(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date

(10) International Publication Number
WO 2007/143156 A1

(51) International Patent Classification:
A61K 9/08 (2006.01)   A61K 9/28 (2006.01)
A61K 9/10 (2006.01)   A61K 9/137 (2006.01)
A61K 9/16 (2006.01)

(21) International Application Number:
PCT/US2007/013048

(22) International Filing Date:
1 June 2007 (01.06.2007)

(25) Filing Language:
English

(26) Publication Language:
English

(30) Priority Data:
60/810,018 1 June 2006 (01.06.2006) US


(72) Inventors; and


(44) An Image Related to the Invention

(54) Title: PHENYLPHRINE PULSED RELEASE FORMULATIONS AND PHARMACEUTICAL COMPOSITIONS

(57) Abstract: The invention discloses a pulsed-release formulation or a pharmaceutical composition comprising phenylphrine. The pharmaceutical composition comprises an immediate-release component and an enteric-coated component formulated together either in solid form or in a suspension. The enteric-coated component comprises microcrystals seeded with phenylphrine as an active ingredient and coated with a pH sensitive coating to delay release of the phenylphrine. The pharmaceutical composition can further comprise at least one active selected from the group consisting of an antihistamine, an analgesic, anti-pyretic, non-steroidal anti-inflammatory and mixtures of two or more said actives.
PHENYLEPHRINE PULSED RELEASE FORMULATIONS

AND PHARMACEUTICAL COMPOSITIONS

FIELD OF THE INVENTION

The field of the invention is a pulsed-release formulation for a pharmaceutical composition comprising phenylephrine. The pharmaceutical composition comprises an immediate-release component and an enteric-coated component formulated together as a solid form or as a liquid suspension for administration to an individual.

BACKGROUND OF THE INVENTION

Phenylephrine and its pharmaceutically acceptable salts are recognized by those skilled in the art as safe and effective nasal decongestants when administered at frequent intervals. Commercially-available formulations include nasal jelly, nasal drops, and nasal spray (i.e. Alconefrin® Nasal Drops or Neo-Synephrine® Nasal Jelly) as well as immediate release oral tablets or gelatin capsules (i.e. Sudafed PE™ or DayQuil® LiquiCaps). Due to a short half-life in vivo, phenylephrine and its pharmaceutically acceptable salts as currently formulated are commonly administered every four to six hours for the relief of nasal congestion.

Pulsed delivery formulations result in a decrease in the frequency of drug administration thereby improving patient compliance. Furthermore, pulsed delivery systems may produce more consistent therapeutic plasma levels of active ingredient as compared to multiple doses of a conventional immediate release formulation given at variable times. Thus, pulsed drug delivery systems may decrease the severity and frequency of side effects. As used herein, pulsed-release is synonymous with pulsatile release.

SUMMARY OF THE INVENTION

An object of the present invention is to provide a formulation or pharmaceutical composition of phenylephrine that can be administered on a twice-daily basis. An additional object of the
invention is to provide a pharmaceutical composition or a formulation of phenylephrine that can be administered on a twice-daily basis compatible with incorporation of another active ingredient such as one or more of an antihistamine, an analgesic, an anti-pyretic and an NSAID and mixtures of two or other active ingredients. In preferred embodiments, the other active ingredient is desloratadine or loratadine. A further object of the invention is to provide pharmaceutical compositions for administration to patients of all ages including but not limited to children between the ages of 2 to 6.

To meet at least one of the above objects, the present invention provides pharmaceutical compositions comprising an immediate-release component in a solid form and a delayed-release component in a solid form, wherein the immediate-release component comprises phenylephrine or a pharmaceutically acceptable salt thereof and further wherein the delayed-release component comprises microcrystals coated with an enteric coating and seeded with phenylephrine or a pharmaceutically acceptable salt thereof. In certain embodiments, the pharmaceutical compositions of the invention further comprise at least one active selected from the group consisting of an antihistamine, an analgesic, anti-pyretic, non-steroidal anti-inflammatory and mixtures of two or more thereof in immediate release form. The pharmaceutical compositions can be prepared and stored in solid (powder) form which can, when desired, be dissolved or suspended in a liquid. In a preferred embodiment, the liquid form of the pharmaceutical composition is a syrup suitable for administration to a child of about 2 to about 6 years on a twice daily basis. The invention also provides methods of making and using the pulsed release formulations and pharmaceutical compositions comprising phenylephrine in immediate and delayed release forms.

DETAILED DESCRIPTION OF THE INVENTION

According to one embodiment of the invention, the active ingredient for the pharmaceutical compositions according to the invention is phenylephrine or a pharmaceutically-acceptable salt thereof. According to other embodiments of the invention, the active ingredients for the pharmaceutical compositions according to the invention, are phenylephrine or a pharmaceutically acceptable salt thereof in combination with one or more of an antihistamine, an analgesic, an anti-pyretic, a non-steroidal anti-inflammatory drug (NSAID) or a mixture of two or more thereof.
According to the invention, the pharmaceutical compositions of the invention comprise an amount of phenylephrine for immediate-release and an amount of phenylephrine for delayed release. The delayed-release phenylephrine is released from enteric-coated microcrystals seeded with phenylephrine and coated with a pH-sensitive coating. When combined, the immediate-release component and the enteric-coated component allow extended release of phenylephrine in two pulses—a first pulse of phenylephrine upon administration of the formulation to an individual and a second pulse following entry of the microcrystals into the higher pH environment of the intestines.

For purposes of distribution and storage, the immediate-release portion of phenylephrine may be combined in solid form with the delayed-release enteric-coated microcrystals containing a second portion of phenylephrine as a mixture of solids. For example, powdered phenylephrine may be physically mixed with a powder of phenylephrine-containing enteric-coated microcrystals. The combined powder can be packaged for distribution to hospitals or pharmacies, and stored for a prolonged period such as two years. For ease of administration to an individual, a liquid formulation can be made or “reconstituted” by addition of the mixed powder to water or other liquid to yield a suspension or dispersion of particles in a liquid. In one embodiment, the “reconstituted” liquid suspension is administered to an individual within about two weeks from the time the suspension is made or reconstituted. The liquid portion of the suspension may be aqueous or non-aqueous or a mixture of aqueous and non-aqueous as in an emulsion, or may be described as a syrup. Examples of suitable liquids include water, sorbitol, glycerin, or one or more edible oils. In a preferred embodiment, the reconstituted formulation is aqueous.

According to the invention, an amount of phenylephrine is formulated for immediate release. By immediate release is meant that the active agent is available for absorption by the processes of disintegration and dissolution such that the active agent begins to elicit its decongestant effect essentially upon administration. In a preferred embodiment, the immediate-release portion of phenylephrine is dissolved or suspended by the liquid in forming a liquid formulation.

A second amount of phenylephrine in the pharmaceutical compositions according to the invention is incorporated in an enteric-coated microcrystal which can be suspended in the liquid formulation. The term microcrystal is not intended to be limiting, and includes particles, microparticles, beads, microbeads, powders, granules, pellets, micropellets, non-
pareil seeds, and microcapsules. A preferred embodiment includes micro-repetabs. Micro-
repetab technology is described in U.S. Patent Nos. 5,178,878 and 5,607,697, the entire
disclosures of which are incorporated herein by reference in their entireties. The
microcrystals can be formed from standard pharmaceutical ingredients such as one or more of
lactose, microcrystalline cellulose, sodium carboxy methyl cellulose, starch, starch
derivatives, sugar, polyvinylpyrrolidone, croschvidone, and the like. The microcrystals may
further contain one or more standard excipients in the art such as calcium, dicalcium
phosphate, calcium sulfate, disintegrants, glidants, magnesium stearate, matrix-forming
agents, acacia, butylparaben, carnauba wax, rosin, and the like. The microcrystals preferably
have an average particle size of about 200 to about 300 microns. In one embodiment, about
90% or more of the microcrystals have a particle size between about 200 to about 300
microns. In other less preferred embodiments, the particles may be in the range of 100 – 500
microns.

Methods of forming microcrystals containing an active pharmaceutical agent are known in
the art. For example, the phenylephrine or pharmaceutically acceptable salt thereof may be
incorporated into the core of the microcrystal, or the active agent(s) may be coated on the
surface of the microcrystal as a dusting powder. In one embodiment, the enteric-coated
microcrystal contains from about 90% to about 70% combined coating and core material by
weight and from about 10% to about 30% by weight active ingredient(s). In a preferred
embodiment, the microcrystal contains about 80% by weight combined coating and core
material and about 20% by weight active ingredient(s).

A wide variety of conventional enteric coatings may be employed to coat the phenylephrine-
containing microcrystals, including, for example: cellulose acetate phthalate; hydroxypropyl
methylcellulose phthalate (HPMCP); hydroxypropyl cellulose acetyl succinate; polyvinyl
acetate phthalate; acrylate copolymers, ammonio-containing acrylate copolymers, and
copolymerized methacrylic acid/methacrylic acid methyl esters, such as Eudragit L 12.5,
Eudragit L 100 55, Eudragit S 100, and Eudragit RS; and mixtures thereof. Such copolymers
are available as aqueous dispersions of copolymers of acrylic and methacrylic acid esters
with a low (substitution) content of quaternary ammonium groups present as salts, (e.g.,
quaternary ammonium chlorides). Eudragit RL 30D and Eudragit RS 30D are available as
30% aqueous dispersions. The enteric coating may further contain one or more conventional
plasticizers, pigments and/or dispersants, including, for example, polyethylene glycols, triacetin, triethyl citrate, Citroflex and dibutyl sebacate.

One or more viscosity-modifying agents may be included in the formulation to maintain uniformity. In addition, one or more viscosity-modifying agents may prevent caking or separation upon storage. Viscosity-modifying agents may include polyvinylpyrrolidone (PVP), hydroxypropylmethylcellulose, and mixtures thereof.

The pharmaceutical compositions may include a buffer system to reduce dissolution of the enteric coating on the microcrystals. In one embodiment, the pharmaceutical composition is buffered to a pH of about 3 to about 4. A preferred buffer system is citric acid and sodium citrate.

Pharmaceutical compositions according to the present invention may further comprise one or more additives. Additives include stabilizing agents (sodium edetate, etc.), tonicity agents (sodium chloride, glycerin, mannitol, etc.), pH adjustors (hydrochloric acid, citric acid, sodium hydroxide, etc.), and suspending agents (methylcellulose, sodium carboxymethylcellulose, etc.). Examples of particularly useful additives include sweeteners such as Sucralose, sucrose, saccharin, etc., preservatives such as sodium benzoate, and food coloring. It will be appreciated that the pharmaceutical compositions of the invention may also contain any one or more other additives conventionally used in the formulation of pharmaceutical compositions.

In a preferred embodiment, the pharmaceutical compositions include an antihistamine. Long-acting antihistamines selected from the group consisting of loratadine, desloratadine, azatidine, fexofenadine, terfenadine, cetirizine, astemizole, and levocabastine, or their pharmaceutically acceptable salts are suitable for the pharmaceutical compositions of the invention. Preferred antihistamines include loratadine and desloratadine. Loratadine is disclosed in U.S. Pat. No. 4,282,233 as a non-sedating antihistamine useful, for example, in alleviation of seasonal allergic rhinitis symptoms such as sneezing and itching. The active metabolite of loratadine is desloratadine, which has a half-life \( t^{1/2} \) of approximately 15 to 19 hours. U.S. Pat. No. 5,595,997 discloses methods and compositions for treating seasonal allergic rhinitis symptoms using desloratadine. Loratadine and desloratadine are available in the form of conventional tablets that release the active agent in a conventional manner. Due to the long half life of loratadine compared to phenylephrine, the loratadine in the
formulation according to the present invention is preferably available for immediate release. For example, loratadine or desloratadine may be present in solution or dissolution in the carrier liquid.

The subject to which the composition according to the invention is to be administered is not restricted. In a preferred embodiment, the formulation is administered to a child between the ages of about 2 to about 6. The dosage varies depending on the size and age of the patient, the severity of the symptoms, and the like. The administration is preferably carried out by adjusting the dosage based on the subject's response, and is preferably administered once or twice daily.

EXAMPLE

The following non-limiting example is shown in order that the present invention may be more readily understood.

Formulation Example 1

A suspension can be obtained by "reconstitution" of the following in water:

- desloratadine or loratadine powder: 2.5 mg
- phenylephrine: 2.5 mg
- enteric-coated phenylephrine<sup>1</sup>: 12.5 mg
- citric acid and sodium citrate: to adjust pH to 3-4
- polyvinylpyrrolidone (PVP): viscosant, as needed to maintain uniformity
- Sucralose: sweetener, as needed
- sodium benzoate: preservative, as needed
- FD&C color: coloring, as needed
- water: to 5 mL

<sup>1</sup> micro-cellulose particles seeded with phenylephrine and coated with Eudragit RS® with a loading rate of 20% active ingredient (i.e. 2.5 mg phenylephrine out of 12.5 mg particles). The above ingredients are mixed until a uniform suspension is obtained and administered to a patient within 15 days of mixing.
From the above description, one can ascertain the essential characteristics of the present invention and, without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various uses and conditions.
CLAIMS

1. A pharmaceutical composition comprising an immediate-release component in a solid form and a delayed-release component in a solid form, wherein the immediate-release component comprises phenylephrine or a pharmaceutically acceptable salt thereof and further wherein the delayed-release component comprises microcrystals coated with an enteric coating and seeded with phenylephrine or a pharmaceutically acceptable salt thereof.

2. A pharmaceutical composition comprising an immediate-release component and a delayed-release component suspended or dissolved in a liquid, wherein the immediate-release component comprises phenylephrine or a pharmaceutically acceptable salt thereof and further wherein the delayed-release component comprises microcrystals coated with an enteric coating and seeded with phenylephrine or a pharmaceutically acceptable salt thereof.

3. The composition according to claim 2, wherein the liquid is aqueous.

4. The composition according to claim 2, further comprising buffer.

5. The composition according to claim 4, wherein the buffer comprises citric acid and sodium citrate.

6. The composition according to claim 4, wherein the pH of the composition is about 3 to about 4.

7. The composition according to claim 2, further comprising a viscosity-modifying agent.

8. The composition according to claim 7, wherein the viscosity-modifying agent is selected from the group consisting of polyvinylpyrrolidone, hydroxypropylmethylcellulose, and mixtures thereof.

9. The composition according to claim 2, wherein the immediate-release component further comprises loratadine or desloratadine.

10. The composition according to claim 2, wherein the average particle size of the microcrystals is from about 200 microns to about 300 microns.
11. The composition according to claim 2, wherein greater than about 90% of the microcrystals have a particle size from about 200 microns to about 300 microns.

12. The composition according to claim 2, wherein the coated microcrystals contain about 10% to about 30% by weight phenylephrine.

13. The composition according to claim 12, wherein the coated microcrystals contain about 20% by weight phenylephrine.

14. The composition according to claim 2, wherein the microcrystals are formed from one or more ingredients selected from the group consisting of starch, lactose, talc, polyvinylpyrrolidone, cellulose, methylcellulose and mixtures of two or more thereof.

15. The composition according to claim 2, wherein the microcrystals contain cellulose.

16. The composition according to claim 2, wherein the enteric coating is formed from one or more polymers selected from the group consisting of hydroxypropyl methylcellulose phthalate, hydroxypropyl cellulose acetyl succinate, cellulose acetate phthalate, polyvinyl acetate phthalate, ammoniomethacrylate copolymers, and mixtures of two or more thereof.

17. The composition according to claim 16, wherein the enteric coating includes one or more polymers selected from the group consisting of ammoniomethacrylate copolymers.

18. The composition according to claim 2, wherein the composition comprises about 2.5 mg/5mL of phenylephrine in the immediate-release component and about 2.5 mg/5mL in the delayed-release component.

19. The composition according to claim 1 or 2, further comprising at least one active selected from the group consisting of an antihistamine, an analgesic, anti-pyretic, non-steroidal anti-inflammatory and mixtures of two or more said actives.

20. A method of preparing a composition according to claim 2, comprising mixing phenylephrine-containing enteric-coated microcrystals, bulk phenylephrine, and a liquid.

21. A method of treating the symptoms of cold, flu, or allergies in an individual comprising administering to said individual a composition according to claim 1 or 2 on a twice daily dosing schedule.
22. A method of treating the symptoms of cold, flu, or allergies in a child between about 2 to about 6 years old comprising administering a composition according to claim 2 to a child between about 2 to about 6 years old on a twice-daily dosing schedule.
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

|------|----------|----------|----------|----------|-----------|

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 database consulted during the international search (name of database and, where practical, search terms used)

EPO-Internal, WPI Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
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<td>WO 00/50015 A (YUHAN CORP [KR]) 31 August 2000 (2000-08-31) claim 1</td>
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Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:

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

**E** earlier document but published on or after the international filing date

**L** document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

**O** document referring to an oral disclosure, use, exhibition or other means

**P** document published prior to the international filing date but later than the priority date claimed

**T** later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

**X** document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

**Y** document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

**S** document member of the same patent family

Date of the actual completion of the international search

23 October 2007

Date of mailing of the international search report

30/10/2007

Name and mailing address of the ISA/
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Authorized officer

Giese, Hans-Hermann
INTERNATIONAL SEARCH REPORT

Box II  Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. □ Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
   Although claims 21-22 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. □ Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. □ Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III  Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. □ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. □ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. □ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. □ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

□ The additional search fees were accompanied by the applicant's protest.

□ No protest accompanied the payment of additional search fees.

Form PCT/SA/210 (continuation of first sheet (2)) (January 2004)
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