate, sodium stearyl fumarate, polyoxyethylene alkyl ethers, sorbitan fatty acid esters, polyethylene glycols (PEG), polyoxyethylene castor oil derivatives, docusate sodium, quaternary ammonium compounds, amino acids such as L-leucine, sugar esters of fatty acids and glycerides of fatty acids.

Pharmaceutically acceptable solvents can be selected from a group comprising toluene, benzene, acetone, methyl acetate, tetrahydrofurane, heptane, hexane, acetonitrile, alcohol and/or alcohol mixtures or combinations thereof.

In addition to these, other pharmaceutically acceptable excipients such as solubility modulators, colouring agents and coating agents can be used in the formulation.

According to the present invention, pharmaceutical compositions can preferably be formulated in the form of water-soluble powder, tablet or granule. More preferred form is effervescent form.

The absorption from the gastrointestinal tract and thus the bioavailability of the pharmaceutical formulation increases when it is formulated in effervescent dosage form. In addition, effervescent dosage forms are also advantageous in respect to ease of use and appealing to a wide patient profile range.

Effervescent formulations of the invention comprise at least one pharmaceutically acceptable sweetener, at least one flavouring agent, at least one binder, at least one solvent, at least one effervescent acid-base couple, at least one lubricant and optionally at least one other pharmaceutically acceptable excipient together with active agents.

However, as a result of the studies conducted within the scope of the invention, the inventors have found that xanthine derivative compound in the combination product does not dissolve in water sufficiently and thus there are some difficulties in the production of effervescent formulations. Said solubility problem has been solved by the new production method developed in scope of the present invention.

A characteristic feature of this production method is that the production is carried out as wet granulating the xanthine derivative compound after mixing it with at least one other pharmaceutically acceptable excipient. Xanthine derivative compound is preferably mixed with

at least one effervescent acid and at least one effervescent base. The effervescent acid preferred to be used in effervescent formulations of the invention is citric acid or a pharmaceutically acceptable derivative thereof and the preferred effervescent base is sodium hydrogen carbonate.

Another characteristic feature of the production method is that the production is carried out as wet granulating the xanthine derivative compound after mixing it with at least one pharmaceutically acceptable effervescent acid and at least one effervescent base. The ratio of effervescent acid to effervescent base herein is in the range of 0.1 to 5, preferably in the range of 0.1 to 4, more preferably in the range of 0.1 to 3.

Another characteristic feature of the production method is that the production is carried out as wet granulating the xanthine derivative compound after mixing it with at least one pharmaceutically acceptable effervescent acid and at least one effervescent base; and adding a pharmaceutically effective amount of NAC and optionally at least one pharmaceutically acceptable sweetener, lubricant and flavouring agent to the obtained granules so as to obtain the final granules.

Another characteristic feature of the production method is that the granulation solution comprises at least one pharmaceutically acceptable binder, at least one solvent or solvent mixture and deionised water. The pharmaceutically acceptable solvent in the granulation solution is preferably alcohol derivative and it composes at least 50% of the granulation solution by weight.

The amount of the pharmaceutically acceptable binder in the granulation solution is in the range of 1-30% by weight.

The solubility of the xanthine derivative compound in the effervescent product produced by this method has been successfully provided.

The combination of the present invention and the pharmaceutical compositions comprising said combination and their preparation methods can be explained with the help of following examples, yet the invention should not be limited to these examples.

EXAMPLES

EXAMPLE 1:

Content	% of amount in unit dose
Active Agent	
N-Acetylcysteine	40
Theophylline	10
Excipients	
Binder	25
Diluent	15
Filling agent	8
Other excipients	2
Total	**100**

The active agents N-Acetylcysteine and theophylline can be formulated as a pharmaceutical composition by the conventional techniques in the prior art. Then, the homogenous mixture obtained is dried and shaped as required.

EXAMPLE 2:

Content	% of amount in unit dose
Active Agent	
N-Acetylcysteine	35
Doxophylline	15
Excipients	
Binder	25
Diluent	15
Filling agent	8
Other excipients	2
Total	**100**

The active agents N-Acetylcysteine and doxophylline can be formulated as a pharmaceutical composition by the conventional techniques in the prior art. Then, the homogenous mixture obtained is dried and shaped as required.

EXAMPLE 3:

Content	% of amount in unit dose
Active Agent	
N-Acetylcysteine	15
Doxophylline	5
Excipients	
Effervescent acid	32
Effervescent base	45
Flavouring agent	1
Binder	1
Sweetener	0.5
Lubricant	0.5
Ethyl alcohol	s.a.*
Deionised water	s.a.*
Total	**100**

** s.a.: sufficient amount*

The method for producing the effervescent doxophylline & NAC formulation given above is as follows:

1. The granulation solution is prepared by mixing sufficient amount of deionised water, ethyl alcohol and binder,
2. Doxophylline, the effervescent acid and the effervescent base are sieved and mixed,
3. The mixture obtained in the second step is wet granulated with the granulation solution obtained in the first step,
4. The granules are dried and sieved,
5. NAC, sweetener, flavouring agent and lubricant are added to the sieved granules and mixed again,
6. The mixture is optionally compressed in tablet form.

CLAIMS

1. An effervescent pharmaceutical composition comprising doxophylline or theophylline together with N-Acetylcysteine as active agents.
2. The pharmaceutical composition according to claim 1 characterized in that the active agents composing the composition is in free form or in the form of pharmaceutically acceptable salts, enantiomers, racemates, solvates, hydrates, different polymorphic forms and amorphous forms of related active agents.
3. The pharmaceutical composition according to claim 1 characterized in that said composition comprises NAC in the range of 1-50% by weight and doxophylline and/or theophylline in the range of 1-40% by weight.
4. The pharmaceutical composition according to claims 1-3 characterized in that said composition comprises at least one pharmaceutically acceptable sweetener, at least one flavouring agent, at least one binder, at least one solvent, at least one effervescent acid-base couple, at least one lubricant and optionally at least one other pharmaceutically acceptable excipient together with the active agents.
5. The pharmaceutical composition according to claim 4 characterized in that the ratio of effervescent acid to effervescent base in said compositions is in the range of 0.1 to 5 by weight.
6. The pharmaceutical composition according to claim 5 characterized in that the ratio of effervescent acid to effervescent base in said compositions is in the range of 0.1 to 4 by weight.
7. The pharmaceutical composition according to claim 6 characterized in that the ratio of effervescent acid to effervescent base in said compositions is in the range of 0.1 to 3 by weight.
8. A method for the production of the pharmaceutical composition according to any preceding claims characterized in that said method is wet-granulation method.
9. The method according to claim 8 characterized in that the mixture is wet-granulated after doxophylline or theophylline is mixed with at least one pharmaceutically acceptable effervescent acid and at least one effervescent base.
10. The method according to claim 9 characterized in that the mixture is wet-granulated after doxophylline or theophylline is mixed with at least one pharmaceutically acceptable effervescent acid and at least one effervescent base; and a pharmaceutically effective amount of NAC and optionally at least one pharmaceutically acceptable sweetener,

lubricant and flavouring agent are added to the obtained granules so as to obtain the final granules.

11. The method according to claims 8-10 characterized in that the pharmaceutically acceptable effervescent acid is citric acid or pharmaceutically acceptable derivative thereof; and effervescent base is sodium hydrogen carbonate.

12. The pharmaceutical composition according to claim 1 characterized in that said composition is used for expectorating and decreasing phlegm in respiratory tract diseases; chronic obstructive pulmonary disease (COPD), allergic rhinitis, acute or chronic bronchitis, catarrh and cold; in the cases that expectoration must be eased; and in treatment of pulmonary diseases, bronchopulmonary diseases, bronchial secretion disorders.

INTERNATIONAL SEARCH REPORT

International application No
PCT/TR2012/000082

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/00 A61K9/20 A61K31/198 A61K31/522 A61P11/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, BIOSIS, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 2011/146031 A1 (MAHMUT BILGIC [TR]) 24 November 2011 (2011-11-24) the whole document	1-12
Y	GB 2 192 790 A (INPHARZAM INT SA INPHARZAM INT SA [CH]) 27 January 1988 (1988-01-27) the whole document	1-12
Y	DE 28 42 822 A1 (MERZ & CO) 3 April 1980 (1980-04-03) claims 1-2 page 5, lines 4-16 page 7, lines 10-11	1-12
Y	EP 2 130 443 A1 (FINZELBERG GMBH & CO KG [DE]) 9 December 2009 (2009-12-09) paragraphs [0026] - [0028]; example 8	1-7

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
15 February 2013	25/02/2013

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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