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(54) **Title:** NEW PHARMACEUTICAL COMPOSITIONS CONTAINING EPINASTINE AND PSEUDOEPHEDRINE

(57) **Abstract:** The present invention relates to novel oral pharmaceutical compositions comprising as pharmaceutically active compounds a combination of an antihistaminic-effective amount of epinastine or a pharmaceutically acceptable salt thereof and of a decongestant-effective amount of pseudoephedrine or a pharmaceutically acceptable salt thereof and further comprising suitable pharmaceutically acceptable carriers or excipients. The invention further relates to methods for the preparation these compositions and methods of using them in the treatment of allergic diseases and/or disorders.

New pharmaceutical compositions containing epinastine and pseudoephedrine

Background of the invention

The present invention relates to novel oral pharmaceutical compositions comprising as pharmaceutically active compounds a combination of an antihistaminic-effective amount of epinastine or a pharmaceutically acceptable salt thereof and of a decongestant-effective amount of pseudoephedrine or a pharmaceutically acceptable salt thereof and further comprising suitable pharmaceutically acceptable carriers or excipients. The invention further relates to methods for the preparation these compositions and methods of using them in the treatment of allergic diseases and/or disorders.

Description of the invention

A first aspect of the present invention provides for oral pharmaceutical compositions comprising as pharmaceutically active compounds a combination of an antihistaminic-effective amount of epinastine or a pharmaceutically acceptable salt thereof and of a decongestant-effective amount of pseudoephedrine or a pharmaceutically accptable salt thereof and further comprising pharmaceutically acceptable carriers or excipients under the proviso that the composition does not contain a leukotriene antagonist.

As an additional active compound the compositions may optionally contain one or several compounds selected from the group consisting of mucolitic and analgesic-antipyretic compounds and vitamines. Preferred mucolitic ingredients may be selected from bromhexine and ambroxol. Preferred analgesic-antipyretic compounds can be selected from paracetamol and obuprofen. Preferred vitamines may be selected from vitamine B2, B6 and C.

A second aspect of the present invention provides a use of a pharmaceutical composition according to the above in the manufacture of a medicament for the treatment of allergic rhinitis, allergic congestion of the Eustachian tubes and / or other diseases from allergic origin deserving the administration of antihistamine and decongestant drugs, common cold and in the symptomatic relief associated with cough, cold and flu symptoms. The use of the pharmaceutical compositions in the manufacture of a medicament for the treatment of allergic rhinitis, allergic

congestion of the Eustachian tubes and / or other diseases from allergic origin deserving the administration of antihistamine and decongestant drugs is preferred.

In a preferred embodiment the pharmaceutical composition may contain as the active ingredients only an antihistaminic-effective amount of epinastine or a pharmaceutically acceptable salt thereof and a decongestant-effective amount of pseudoephedrine or a pharmaceutically accptable salt thereof

In a preferred embodiment the present invention may relate to an oral pharmaceutical composition, preferably a bilayer tablet, providing for a sustained release of the decongestant effective amount of pseudoephedrine and an immediate release of an antihistaminic effective amount of epinastine.

Particularly preferred can be a bilayer tablet wherein a first layer A, providing for the sustained release of pseudoephedrine, comprises a decongestant effective amount of pseudoephedrine or a pharmaceutically acceptable salt thereof and wherein a second layer B, providing for the immediate release of epinastine, comprises an antihistaminic effective amount of epinastine or a pharmaceutically acceptable salt thereof. The bilayer tablet may additionally contain a tablet coating C consisting of pharmaceutically acceptable excipients which mask the bitter taste of one of the active compounds.

In a preferred embodiment layer A of the bilayer tablet may comprise a decongestant effective amount of pseudoephedrine or a pharmaceutically acceptable salt thereof in a matrix of a swellable hydrophilic polymer which provides a sustained release profile in a period of 3 to 24, preferably 6 to 18, most preferably about 12 hours.

According to the invention the term pharmaceutically acceptable salts stands for acid addition salts of the active compounds pseudoephedrine and epinastine. These acid addition salts can be formed with anorganic acids like hydrochloric acid, hydrobromic acid or sulfuric acid or with organic acids as for instance oxalic acid, fumaric acid or methansulfonic acid. Epinastine is preferably used as its hydrochloric acid addition

salt. Pseudoephedrine is preferebly used as the hydrochloride or the sulfate. Within the present invention pseudoephedrine sulfate is most preferred.

The release of pseudoephedrine takes place over 3 to 24, preferably 6 to 18, most preferably about 12 hours. This bilayer tablet is designed to be preferably administered twice daily.

The concentration range of pseudoephedrine salt in the compositions may be between 5 and 240 mg/tablet, preferably 10 to 200 mg/tablet, more preferably 60 to 180 mg/tablet, preferably 80 to 140 mg/tablet, most preferably 120 mg/tablet. The concentration range of epinastine salt in the compositions can be between 2 and 20 mg/tablet, preferably 5 to 10 mg/tablet, more preferably 10 mg/tablet.

Each layer of the tablet is in contact with each other in a portion of their surface, but provides independent release profiles for both active substances mentioned before. The sustained release layer A consists of pseudoephedrine or a pharmaceutically acceptable salt thereof and a swellable hydrophilic polymer .
Typical swellable hydrophilic polymers include cellulosic ethers such as methylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, carboxymethylcellulose and carboxyethylcellulose or mixtures thereof. The use of hydroxypropylmethylcellulose (HPMC) is preferred. Particularly useful are the HPMC polymers HPMC USP2910 and USP2208 like for instance Methocel E5, E4M, E15M, K15M, and K100M supplied by the Dow Chemical Company. In the aformentioned abbreviations the designation "E" refers to USP2910 whereas "K" refers to USP2208. The number designation refers to the viscosity in a 2% aqueous solution (e.g. 5 designates a viscosity of 5 cps; 15M designates a viscosity of 15000 cps).

The excipients that could be optionally used in the sustained release layer A are insoluble polymers, soluble or insoluble fillers, antiadherents, coloring agents, lubricants and additional binders. Typical fillers are for example lactose, microcrystalline cellulose, dibasic calcium phosphate and cornstarch. Examples of antiadherents, which are used to prevent tablets from sticking to the tablet press, are

colloidal silicon dioxide and talc. Magnesium stearate, talc and stearic acid are typical lubricants. Typical binders are povidone, and cornstarch.

The immediate release matrix layer B comprises epinastine within different combinations of excipients. The excipients that could be optionally used in the immediate release layer B are insoluble polymers, soluble or insoluble fillers, antiadherents, lubricants, coloring agents,disintegrants and additional binders. Typical fillers are for example lactose, microcrystalline cellulose, dibasic calcium phosphate and cornstarch. Examples of antiadherents, which are used to prevent tablets from sticking to the tablet press, are colloidal silicon dioxide and talc. Typical disintegrants are crospovidone, sodium starch glycolate and crosscarmellose sodium. Typical coloring agents are selected from FD&C red 40 HT Aluminum lake, 2-hydroxy-1,1'-azonaphthalene-3,6,4'-trisulfonic acid trisodium salt, erythrosine, iron oxides, 1-(4-sulpho-1-naphthylazo)-2-naphthol-6,8-disulphonic acid trisodium salt, 2',4',5',7'-tetrabromo-4,5,6,7-tetrachloro-fluorescein disodium salt, 2,4,5,7-Tetraiodo-3,6-dihydroxyxanthene-9-spiro-1'-(4',5',6',7'-tetrachloro-3'H-isobenzofuran-3'one dipotassium salt, trisodium 3-carboxy-5-hydroxy-1-p-sulphophenyl-4-p-sulfophenylazopyrazole, 6-hydroxy-5-((4-sulphonphenyl)azo-2-naphthalenesulphonic acid disodium salt and optionally aluminium lakes thereof. Magnesium stearate, talc and stearic acid are typical lubricants. Typical binders are povidone, and cornstarch.

Water and ethanol are examples of volatile components which can be used in the manufacture process of both layers to granulate powders. These volatile components are removed during processing and therefore do not appear in the finished product.

The tablet coating is optional since the presence of it does not modifies significantly the release rates of the active substances present in the core layers. The presence of the coating is preferred because it masks the bitter taste of one of the active substances and enhances the properties of dosage form. Because of that a lot different coatings with different polymers, and plasticizers and other excipients could be used with the condition of not modifying significantly the release profile of the active substances present in the core tablet. A typical coating comprises a polymer such as hydroxypropylmethylcellulose and a plasticizer such as polyethylene glycol.

Optional excipients could be added to the coating like antifoaming agents and opacifying. Example of an antifoaming agent is silicone. Examples of opacifying agents are Titanium dioxide, talc and aluminum lake dyes.

The invention will be further described by the following examples. These examples disclose certain preferred embodiments of the invention. The methods of manufacturing the compositions according to the invention like for instance granulation, tablet compression, tablet coating etc. are well known to the person skilled in the art. Those skilled in the art will appreciate that various changes, modifications and substitutions can be made therein without departing from the spirit of the invention. Accordingly, it is intended that the invention be not limited to the following explicitly disclosed examples.

Example N°1 - Composition

Core

A. First layer

Layer pseudoephedrine	**mg/tablet**
Pseudoephedrine sulfate	120.00
Methocel K 15 M PRCR *	198.00
Lactose Monohydrate	105.10
Microcrystalline cellulose	106.00
Colloidal silicon dioxide	1.65
Magnesium Stearate	2.75
Povidone	16.50
Total first layer	**550.00**

B. Second layer

Layer Epinastine	**mg / tablet**
Epinastine HCl	10.00
FD&C red 40 HT Aluminum lake (allura red AC)	0.38
Microcrystalline cellulose	70.00
Lactose Monohydrate	154.62
Povidone	12.50

Magnesium Stearate	2.50
Total second layer	**250.00**

Total core	**800.00**

C. Coating

Film Coating	**mg/ tablet**
Methocel E5	15.00
Polyethylene Glycol 6000	1.97
Silicone antifoam S184	0.03
Total film coating	**17.00**

Total Film coated tablet	**817.00**

* PR means Premium grade and CR means Controlled Released grade.

Method of Manufacture

A. First layer:

A1. Dissolve povidone in a hydroalcoholic mixture;

A2. Blend pseudoephedrine sulfate, a portion of the microcrystalline cellulose, lactose and Methocel K15M for 5-30 minutes in a suitable mixer.

A3. Use alcoholic or hydroalcoholic solution prepared previously in step A1. to granulate the powder mix.

A4. Dry and mill the pseudoephedrine sulfate granulation from step A3, using suitable size screen.

A5. Blend the screened pseudoephedrine sulfate granulation with a portion of the microcrystalline cellulose and colloidal silicon dioxide for 3-15 minutes.

A6. Add magnesium stearate and blend for 3-15 minutes.

B Second layer:

B1. Pass through a suitable screen Epinastine HCL, Allura red AC (FD & C red 40 HT) aluminum lake and microcrystalline cellulose. Blend for 5-30 minutes in a suitable mixer.

B2. Add lactose and povidone. Blend for 60 minutes 15-120 minutes in a suitable mixer.

B3. Add magnesium stearate. Blend for 3-20 minutes in a suitable mixer.

C. Compression:

Compress A and B into a suitable bilayer tableting machine in suitable size tablets.

D. Coating

D1. Dissolve Methocel E5 and Polyethylene Glycol in suitable amount of water.

D2. Dissolve silicone antifoam in suitable amount of isopropilic alcohol.

D3. Add 2. to 1. and mix.

D4. Coat tablets with the Methocel E5 /Polyethylene glycol solution from step D3. in a suitable coater.

Example N° 2 - Composition

Core

A. First layer

Layer pseudoephedrine	**Mg/tablet**
Pseudoephedrine sulfate	120.00
Methocel K 15 M PRCR *	198.00
Lactose Monohydrate	126.50
Microcrystalline cellulose	100.00
Colloidal silicon dioxide	2.75
Magnesium Stearate	2.75
Total first layer	**550.00**

B. Second layer

Layer Epinastine	**Mg / tablet**
Epinastine HCl	10.00
Lactose Monohydrate	168.40
Microcrystalline cellulose	70.00
Punceau 4R red aluminum lake	0.38
Magnesium Stearate	1.25
Total second layer	**250.00**

Total core	**800.00**

C. Coating

Film Coating	mg/ tablet
Methocel E5	4.42
Polyethylene Glycol 6000	2.72
Talc	8.76
Titanium dioxide	1.10
Total film coating	**17.00**

Total Film coated tablet	**817.00**

* PR means Premium grade and CR means Controlled Released grade.

Method of Manufacture

A. First layer:

A1. Blend pseudoephedrine sulfate, microcrystalline cellulose, lactose, colloidal silicon dioxide and HPMC K15M for 5-30 minutes in a suitable mixer.

A2. Add magnesium stearate and blend for 3-15 minutes.

B. Second layer:

B1. Pass through a suitable screen Epinastine HCl, and microcrystalline cellulose. Blend for 5-30 minutes in a suitable mixer.

B2. Add lactose. Blend for 60 minutes 15-120 minutes in a suitable mixer.

B3. Add magnesium stearate. Blend for 3-20 minutes in a suitable mixer.

C. Compression:

Compress A and B into a suitable bilayer tableting machine in suitable size tablets.

D. Coating

D1. Dissolve Methocel E5 and Polyethylene Glycol in suitable amount of water.

D2. Add Titanium Dioxide and Talc in suitable amount of water and mix

D3. Add 2. to 1. And mix.

D4. Coat tablets with the Methocel E5 /Polyethylene glycol solution from step D3. in a suitable coater.

Example N° 3

Core

A. First layer

Layer pseudoephedrine	Mg/tablet
Pseudoephedrine sulfate	120.00
Methocel K4M PRCR	247.50
Lactose Monohydrate	166.00
Talc	11.00
Magnesium Stearate	5.50
Total first layer	**550.00**

* PR means Premium grade and CR means Controlled Released grade.

Second layer and coating are identical to example 2; the manufacture method was conducted analogously to the method outlined in example 2;

Example N° 4

Core

A. First layer

Layer pseudoephedrine	Mg/tablet
Pseudoephedrine sulfate	120.00
Methocel K15 M PRCR	198.00
Lactose Monohydrate	99.50
Microcrystalline cellulose	99.50
Colloidal silicon dioxide	2.75
Povidone	27.50
Magnesium stearate	2.75
Total	**550.00**

* PR means Premium grade and CR means Controlled Released grade.

Second layer and coating are identical to example 1; the manufacture method was conducted analogously to the method outlined in example 1;

Example N° 5

Core

A. First layer

Layer pseudoephedrine	Mg/tablet
Pseudoephedrine sulfate	120.00
Methocel K15M CR	330.00
Lactose	83.50
Talc	11.00
Magnesium Stearate	5.50
Total	**550.00**

* CR means Controlled Released grade.

Second layer and coating are identical to example 1; the manufacture method was conducted analogously to the method outlined in example 1;

Example N° 6

Core

A. First layer

Layer pseudoephedrine	Mg/tablet
Pseudoephedrine sulfate	120.00
Methocel K15M CR	275.00
Microcrystalline Cellulose	138.50
Talc	11.00
Magnesium Stearate	5.50
Ethanol	sq.
Total	**550.00**

* CR means Controlled Released grade.

Second layer and coating are identical to example 1; the manufacture method was conducted analogously to the method outlined in example 1;

Example N° 7

Core

A. First layer

Layer pseudoephedrine	Mg/tablet
Pseudoephedrine sulfate	120.00
Methocel K15M CR	215.00
Dibasic Calcium phosphate	108.50
Ethylcelullose	40.00
Talc	11.00
Magnesium Stearate	5.50
Ethanol	s.q.
Total	**500.00**

* CR means Controlled Released grade.

Second layer and coating are identical to example 1; the manufacture method was conducted analogously to the method outlined in example 1;

Example N° 8

Core

A. First layer

Layer pseudoephedrine	Mg/tablet
Pseudoephedrine sulfate	120.00
Methocel K15M CR	137.50
Methocel K100M CR	137.50
Lactose	138.50
Talc	11.00
Magnesium Stearate	5.50
Ethanol	s.q.
Total	**550.00**

* CR means Controlled Released grade.

Second layer and coating are identical to example 1; the manufacture method was conducted analogously to the method outlined in example 1;

Example N° 9

Core

A. First layer

Layer pseudoephedrine	Mg/tablet
Pseudoephedrine sulfate	120.00
Methocel K100M CR	275.00
Lactose	138.50
Talc	11.00
Magnesium Stearate	5.50
Ethanol	s.q.
Total	**550.00**

* CR means Controlled Released grade.

Second layer and coating are identical to example 1; the manufacture method was conducted analogously to the method outlined in example 1;

Example N° 10

Core

A. First layer

Layer pseudoephedrine	Mg/tablet
Pseudoephedrine sulfate	120.00
Methocel K15M CR	206.20
Methocel K100M CR	68.80
Lactose	138.50
Talc	11.00
Magnesium Stearate	5.50
Ethanol	s.q.
Total	**550.00**

* CR means Controlled Released grade.

Second layer and coating are identical to example 1; the manufacture method was conducted analogously to the method outlined in example 1;

Example N° 11

Core

A. First layer

Layer pseudoephedrine	Mg/tablet
Pseudoephedrine sulfate	120.00
Methocel K15M CR	235.00
Dibasic Calcium phosphate	108.50
Ethylcellulose	20.00
Talc	11.00
Magnesium Stearate	5.50
Ethanol	s.q.
Total	**500.00**

* CR means Controlled Released grade.

Second layer and coating are identical to example 1; the manufacture method was conducted analogously to the method outlined in example 1;

Example N° 12

Core

A. First layer

Layer pseudoephedrine	Mg/tablet
Pseudoephedrine sulfate	120.00
Methocel K15M CR	255.00
Lactose	40.00
Microcrystalline Cellulose	68.50
Talc	11.00
Magnesium Stearate	5.50
Ethanol	s.q.
Total	**500.00**

* CR means Controlled Released grade.

Second layer and coating are identical to example 1; the manufacture method was conducted analogously to the method outlined in example 1;

Example N° 13

Core

A. First layer

Layer pseudoephedrine	**Mg/tablet**
Pseudoephedrine sulfate	120.00
Methocel K15M CR	255.00
Dibasic calcium phosphate	108.50
Talc	11.00
Magnesium Stearate	5.50
Ethanol	s.q.
Total	**500.00**

* CR means Controlled Released grade.

Second layer and coating are identical to example 1; the manufacture method was conducted analogously to the method outlined in example 1;

Claims

1) Oral pharmaceutical compositions comprising as pharmaceutically active compounds a combination of an antihistaminic-effective amount of epinastine or a pharmaceutically acceptable salt thereof and of a decongestant-effective amount of pseudoephedrine or a pharmaceutically acceptable salt thereof and further comprising pharmaceutically acceptable carriers or excipients under the proviso that the composition does not contain a leukotriene antagonist.

2) Oral pharmaceutical composition according to claim 1, characterized in that it contains as the active ingredients only an antihistaminic-effective amount of epinastine or a pharmaceutically acceptable salt thereof and a decongestant-effective amount of pseudoephedrine or a pharmaceutically accptable salt thereof.

3) Oral pharmaceutical composition according to claim 1 or 2, providing for a sustained release of the decongestant effective amount of pseudoephedrine and an immediate release of an antihistaminic effective amount of epinastine.

4) Oral pharmaceutical composition according to claims 1, 2 or 3, characterized in that it represents a bilayer tablet.

5) Bilayer tablet according to claim 4, wherein a first layer A, providing for the sustained release of pseudoephedrine, comprises a decongestant effective amount of pseudoephedrine or a pharmaceutically acceptable salt thereof and wherein a second layer B, providing for the immediate release of epinastine, comprises an antihistaminic effective amount of epinastine or a pharmaceutically acceptable salt thereof.

6) Bilayer tablet according to claim 5, characterized in that it additionally contains a tablet coating C consisting of pharmaceutically acceptable excipients.

7) Bilayer tablet according to claim 4, 5 or 6, characterized in that layer A comprises a decongestant effective amount of pseudoephedrine or a pharmaceutically acceptable salt thereof in a matrix of a swellable hydrophilic polymer.

8) Bilayer tablet according to claim 4, 5, 6 or 7, characterized in that the concentration range of pseudoephedrine salt is 5 and 240 mg/tablet and the concentration range of epinastine salt in the compositions according to the invention is between 2 and 20 mg/tablet.

9) Bilayer tablet according to one of claims 4 to 8, characterized in that layer A comprises 120 mg pseudoephedrine sulfate and layer B comprises 10 mg epinastine-HCl.

10) Use of a pharmaceutical composition according to one of claims 1 to 9 in the manufacture of a medicament for the treatment of allergic rhinitis, allergic congestion of the Eustachian tubes and / or other diseases from allergic origin deserving the administration of antihistamine and decongestant drugs, common cold and in the symptomatic relief associated with cough, cold and flue symptoms.

11) Use of a pharmaceutical composition according to claim 10 in the manufacture of a medicament for the treatment of allergic rhinitis, allergic congestion of the Eustachian tubes and / or other diseases from allergic origin deserving the administration of antihistamine and decongestant drugs, preferably of allergic rhinitis.