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(54) **Title:** A PHARMACEUTICAL COMPOSITION CONTAINING IBUPROFEN, PSEUDOEPHEDRINE AND VITAMIN C

(57) **Abstract:** This invention relates to the bilayer tablet composition comprising ibuprofen, pseudoephedrine and vitamin C, wherein ibuprofen compound and pseudoephedrine compound are in the same layer and vitamin C is in the separate layer.



A PHARMACEUTICAL COMPOSITION CONTAINING IBUPROFEN, PSEUDOEPHEDRINE AND VITAMIN C

Field of invention

This invention relates to stable pharmaceutical composition comprising ibuprofen, pseudoephedrine and vitamin C.

Background of the invention

Non-steroidal anti-inflammatory drugs (NSAIDS) are ideally suited for use in cold formulations for their analgesic, anti-inflammatory, and antipyretic activity and low incidence of untoward side effects.

Decongestants are effective for controlling symptoms of nasal and sinus congestion. Swollen, inflamed mucous membranes cause congestion. Decongestants constrict the blood vessels in swollen mucous membranes. This constriction makes tissues shrunk and decongested because constricted blood vessels allow for less fluid to leak into the inflamed tissues.

Vitamins are substances that human body needs to grow and develop normally. There are many vitamins human body needs. Some of them; vitamin A, B vitamins (thiamine, riboflavin, niacin, pantothenic acid, biotin, vitamin B-6, vitamin B-12 and folate), vitamin C, vitamin D, vitamin E, vitamin K. Each vitamin has specific jobs.

Ibuprofen, chemical name is 2-(4-isobutylphenyl) propionic acid, is a well-known anti-inflammatory drug having a molecular weight of 206.28. Ibuprofen is now marketed generically and is patented in the 60's.

Ibuprofen has been used in humans for many years. It is a member of nonsteroidal antiinflammatory drugs (NSAID). Ibuprofen is used for relieving pain and reducing inflammation. And also it has antipyretic properties to reduce fever. Ibuprofen is regarded one of the safest NSAIDs available. However ibuprofen can not be very effective to relief flu, if used alone. Researchers have improved combinations of ibuprofen with decongestants to get quick and effective solutions to treat flu syndromes. Ibuprofen is combined pseudoephedrine, phenylefrine, diphenhydramine in market.

As is apparent from its chemical nomenclature, ibuprofen is a racemic mixture. It is only the racemic mixture which has in fact ever been marketed. The S(+) enantiomer is the active form of ibuprofen.

Pseudoephedrine, chemical name is (1S,2S)-2-methylamino-1-phenylpropan-1-ol, is a well known sympathomimetic drug belongs to phenethylamine and amphetamine classes. Pseudoephedrine is commonly used as decongestant. Pseudoephedrine has been used either as a single ingredient or (more commonly) in combination with dextromethorphan or paracetamol or NSAIDs.

The combination of ibuprofen and pseudoephedrine hydrochloride in suspension and tablet is marketed.

EP2139455 relates to a tablet comprising at least a first (pseudoephedrine) and second active (ibuprofen). The first and second active are blended together optionally with other excipients and formed into a tablet.

Additionally, the combinations of pseudoephedrine with cetirizine, dextropheniramine, fexofenadine, guaifenesin, loratadine, naproxen are present.

There is an endless list of supplements which people use to prevent or treat colds and flu. These supplements, however, have shown an ability to help prevent or shorten a cold in most studies and, especially Vitamin C when it is used to correct vitamin deficiency followed by influenza. Vitamin deficiency is one of the most important parameters to catch flu. Combinations that have been used to treat flu mainly consist of a decongestant and a pain killer agent. There is a need to get a combination that includes vitamins in it.

Summary of the invention

In one aspect the present invention relates to administration of solid oral dosage form comprising ibuprofen, pseudoephedrine, vitamin C and one or more pharmaceutically acceptable excipients, to a patient in need of Vitamin C combined with ibuprofen-pseudoephedrine treatment having a flu and/or prone to that.

The invention provides a pharmaceutical composition in the form of bilayer tablet consisting essentially of:

- a) a first portion containing first active ingredient, such as ibuprofen, wherein the second active ingredient pseudoephedrine is mixed with the first active with additional excipients.
- b) a second portion containing a third active ingredient vitamin C with additional excipients same or different from excipients used at first portion.

In one embodiment, first portion mixture and the second portion mixture is compressed as bilayer tablet wherein the compressed two portions are going to be coated.

Detailed Description of the invention

In this invention, pharmaceutical composition may include many active ingredients. These active ingredients can be a vitamin, an analgesic, a NSAID or a decongestant drug.

In one embodiment, taking vitamins during cold&flu symptoms is extremely important to get the body stronger. Present invention has the advantage to shorten the period of illness compared to vitamin unused treatment conditions. Therefore, it becomes important to support cold relief combinations with vitamins for an effective treatment period.

In this invention, pharmaceutical composition is a bilayer tablet composition for use in the treatment of cold and flu, characterized in that it comprises

- a) a therapeutically effective amount of ibuprofen or pharmaceutical a enantiomer thereof,
- b) a therapeutically effective amount of pseudoephedrine or pharmaceutical acceptable salts thereof,
- c) a therapeutically effective amount of vitamin C.

wherein ibuprofen compound and pseudoephedrine compound are in the same layer and vitamin C is in the separate layer.

In one embodiment, pharmaceutical composition may be formulated, for example, in the form of pharmaceutical compositions for oral administration such as granules, fine granules, powders, tablets, caplets, hard capsules, soft capsules, syrups, emulsions, suspensions, solutions and the like, or in the, form for sublingual a buccal administration. Preferably tablet may include multiple layer-compressed tablets, bilayer tablets, mouth dissolving tablets or orally disintegrating tablets, water dispersible tablets, and chewable tablets wherein tablet is scored or unscored.

In one embodiment, pharmaceutical composition can be prepared by various formulation techniques known to the person skilled in the art, such as, but not limited to direct compression, wet or dry granulation, slugging, hot melt granulation, extrusion-spheronization, hot melt extrusion, fluidized bed granulation, spray drying spray coating, and solvent evaporation and the like.

In one embodiment, present invention is a pharmaceutical composition containing a therapeutically effective amount of ibuprofen, pseudoephedrine and Vitamin C both active ingredients being present in the free state or in the form of a pharmaceutically acceptable salt, solvate, enantiomer. Another object of the present invention is a pharmaceutical composition in a form being able to be administered by the oral route.

In preferred embodiment, present invention relates to bilayer coated tablet formulations of three active ingredients.

In a particular embodiment the second active ingredient that is granulated with first active ingredient selected from pseudoephedrine or pharmaceutical acceptable salts thereof. In one embodiment pseudoephedrine is in the form of hydrochloride or hydrobromide salt thereof.

In one embodiment of the invention, L- ascorbic acid is mixed with one or more excipients as the second portion of the invention.

In an embodiment, the process of preparing the stable pharmaceutical composition comprises steps of preparing a first layer comprising ibuprofen or pharmaceutical acceptable salts or enantiomer thereof, and pseudoephedrine or pharmaceutical acceptable salts thereof, the second layer comprising Vitamin C followed by compressing of bilayer tablet and coating by a protective layer.

In one embodiment, pharmaceutical composition and its formulation process involve avoiding chemical interaction of ibuprofen and pseudoephedrine with ascorbic acid, using pharmaceutically acceptable formulation technique and excipients in the dosage form. An object of the invention is a pharmaceutical composition having a first layer containing

ibuprofen and pseudoephedrine, being present in the free state or in the form of a salt, being intimately mixed in the composition; and a second layer containing ascorbic acid not being intimately mixed with the first layer.

In a further embodiment, the process of preparing a stable pharmaceutical composition comprising:

- (a) preparing a first portion comprising granulation of ibuprofen or salt thereof with one or more excipients, followed by mixing of pseudoephedrine or a salt thereof with one or more excipients same or different from the excipients used with ibuprofen;
- (b) optionally, granulation of ibuprofen and pseudoephedrine followed sieving by 30 mesh sieve;
- (c) preparing a second portion comprising ascorbic acid and one or more excipients;
- (d) compressing the two portions as a bilayer form of a tablet;
- (e) optionally, coating a protective layer over the bilayer tablet prepared in step (d).

In one embodiment, pharmaceutical composition may comprise single or plurality of multiple-compression tablets which are formed by two or more compression cycles. Each compression cycle uses, alternatively, separate or combined portions of each of ibuprofen, pseudoephedrine and ascorbic acid. This results in a multiple-compression tablet which has at least two discrete layers defined by ascorbic acid is in one layer and other actives combined in the second layer. A multiple-compression tablet can exist as, for example, a layered tablet, as a compression-coated tablet, or as an inlay tablet.

A layered tablet is a tablet which is made up of two or more distinct cores of granulation compressed together with the individual layers lying one on top of another. In one embodiment this formulation discloses a bilayer pharmaceutical compressed tablet capable of liberating two or more drugs at different or same release rates.

In a preferred embodiment of the present invention, the tablet consists of two layers wherein one layer is made from Formulation (A) and the other layer is made from Formulation (B), resulting in a bilayer tablet. The components of the pharmaceutical composition according to the present invention are brought together into a bilayer tablet for oral administration according to standard practice and procedures well known to one of ordinary skill in the art using conventional formulation and manufacturing techniques such as that described in the following examples.

In one embodiment, the barrier layer may be formed by any method, including compression, molding, dipping, or spray coating. An object of the present invention is to provide a pharmaceutical composition in oral dosage form as a bilayer tablet which provides immediate release of a ibuprofen/pseudoephedrine combination and again immediate release of a Vitamin C drug that exhibits acceptable bioavailability of each compound. An additional object of the invention is to provide a pharmaceutical composition in bilayer tablet form of high integrity consisting of an immediate release form of two layers. By this way, chemical interaction of Vitamin C with other active ingredients can be eliminated. Because vitamin C is incompatible with ibuprofen and pseudoephedrine.

Oral daily dose of ibuprofen is varying from 600 mg to 3200 mg. Approve ibuprofen administration includes 200 to 400 mg orally every 4 to 6 hours for dysmenorrhea, 400 to 800 mg orally every 6 to 8 hours for osteoarthritis, for rheumatoid arthritis, 200 to 400 mg orally every 4 to 6 hours for pain, 200 to 400 mg orally every 4 to 6 hours for fever.

The recommended dosage for pseudoephedrine hydrochloride in a sustained release formulation can be 120 mg twice daily (b.i.d.).

In one embodiment, pharmaceutical compositions of the present invention, the active ingredients are generally formulated in dosage units containing from 200 to 600 mg of ibuprofen and 30 to 120 mg of pseudoephedrine and 100 to 400 mg of Vitamin C per unit dosage. Another object of the present invention is a pharmaceutical composition containing 200 mg of ibuprofen and 30 mg of pseudoephedrine and 300 mg of Vitamin C or 400 mg of ibuprofen and 60 mg of pseudoephedrine and 300 mg of Vitamin C.

In one embodiment, the pharmaceutical composition of the invention is suitable for BID, TID or QID administrations. Here BID, TID, QID refer to two times a day, three times a day, four times a day respectively.

In one embodiment, pharmaceutical composition of the present invention may further comprise diluents, binders, suspending agents, disintegrants, stabilizing agents, adsorbents, surfactants, lubricants, disinfectants, glidants, flavoring agents, sweeteners and other pharmaceutical additives or excipient to facilitate the physical formulation of various dosage forms like tablets, capsules, orally disintegrating tablets, chewable tablets and suspensions (including dry powders or granules for suspension).

Binders can be selected from the group, but are not limited to, methylcellulose, sodium carboxymethylcellulose, calcium carboxymethylcellulose, ethyl cellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, silicified microcrystalline cellulose (SMCC), polyvinyl pyrrolidone (Povidon), gelatine, polyvinyl alcohol, acacia, tragacanth, guar, pectin, starch paste, pre-gelatinized starch, alginic acid, compressible sugar, liquid glucose, dextrates, dextrin, dextrose, maltodextrin, magnesium aluminium silicate, polymethacrylates, sorbitol and other materials known to one of ordinary skill in the art. A preferred binder is polyvinylpyrrolidone. A mixture of binders may also be used. The binder is preferably used in an amount of from about 0.5 to about 5% by weight.

Diluents can be selected from the group, but are not limited to, calcium carbonate, calcium phosphate, calcium sulphate, carboxymethylcellulose calcium, carboxymethylcellulose sodium, compressible sugar, confectioner's sugar, dextrates, dextrin, dextrose, dibasic calcium phosphate dihydrate, dibasic calcium phosphate, fructose, glyceryl palmitostearate, glycine, hydrogenated vegetable oil-type 1, kaolin, lactose, maize starch, magnesium carbonate, magnesium oxide, maltodextrin, mannitol, microcrystalline cellulose, polymethacrylates, potassium chloride, powdered cellulose, pregelatinised starch, sodium chloride, sorbitol, starch, sucrose, sugar spheres, talc, tribasic calcium phosphate, and xylitol or mixture thereof. A preferred diluent is calcium hydrogen phosphate and/or microcrystalline cellulose. Diluents are used in general 1% to 20 % amounts.

Disintegrants can be selected from the group, but are not limited to carboxymethylcellulose calcium, carboxymethyl cellulose, carboxymethylcellulose sodium, cross-linked sodium carboxymethylcellulose, low substituted hydroxypropyl cellulose, colloidal silicon dioxide, croscarmellose sodium, crospovidone, guar gum, magnesium aluminium silicate, microcrystalline cellulose, methyl cellulose, polyvinylpyrrolidone, cross-linked polyvinylpyrrolidones, polacrillin potassium, starch, pregelatinised starch, sodium alginate, sodium lauryl sulphate, sodium starch glycolate, crystalline cellulose, hydroxypropyl starch and other materials known to one of ordinary skill in the art. The combination of above-mentioned disintegrants can also be used. The preferred disintegrants are croscarmellose sodium and microcrystalline cellulose. The disintegrant is preferably used in an amount of from about 0.5% to about 20% by weight.

Lubricants can be selected from the group, but are not limited to, vegetable oils, such as hydrogenated vegetable oil or hydrogenated castor oil, polyethylene glycols, such as polyethylene glycol (PEG)-4000 and PEG-6000; stearic acid; derivatives of stearic acid, such as magnesium stearate, sodium stearate, calcium stearate, zinc stearate, glyceryl monostearate, glyceryl palmitostearate and sodium stearyl fumarate; mineral salts, such as talc; inorganic salts; organic salts, such as sodium benzoate, sodium acetate, sodium chloride and sodium oleate; and polyvinyl alcohols, microcrystalline cellulose, sodium lauryl sulfate, silica, colloidal silica, cornstarch, calcium silicate, magnesium silicate, silicon hydrogel and other materials known to one of ordinary skill in the art. The preferred lubricant is talc and hydrogenated castor oil. Preferably, lubricant is used in an amount from about 1 to about 10% by weight.

Glidants can be selected from the group, but are not limited to, colloidal silicon dioxide, colloidal silica, cornstarch, talc, calcium silicate, magnesium silicate, magnesium trisilicate, amorphous silica, colloidal silicon, silicon hydrogel, powdered cellulose, silicon dioxide, talc, tribasic calcium phosphate and other materials known to one of ordinary skill in the art. Glidants are used in an amount from about 0.1 to about 30% percent by weight.

Dispersing agents or dispersants can be selected from the group, but are not limited to, colloidal silicon dioxide, talc, magnesium stearate and titanium dioxide and other materials known to one of ordinary skill in the art.

Stabilizing agent can be selected from the group, but are not limited to, consisting of polysorbates, cellulose derivatives such as hydroxypropylcellulose, hydroxypropylmethylcellulose, poloxamers, carbomers, silicon dioxide, carbonates, sulfates, phosphates, hydroxides of alkaline or alkaline earth metals, sodium carboxymethyl cellulose, polyvinylpyrrolidone, Labrasol®, Gelucire®, gelatin, lecithin (phosphatides), gum acacia, cholesterol, tragacanth, carotenoids, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, sorbitan fatty acid esters, polyethylene glycols, polyoxyethylene stearates, mono and diglycerides, colloidal silicon dioxide, sodium dodecylsulfate, magnesium aluminum silicate, triethanolamine, stearic acid, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, short and medium chain alcohols, Labrafil®, Puro-oleique®, polyvinyl alcohol and combinations thereof.

Polymers can be selected from the group, but are not limited to, hydroxypropylmethyl cellulose, microcrystalline cellulose, hydroxypropyl cellulose, ethyl cellulose,

hydroxypropylmethyl cellulose phthalate, hydroxypropylmethyl cellulose ;
cellulose acetate phthalate; methacrylic polymers, aminoalkyl methacrylate copolymer.

Surfactants can be selected from the group, but are not limited to, also polyoxyethylene hardened castor oil, glyceryl monostearate, sorbitan monostearate, sorbitan monopalmitate, sorbitan monolaurate, polyoxyethylene-polyoxypropylene block copolymers, polysorbates 80, sodium laurylsulfate, macrogols, sucrose esters of fatty acids and other materials known to one of ordinary skill in the art.

To come up with the final formulation; the formulation of ibuprofen and pseudoephedrine combination was taken as a reference as shown in the example 1 and 2. According to fixed ibuprofen/pseudoephedrine combination; additional studies were completed for the final formulation of ibuprofen/pseudoephedrine/vitamin C combination. An additional ascorbic acid layer was improved according to previous studies. Example 1 and 2 show us the development of ibuprofen/pseudoephedrine studies. Final formula of ibuprofen/pseudoephedrine combination is fixed as shown in example 2.

In the present invention, tablet consists of two layers wherein one layer is consisting ibuprofen/pseudoephedrine combination and the other layer is consisting ascorbic acid, resulting in a bilayer tablet. The components of the pharmaceutical composition according to the present invention are brought together into a bilayer tablet for oral administration as shown in examples 3, 4, and 5. The following examples are understood to be illustrative only.

Example 1: Ibuprofen/pseudoephedrine

First layer	mg/unit	%w/w
Ibuprofen	200.0	49.6
Pseudoephedrine Hydrochloride	30.0	7.44
CalciumHydrogen Phosphate (anhydrous)	60.0	14.89
Microcrystalline Cellulose	51.4	12.75
Povidone K-30	7.8	1.94
Croscarmellose Sodium	32.0	7.94
Colloidal Silicon Dioxide	-	
Extra		
Talc	4.0	0.99
Hydrogenated Castor Oil	7.8	1.94
Isopropyl alcohol	10.0	2.48
Coating		
Opadry yellow	10.0	2.48
Sheffcoat yellow	-	
Total	403.0	100

Mixture of ibuprofen, calcium hydrogen phosphate and croscarmellose sodium is granulated and mixed for 10 minutes.

Separately, isopropyl alcohol, povidone and talc is mixed in a stainless container for 10 minutes. The ibuprofen and povidone parts are then combined together to form a next mixture. Then the mixture is dried.

Separately prepared pseudoephedrine hydrochloride and microcrystalline cellulose are added to the final mixture. Then the mixture is lubricated with the addition of talc and hydrogenated castor oil.

The final mixture is then compressed to form a tablet. The tablets are finally coated with opadry yellow.

Example 2: Ibuprofen/pseudoephedrine

First layer	mg/unit	%w/w
Ibuprofen	200.0	49.6
Pseudoephedrine Hydrochloride	30.0	7.44
Calcium Hydrogen Phosphate (anhydrous)	50.0	12.41
Microcrystalline Cellulose	43.7	10.84
Povidone K-30	7.8	1.94
Croscarmellose Sodium	32.0	7.94
Colloidal Silicon Dioxide	12.0	2.98
Extra		
Talc	4.0	0.99
Hydrogenated Castor Oil	7.8	1.94
Isopropyl alcohol	20.0	2.48
Coating		
Opadry yellow	-	
Sheffcoat yellow	10.0	2.48
Total	403.0	100

Mixture of ibuprofen, calcium hydrogen phosphate and croscarmellose sodium is granulated and mixed for 10 minutes.

Separately, isopropyl alcohol, povidone and talc is mixed in a stainless container for 10 minutes. The ibuprofen and povidone parts are then combined together to form a next mixture. Then the mixture is dried.

Separately prepared pseudoephedrine hydrochloride, silicon dioxide and microcrystalline cellulose mixture is added to the final mixture. Then the mixture is lubricated with the addition of talc and hydrogenated castor oil.

The final mixture is then compressed to form a tablet. The tablets are finally coated with sheffcoat yellow.

Example 3: ibuprofen/pseudoephedrine/ascorbic acid

First layer	mg/unit	%w/w
Inside part		
Ibuprofen	200.0	24.84
Calcium Hydrogen Phosphate (anhydrous)	50.0	6.21
Croscarmellose Sodium	15.0	1.86
Povidone K-30	7.8	0.97
Talc	5.85	0.73
Isopropyl alcohol	20.0	2.48
Outside part		
Pseudoephedrine Hydrochloride	30.0	3.73
Microcrystalline Cellulose	43.7	5.43
Colloidal Silicon Dioxide (anhydrous)	12.0	1.49
Croscarmellose Sodium	15.0	1.86
Hydrogenated Castor Oil	7.8	0.97
Talc	5.85	0.73
Second layer		
Vitamin C	300.0	37.27
Colloidal Silicon Dioxide (anhydrous)	3.0	0.37
Hydrogenated Castor Oil	3.0	0.37
Microcrystalline Cellulose	81.0	10.06
Coating		
Opadry 200 200F265017 BROWN	25.0	3.11
Total	805.0	100

Mixture of ibuprofen, calcium hydrogen phosphate and croscarmellose sodium mixture is granulated by addition of separately prepared isopropyl alcohol, povidone and talc mixture and let it to dry. Half amounts of colloidal silicon dioxide and microcrystalline cellulose are added to dried mixture and mixed for extra 10 minutes. The remained parts of colloidal silicon dioxide, microcrystalline cellulose and pseudoephedrine hydrochloride is mixed separately and added to final mixture. First layer mixture is prepared after addition of croscarmellose sodium and oil to the final mixture.

Second layer mixture is prepared separately by mixing ascorbic acid, microcrystalline cellulose, colloidal silicon dioxide and oil.

Separately prepared two parts are then compressed according to specifications to form a bilayer tablet. The tablets are finally coated with opadry brown.

Example 4: Ibuprofen/pseudoephedrine/ascorbic acid

First layer	mg/unit	%w/w
Inside part		
Ibuprofen	200.0	24.84
CalciumHydrogen Phosphate (anhydrous)	50.0	6.21
Croscarmellose Sodium	15.0	1.86
Povidone K-30	7.8	0.97
Talc	5.85	0.73
Isopropyl alcohol	20.0	2.48
Outside part		
Pseudoephedrine Hydrochloride	30.0	3.73
Microcrystalline Cellulose	43.7	5.43
Colloidal Silicon Dioxide(anhydrous)	12.0	1.49
Croscarmellose Sodium	15.0	1.86
Hydrogenated Castor Oil	7.8	0.97
Talc	5.85	0.73
Second layer		
Vitamin C	300.0	37.27
Colloidal Silicon Dioxide (anhydrous)	3.0	0.37
Hydrogenated Castor Oil	3.0	0.37
Microcrystalline Cellulose	81.0	10.06
Coating		
Opadry® AMB 80W80941 Blue	25.0	3.11
Total	805.0	100

Tablets are prepared according to procedure followed at example 3. Separately prepared two parts are then compressed according to specifications to form a bilayer tablet. The tablets are finally coated with opadry blue.

Claims

1. A bilayer tablet composition for use in the treatment of cold and flu, characterized in that it comprises

a) a therapeutically effective amount of ibuprofen or pharmaceutical acceptable salts or enantiomer thereof,

b) a therapeutically effective amount of pseudoephedrine or pharmaceutical acceptable salts thereof,

c) a therapeutically effective amount of vitamin C.

wherein ibuprofen compound and pseudoephedrine compound are in the same layer and vitamin C is in the separate layer.

2. A bilayer tablet composition according to claim 1, wherein pseudoephedrine pharmaceutical acceptable salt is pseudoephedrine hydrochloride.

3. A bilayer tablet composition according to claim 1, characterized in that it is provided in a form containing 100 to 600 mg of ibuprofen, 10 to 60 mg of pseudoephedrine and 100 to 400 mg of vitamin C per unit dose.

4. A bilayer tablet composition according to claim 3, characterized in that it is provided in a form containing 200 mg of ibuprofen, 30 mg of pseudoephedrine and 300 mg of vitamin C per unit dose.

5. A bilayer tablet composition according to claim 3, characterized in that it is provided in a form containing 400 mg of ibuprofen, 60 mg of pseudoephedrine and 300 mg of vitamin C per unit dose.

6. A bilayer tablet composition according to any one of the preceeding claims, wherein it comprises microcrystalline cellulose and calcium hydrogen phosphate as filler, croscarmellose sodium as disintegrant, colloidal silicon dioxide as glidant, povidone as binder, hydrogenated castor oil and talc as lubricant.

INTERNATIONAL SEARCH REPORT

International application No
PCT/TR2015/000046

A. CLASSIFICATION OF SUBJECT MATTER INV. A61K9/20 A61K9/24 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, EMBASE		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JP 2007 302578 A (SORM CO LTD) 22 November 2007 (2007-11-22) example 12 claims; examples -----	1-6
X	US 2001/043959 A1 (GELBER DANIEL [US] ET AL) 22 November 2001 (2001-11-22) examples paragraph [0069] -----	1-6
X	US 6 120 802 A (BREITENBACH JOERG [DE] ET AL) 19 September 2000 (2000-09-19) claim 8 examples column 5 - column 6 -----	1-6
A	US 6 251 945 B1 (EINIG HEINZ [DE] ET AL) 26 June 2001 (2001-06-26) -----	1-6
☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
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