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(54) Title: PARTICULATE FORMULATIONS OF TADALAFIL IN EFFERVESCENT FORM

(57) Abstract: The present invention relates to pharmaceutical formulations in effervescent form comprising tadalafil for use in the treatment of erectile dysfunction.

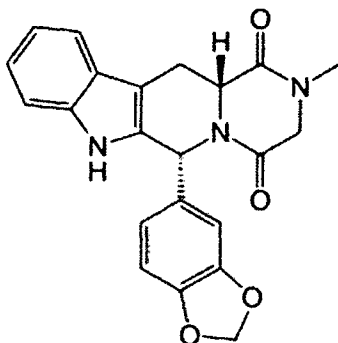


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PARTICULATE FORMULATIONS OF TADALAFIL IN EFFERVESCENT

The present invention relates to pharmaceutical effervescent formulations comprising tadalafil for use in the treatment of erectile dysfunction.

Tadalafil was first disclosed in the application numbered WO9519978. Use of tadalafil for the treatment of erectile dysfunction is disclosed in said document.



Tadalafil is available in 5 mg, 10 mg and 20 mg tablet forms on the market.

However, currently available dosage forms have some disadvantages, especially for geriatric patients and for those who have swallowing difficulties. Therefore, they are not preferred by most of the patients. Considering the fact that an effective treatment mostly requires systematic use of the drugs, this may cause a serious problem. This problem could be solved by formulating the pharmaceutical composition in effervescent form.

Particle size of the active agent is of great importance for the effervescent tablet forms. It generally affects the granule formulation, the solubility and bioavailability of the active agent and overall the dissolution of the effervescent tablet forms.

Since good solubility is an essential feature for the effervescent tablets and tadalafil is known to have low solubility in water, there is a need for new approaches and solutions for development of effervescent tablet formulations comprising tadalafil which dissolve easily in water.

The inventors have surprisingly found that in the case where $d_{10}:d_{50}$ ratio of the active agent tadalafil is in the range of 1:1.1 to 1:15 and $d_{50}:d_{90}$ ratio of the active agent tadalafil is in the range of 1:1.1 to 1:5, said formulations dissolve easily in water and thus high absorption and bioavailability of active agent tadalafil, and effective treatment can be provided.

The present invention relates to the effervescent formulations comprising tadalafil wherein $d_{10}:d_{50}$ ratio of the active agent tadalafil is in the range of 1:1.1 to 1:15 and $d_{50}:d_{90}$ ratio of the active agent tadalafil is in the range of 1:1.1 to 1:5.

In a preferred embodiment of the present invention, $d_{10}:d_{50}$ ratio of the active agent tadalafil is preferably in the range of 1:5 to 1:10 and $d_{50}:d_{90}$ ratio of the active agent tadalafil is preferably in the range of 1:2 to 1:4.

The term " d_{50} " used herein signifies that half of the said substance by volume has a particle size below the value stated with d_{50} and the other half of the substance by volume has a particle size over the value stated with d_{50} .

The term d_{10} used herein signifies that 10 % of the said substance by volume has a particle size below the value stated with d_{10} and the rest of the substance has a particle size over the value stated with d_{10} .

The term d_{90} used herein signifies that 90 % of the said substance by volume has a particle size below the value stated with d_{90} and the rest of the substance has a particle size over the value stated with d_{90} .

d_{50} , d_{10} , d_{90} values can be measured by one of the known measuring devices, for instance with a device which measures particle distribution by laser diffraction (for instance, Malvern Mastersizer etc.).

Another characteristic feature of the effervescent formulations of the present invention is that said formulations comprise tadalafil in the range of 0.01-10 %, preferably in the range of 0.05-5 %, more preferably in the range of 0.1-3 % by weight of the total amount of formulation.

Tadalafil that is comprised in the formulations of the present invention is in the form of its pharmaceutically acceptable salts, hydrates, solvates, esters, enantiomers, diastereomers or combinations thereof in terms of chemical structure; in amorphous or crystalline form or a combination thereof in terms of polymorphic structure.

Another characteristic feature of the effervescent formulations of the present invention is that said formulations comprise at least one pharmaceutically acceptable excipient along with tadalafil.

The pharmaceutically acceptable excipients that can be used in the effervescent formulations of the present invention can be selected from a group comprising effervescent acid, effervescent base, binder, sweetener and/or taste modifying agent, flavouring agent, lubricant, coloring agent and anti-foaming agent.

The effervescent acid that can be used in the effervescent formulations of the present invention and comprising tadalafil can be selected from a group comprising acetic acid, citric acid, lactic acid, malic acid, phosphoric acid, propionic acid and tartaric acid or a combination thereof.

The effervescent base that can be used in the effervescent formulations of the present invention and comprising tadalafil can be selected from a group comprising sodium bicarbonate, sodium citrate dihydrate, sodium hydroxide or combinations thereof.

The binders that can be used in the effervescent formulations of the present invention and comprising tadalafil can be selected from a group comprising ethyl cellulose, gelatine, hydroxyethyl cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, hypromellose, magnesium aluminium silicate, sorbitol, methylcellulose, povidone or a combination thereof.

Another important factor affecting solubility of effervescent formulations is the solubility characteristics of the granules which are obtained during the preparation of the formulation. Granules having low flow characteristics may cause deviations in the tablet weight uniformity which results in unevenly distributed dose of the active agent. An optimal binder composition is of a significant importance for obtaining granules with desired flow characteristics.

The inventors have surprisingly found that using a binder combination of two binding agents shows significant improvement in the problems known in the prior art and helps the granules to have desired flow characteristics. The binder combination comprises the first binding agent and the second binding agent.

The first binding agent of the binder combination is preferably povidone and the second binding agent of the binder combination is preferably sorbitol.

The inventors have also surprisingly found that in the case that the ratio of the first binding agent to the second binding agent is between 1:10 and 10:1, preferably between 1:5 and 5:1, the granules having proper flow and high solubility can be provided.

Accordingly, another embodiment of the present invention is the effervescent formulation comprising tadalafil wherein said formulation comprises a binder combination comprising the first binding agent and the second binding agent and wherein the ratio of the first binding agent to the second binding is in the range of 1:10 to 10:1, preferably 1:5 to 5:1 by weight.

The sweetener and/or taste modifying agent that can be used in the effervescent formulations of the present invention can be selected from a group comprising acesulfame potassium, aspartame, fructose, maltitol, xylitol, saccharin, sodium cyclamate, sucralose, sucrose, sodium chloride.

The flavouring agent that can be used in the effervescent formulations of the present invention can be selected from menthol, methane, anethole, methyl salicylate, eucalyptol; cinnamon, 1-methyl acetate, sage, eugenol, oxanone, lemon, orange, strawberry, blackberry or combinations thereof.

The colouring agent that can be used in the effervescent formulations of the present invention can be selected from titanium dioxide, chlorophyll, yellow iron oxide, other synthetic iron oxides, beta-carotene or combinations thereof.

The lubricant that can be used in the effervescent formulations of the present invention can be selected from calcium stearate, magnesium stearate, talc, polyethylene glycol, PEG 6000, sodium benzoate, potassium benzoate, sodium lauryl sulphate, stearic acid, zinc stearate or combinations thereof.

The anti-foaming agent that can be used in the effervescent formulations of the present invention can be selected from polydimethylsiloxane, simethicone, other silicones, stearates, alcohols, glycols or combinations thereof.

The effervescent formulations of the present invention comprising tadalafil are characterized in that the amount of the active agent is in the range of 0.01-10 %, effervescent acid in the range of 1-80 %, effervescent base in the range of 1-70 %, binder in the range of 1-30 %, sweetener and/or taste modifying agent in the range of 1-30 %, lubricant in the range of 0.1-5 %, flavouring agent in the range of 0.1-10 %, colouring agent in the range of 0.01-10 %, anti-foaming agent in the range of 0.001-2 % in proportion to total weight of the formulation.

The method for preparation of the effervescent formulations of the present invention comprising tadalafil can be composed of the following steps:

- I. Tadalafil, a solvent and effervescent acid are mixed and the granulation solution is obtained.
- II. The effervescent acid, the effervescent base, the binder combination, the sweetener and the anti foaming agent are granulated with the granulation solution obtained in Step I.
- III. The granules obtained in the step II are dried and sieved.
- IV. The flavouring agent, the colouring agent, and the taste modifying agent are added into the granules obtained in the step III and the final mixture is obtained.
- V. The final mixture obtained in step IV is compressed into tablet form.

The pharmaceutical formulation according to the present invention can be used in prevention and treatment of erectile dysfunction.

EXAMPLES

Example 1: Formulation and process for preparation of tadalafil effervescent tablet

Content	% of amount in unit dose
Tadalafil	5
Effervescent Acid	70
Effervescent Base	10
Binder combination	6
Lubricant	4
Flavouring Agent	0,5
Anti-Foaming Agent	0,5
Colouring Agent	1,5
Sweetener and/or taste modifier	2,5

- I. Tadalafil, a solvent and effervescent acid are mixed and the granulation solution is obtained.
- II. The effervescent acid, the effervescent base, the binder combination, the sweetener and the anti foaming agent are granulated with the granulation solution obtained in Step I.
- III. The granules obtained in the step II are dried and sieved.
- IV. The flavouring agent, the colouring agent, and the taste modifying agent are added into the granules obtained in the step III and the final mixture is obtained.
- V. The final mixture obtained in step IV is compressed into tablet form.

CLAIMS

1. A pharmaceutical formulation in effervescent form comprising tadalafil in the amount of 0.01-10 %, characterized in that $d_{10}:d_{50}$ ratio of tadalafil is in the range of 1:1,1 to 1:15 and $d_{50}:d_{90}$ ratio of tadalafil is in the range of 1:1,1 to 1:5.
2. The formulation according to claim 1, characterized in that $d_{10}:d_{50}$ ratio of tadalafil is in the range of 1:5 to 1:10, and $d_{50}:d_{90}$ ratio of tadalafil is in the range of 1:2 to 1:4.
3. The formulation according to claims 1-2, characterized in that said formulation is in form of effervescent tablet, effervescent granule and effervescent powder.
4. The formulation according to claim 3, characterized in that said formulation is in effervescent tablet form.
5. The formulation according to any preceding claims, characterized in that the active agent tadalafil is in the form of its pharmaceutically acceptable salts, hydrates, solvates, esters, enantiomers, diastereomers or combinations thereof in terms of chemical structure; in amorphous or crystalline form or a combination thereof in terms of polymorphic structure.
6. The formulation according to any preceding claims, characterized in that said formulation comprises at least one pharmaceutically acceptable excipient in addition to tadalafil.
7. The formulation according to claim 6, characterized in that said excipients that can be comprised in the formulation are selected from a group comprising effervescent acid, effervescent base, binder, sweetener and/or taste modifying agent, lubricant, flavouring agent, colouring agent and anti-foaming agent or combinations thereof.
8. The formulation according to claim 7, characterized in that the effervescent acid that is comprised in the formulation is selected from a group comprising acetic acid, citric acid, lactic acid, malic acid, phosphoric acid, propionic acid and tartaric acid or a combination thereof.
9. The formulation according to claim 7, characterized in that the effervescent base that is comprised in the formulation is selected from a group comprising sodium bicarbonate, sodium citrate dihydrate, sodium hydroxide or combinations thereof.
10. The formulation according to claim 7, characterized in that the binder combination that is comprised in the formulation is selected from a group comprising ethyl cellulose, gelatine, hydroxyethyl cellulose, hydroxymethyl cellulose, hydroxypropyl

cellulose, hypromellose, magnesium aluminium silicate, sorbitol, methyl cellulose, povidone.

11. The formulation according to any preceding claims, characterized in that it contains a binder combination comprising a first binding agent and a second binding agent.
12. The formulation according to claim 11, characterized that the first binding agent of the binder combination is povidone and the second binding agent of the binder combination is sorbitol.
13. The formulation according to claim 11-12, characterized in that the weight ratio of the first binder to second binder is between 1:10 and 10:1.
14. The formulation according to claim 11-13, characterized in that the weight ratio of the first binder to second binder is between 1:5 and 5:1.
15. The effervescent formulation according to any preceding claims, characterized in that the amount of the active agent is in the range of 0.01-10 %, effervescent acid in the range of 1-80 %, effervescent base in the range of 1-70 %, binder in the range of 1-30 %, sweetener and/or taste modifying agent in the range of 1-30 %, lubricant in the range of 0.1-5 %, flavouring agent in the range of 0.1-10 %, colouring agent in the range of 0.01-10 %, anti-foaming agent in the range of 0.001-2 % in proportion to total weight of formulation.
16. The production method of the effervescent formulation comprising tadalafil according to any preceding claims, wherein said method comprises the following steps:
 - I. Tadalafil, a solvent and effervescent acid are mixed and the granulation solution is obtained.
 - II. The effervescent acid, the effervescent base, the binder combination, the sweetener and the anti foaming agent are granulated with the granulation solution obtained in Step I.
 - III. The granules obtained in the step II are dried and sieved.
 - IV. The flavouring agent, the colouring agent, and the taste modifying agent are added into the granules obtained in the step III and the final mixture is obtained.
 - V. The final mixture obtained in step IV is compressed into tablet form.

INTERNATIONAL SEARCH REPORT

International application No
PCT/TR2013/000035

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K9/46 A61K31/4985 A61K9/14
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)

EP0-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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

☒ See patent family annex.

* Special categories of cited documents :

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"E" earlier application or patent but published on or after the international filing date

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"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

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"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

"&" document member of the same patent family

Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

International application No
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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Information on patent family members

International application No

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