(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
25 July 2013 (25.07.2013)

WIPO | PCT

(10) International Publication Number
WO 2013/109230 A1

(51) International Patent Classification:
A61K 9/46 (2006.01) *A61K 31/4985* (2006.01)

(21) International Application Number:
PCT/TR2013/000043

(22) International Filing Date:
18 January 2013 (18.01.2013)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2012/00601 18 January 2012 (18.01.2012) TR

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

WO 2013/109230 A1

(54) Title: PHARMACEUTICAL COMPOSITIONS COMPRISING TADALAFIL

(57) Abstract: The present invention relates to the pharmaceutical formulations comprising tadalafil that shall be used in the treatment of erectile dysfunction. Said formulations are characterized by being in effervescent form.

PHARMACEUTICAL COMPOSITIONS COMPRISING TADALAFIL

The present invention relates to pharmaceutical formulations comprising tadalafil that shall be used in the treatment of erectile dysfunction. Said formulations are characterized by being in effervescent form.

Tadalafil was first disclosed in the application numbered WO9519978. In said document, it has been disclosed that tadalafil is effective in the treatment of erectile dysfunction.

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

However, these dosage forms in the prior art are disadvantageous for pediatric and geriatric patients and for people who have swallowing difficulties; furthermore, they are not preferred by most of the patients.

An alternative to remove this problem can be to formulate the pharmaceutical composition in suspension form. However, suspension forms are mostly not preferred due to the reasons that they carry the possibility of uncontrolled dose intake, their production costs are high, they have physical and chemical instability problems, they pose problems during use and carrying phases. Although suspension forms have higher bioavailability values as compared to solid dosage forms, it is seen that they are more inconvenient than solid dosage forms when evaluated in terms of stability and shelf-life.

In the prior art, the pharmaceutical compositions comprising tadalafil have been prepared in tablet and suspension forms. However, use of tablet dosage forms causes problems for people who have swallowing difficulties such as children, elderly and disabled people or for those who do not want to swallow tablets and capsules. Solution dosage forms, on the other hand, are not preferred since they complicate compliance of the patients with the treatment as they carry the possibility of uncontrolled dose intake, have bad taste and are not user-friendly and since they have shorter shelf life than solid dosage forms due to their low stability.

When the prior art is taken into consideration, it has been seen that there is need for new dosage forms comprising tadalafil which have fast dissolution and impact, are also easy to use for patients, are convenient for patients who have swallowing difficulties, have long shelf-life.

The inventors have surprisingly found that the problems in the prior art can be solved by the effervescent formulations which are prepared according to the subject of the present invention.

Description of the Invention

The present invention relates to the pharmaceutical formulations which comprise tadalafil and are characterized by being in effervescent form that shall be used in the treatment of erectile dysfunction.

The formulations of the present invention are characterized in that they are in the form of effervescent powder, tablet and granule which have the advantages of both tablet and suspension forms together and they remove the problems encountered in said dosage forms. Effervescent dosage forms are useful especially for patients who have swallowing difficulties.

The pharmaceutical formulations of the present invention comprise effervescent oral dosage forms comprising at least one pharmaceutically acceptable excipient in addition to tadalafil and effervescent couple or comprising only tadalafil and effervescent couple.

In one aspect, the present invention relates to effervescent oral dosage forms comprising the active agent tadalafil, effervescent couple and at least one pharmaceutically acceptable excipient.

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

One characteristic feature of the effervescent formulations of the present invention is that the amount of tadalafil comprised in the formulations is in the range of 1% to 90% by weight, preferably in the range of 1% to 85% by weight, more preferably in the range of 1% to 80% by weight.

Another characteristic feature of the effervescent formulations of the present invention is that said formulations are in effervescent powder, tablet and granule forms.

The characteristic feature of the effervescent formulations of the present invention is that;

- said formulations are in effervescent powder, tablet and granule forms and
- the amount of tadalafil comprised in the formulations is in the range of 1% to 90% by weight, preferably in the range of 1% to 85% by weight, more preferably in the range of 1% to 80% by weight.

The effervescent formulations of the present invention are preferably used as dissolved in a glass of water or in another suitable liquid. At this point, it is clear that water solubility of the formulation is a very important parameter in order to provide an effective treatment and therefore bioavailability.

The inventors have found that the highest solubility is obtained with the formulations wherein the average particle size of tadalafil is less than 50 μm in the effervescent formulations comprising tadalafil as the active agent.

According to this, one characteristic feature of the effervescent formulations of the present invention is to comprise tadalafil having an average particle size less than 50 μm as the active agent.

In another aspect, another characteristic feature of the effervescent formulations of the present invention is to comprise tadalafil having an average particle size in the range of 1 μm to 50 μm as the active agent.

In another aspect, another characteristic feature of the effervescent formulations of the present invention is to comprise tadalafil having an average particle size in the range of 1 μm to 45 μm as the active agent.

The characteristic feature of the effervescent formulations of the present invention comprising tadalafil is that

- said formulations are in effervescent powder, tablet and granule forms,
- the amount of tadalafil comprised in the formulations is in the range of 1% to 90% by weight, preferably in the range of 1% to 85% by weight, more preferably in the range of 1% to 80% by weight and

- the average particle size of tadalafil comprised in the formulations is less than 50 μm, preferably in the range of 1 μm to 50 μm and more preferably in the range of 1 μm to 45 μm.

The term ''average particle size'' used herein refers to average particle size by volume and is shown with d_{50} in short. In this sense, the term d_{50} signifies that half of the said substance by volume has a particle size over the value stated with d_{50} and the other half of the substance by volume has a particle size below the value stated with d_{50}.

D_{50} value can be measured with 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 the formulations comprise at least one pharmaceutically acceptable excipient along with tadalafil and effervescent couple.

The excipients that can be comprised in the effervescent formulations of the present invention can be selected from a group comprising binders, disintegrants, viscosity enhancing components, filling agents, drying agents, surfactants, stabilizing agents, oiling agent, lubricants, diluents, glidants, wetting agents, oiling agent, pH regulators, effervescent acids, effervescent bases, gelling agents, flavoring agent, sweeteners, taste regulating agents, emulsifying agents, antifoaming agents, antioxidants, preservative agents, solvent or solvent mixtures, coloring agents and complexing agents or combinations thereof.

The excipients that can be comprised in the effervescent formulations of the present invention can be selected from a group comprising effervescent acid, effervescent base, binder, sweetener and/or taste regulating agent, flavoring agent, solvent, coloring agent, antifoaming agent, lubricant and/or combinations thereof.

The disintegrant that can be used in the effervescent formulations of the present invention comprising tadalafil can be selected from a group comprising carboxymethyl cellulose, carboxymethyl cellulose calcium, carboxymethyl cellulose sodium, croscarmellose sodium, crospovidone, hydroxypropyl cellulose, microcrystalline cellulose, methyl cellulose, chitosan, starch, sodium starch glycolate.

The diluent that can be used in the effervescent formulations of the present invention comprising tadalafil can be selected from a group comprising calcium carbonate, dibasic calcium phosphate, tribasic calcium phosphate, calcium sulphate, microcrystalline cellulose, dextrose, fructose, lactitol, lactose, magnesium carbonate, magnesium oxide, maltitol, maltodextrin, maltose, mannitol, simethicone, sorbitol, starch, sodium chloride, sucrose, talc, xylitol.

The oiling agent that can be used in the effervescent formulations of the present invention comprising tadalafil can be selected from a group comprising tribasic calcium phosphate, colloidal silicone dioxide, magnesium silicate, magnesium trisilicate, talc.

The binder that can be used in the effervescent formulations of the present invention comprising tadalafil can be selected from a group comprising carboxymethyl cellulose sodium, ethyl cellulose, gelatine, hydroxyethyl cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, hypromellose, magnesium aluminium silicate, maltodextrin, methyl cellulose, povidone, starch.The effervescent acids that can be used in the effervescent formulations of the present invention comprising tadalafil are selected from a group comprising organic acids such as citric acid and acetic acid, tartaric acid, fumaric acid, adipic acid, malic acid or pharmaceutically acceptable hydrates, anhydrates thereof and similar forms or combinations thereof.

The low solubility of tadalafil active agent and slow dissolution rate of the effervescent formulations comprising tadalafil is an important matter for both the patients and drug producers. The inventors have observed that when a combination of organic acid and its acceptable hydrate is used as effervescent acid, the effervescent formulations comprising tadalafil have higher solubility and a rapid dissolution can be provided resulting in a high bioavailability.

Accordingly, another aspect of the present invention is the formulations comprising tadalafil wherein said formulation comprises a combination of organic acid and its acceptable hydrate used as effervescent acid. The effervescent acid is preferably a combination comprising citric acid and monosodium citrate.

Accordingly, another aspect of the present invention is the formulations comprising tadalafil wherein said formulation comprises a combination of citric acid and monosodium citrate used as effervescent acid.

The effervescent bases that can be used in the effervescent formulations of the present invention comprising tadalafil can be selected from a group comprising alkaline or alkaline earth metal carbonates or bicarbonates or combinations thereof.

Potassium carbonate, potassium bicarbonate, potassium citrate, potassium hydroxide, sodium carbonate and sodium bicarbonate or combinations thereof can be given as examples of the effervescent bases which are preferred in the formulations of the present invention.

The effervescent formulations of the present invention comprising tadalafil comprise an effervescent couple composed of at least one pharmaceutically acceptable effervescent acid and effervescent base in the range of 10% to 95%, preferably in the range of 15% to 95%, more preferably in the range of 20% to 95% in proportion to total weight of formulation.

According to this, the term ''effervescent couple'' refers to the mixture of at least one effervescent acid and at least one effervescent base. Both or either of these agents can be in the form of combination of different types in the mixture of effervescent couple. For instance, an effervescent couple comprising two different effervescent acids and one effervescent base or two different effervescent acids and two different effervescent bases can be used.

The ratio of at least one pharmaceutically acceptable effervescent acid to effervescent base comprised in the effervescent formulations of the present invention comprising tadalafil is in the range of 0.1 to 10 by weight.

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

The pH regulating agent that can be used in the effervescent formulations of the present invention comprising tadalafil can be selected from citrate, phosphate, carbonate, tartrate, fumarate, acetate and amino acid salts.

The surfactant that can be used in the effervescent formulations of the present invention comprising tadalafil can be selected from the agents sodium lauryl sulphate, polysorbate, polyoxyethylene, polyoxypropylene glycol and so forth.

The stabilizing agents that can be used in the effervescent formulations of the present invention comprising tadalafil can be selected from a group comprising tocopherol, tetrasodium edetate, nicotinamide, cyclodextrin.

It has been observed that the effervescent formulations comprising tadalafil have an unpleasant taste causing difficulty in using the drug for the patients. After the studies on solving the taste problem of the tadalafil effervescent formulations, the inventors have seen that when a combination comprising at least two, preferably three sweeteners and/or taste regulating agents.

Accordingly, another aspect of the present invention is the formulations comprising tadalafil wherein said formulation comprises a combination comprising at least two, preferably three sweeteners and/or taste regulating agents.

Another aspect of the present invention is the formulations comprising tadalafil wherein said formulation comprises a combination comprising the first taste regulating agent, second taste regulating agent and the third taste regulating agent.

The sweetener and/or taste regulating agents that can be used in the effervescent formulations of the present invention comprising tadalafil can be selected from a group comprising acesulfame, aspartame, dextrose, fructose, maltitol, maltose, mannitol, saccharin, saccharin sodium, sodium cyclamate, sorbitol, sucralose, sucrose, xylitol, sodium chloride.

The inventors have also studied on the development of the taste of the effervescent formulations by using the different sweeteners and/or taste regulating agents. Based on the studies, they have observed that when the first taste regulating agent is sucralose, the second taste regulating agent is aspartame and the third taste regulating agent is sodium chloride, the effervescent formulation obtained has a favorable taste so that the patients have not difficulty while using the drug.

Accordingly, another aspect of the present invention is the effervescent formulations comprising tadalafil wherein said formulation comprises a combination of three different taste

regulating agents and wherein the first taste regulating agent is sucralose, the second taste regulating agent is aspartame and the third taste regulating agent is sodium chloride.

The flavouring agent that can be used in the effervescent formulations of the present invention comprising tadalafil can be selected from the flavors comprising menthol, lemon, orange, vanilla, strawberry, raspberry, caramel and so forth.

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

The solvent that can be used in the effervescent formulations of the present invention comprising tadalafil can be selected from deionized water, acetone, ethyl alcohol or a combination thereof.

The effervescent formulations of the present invention comprising tadalafil can optionally comprise a second active agent in addition to tadalafil. The second active agent can be selected from antacid, anticholinergic, antispasmodic, antiemetic, antidiabetic, antipropulsive, antiallergic, antidiarrheal, antiobesity, antithrombotic, antifibrinolytic, antianemic, antihypertensive, antifungal, antipruritic, antipsoriatic, antibiotic, antiseptic, antiacne, antibacterial, antimycotic, antiviral, antineoplastic, antiarrhythmic, antiadrenergic, antiepileptic, anti-parkinson, antiprotozoal, anthelmintic, anti-inflammatory, diuretic, laxative, sulphonamide, imidazole, corticosteroid, thiazolidinedione, biguanide, immunostimulant, immunosuppressant, myorelaxant, analgesic, psycholeptic, psychoanaleptic peripheral vasodilator, beta blocker, calcium channel blocker and lipid modifying agents; alpha-glucosidase inhibitors, aldose reductase inhibitors, ACE inhibitors; multivitamin and minerals, vitamin A, vitamin D and its analogs, vitamin B_1, vitamin C, vitamin E, vitamin B_6, vitamin B_2, vitamin K, calcium, potassium, sodium, zinc, magnesium, fluoride, selenium.

In the case that two active agents are comprised in the same formulation, the pharmaceutical formulations prepared according to the process of the present invention and comprising a second active agent in addition to tadalafil can be prepared in any of the dosage forms of effervescent tablet, effervescent granule, effervescent dry powder; in the case that the two active agents are comprised in different formulations but in the same dosage form, the

pharmaceutical formulations prepared according to the process of the present invention and comprising a second active agent in addition to tadalafil can be prepared in the dosage forms such as layered tablet, capsule; in the case that the two active agents are comprised in different formulations and in different dosage forms, the pharmaceutical formulations prepared according to the process of the present invention and comprising a second active agent in addition to tadalafil can be prepared in a treatment package form wherein tadalafil is in any dosage forms of effervescent tablet, effervescent granule, effervescent dry powder, and the second active agent, on the other hand, is in any solid dosage forms such as tablet, effervescent tablet, effervescent granule, effervescent dry powder, film coated tablet, enteric-coated tablet, dry powder, granule, capsule, prolonged release tablet, modified release tablet, delayed release tablet.

Preparation method of the formulations of the present invention comprises the steps of formulating the active agent with a suitable excipient composition and giving the said formulation the desired shape.

Any production method in the prior art can be used while formulating of the formulations of the present invention; wet granulation, dry granulation and dry blending methods can be listed among these production methods.

More specifically, the formulations of the present invention can be produced according to any production methods given below;

1. Mixing the active agent tadalafil and, if available, the second active agent with at least one pharmaceutically acceptable excipient homogeneously and, if required, adding at least one of the abovementioned excipients; optionally treating the mixture with at least one pharmaceutically acceptable lubricant; forming the powder mixture obtained in a desired shape,
2. Optionally wet granulating the mixture, which is obtained by mixing the active agent tadalafil and, if available, the second active agent with at least one pharmaceutically acceptable excipient homogeneously, with the granulation solution comprising at least one excipient; drying the granules obtained, optionally adding at least one pharmaceutically acceptable excipient into the dry granules and forming the granules obtained in a desired shape,

3. Optionally wet granulating at least one abovementioned excipients with the granulation solution comprising at least one excipient, drying the granules obtained, adding tadalafil, and, if available, the second active agent and optionally at least one excipient into the dry granules and mixing, forming the granules obtained in a desired shape,
4. Dry granulating the mixture, which is obtained by adding the active agent tadalafil and, if available, the second active agent and at least one of the abovementioned excipients, and forming the granules obtained in a desired shape.

After the formulations of the present invention are prepared according to any of the given methods, they can be

- compressed in tablet form
- filled into sachets

in order to obtain the dosage form required.

The effervescent formulations of the present invention are preferably in tablet form.

The effervescent formulations of the present invention is preferably produced according to the following production method given below;

I. Tadalafil, a solvent and effervescent acid is mixed and the granulation solution is obtained.

II. The effervescent acid, the effervescent base and the binder are granulated with the granulation solution obtained in Step I.

III. The granules obtained in Step II are dried and sieved.

IV. The flavouring agent, coloring agent, anti foaming agent, the taste regulating agent and lubricant are added into the granules obtained in Step III and the final mixture is obtained.

V. Optionally, the final mixture obtained in Step IV is compressed into tablet form.

The inventors have seen that water solubility of the formulations is affected from tablet compression force in the case that these effervescent formulations are prepared in tablet dosage form.

According to this, compressing the formulations which are produced according to any abovementioned methods in the prior art in tablet form under a tablet compression force in the range of 3 kN to 50 kN, preferably in the range of 4 kN to 45 kN, more preferably in the range of 4 kN to 40 kN cause a positive improvement in solubility of the end product.

The characteristic feature of the effervescent formulations of the present invention comprising tadalafil is that

- the formulations are in effervescent form and

the tablet compression force implemented during compressing said formulations in tablet form is in the range of 3 kN to 50 kN, preferably in the range of 4 kN to 45 kN, more preferably in the range of 4 kN to 40 kN.

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

The examples below are given in order to explain the pharmaceutical compositions of the present invention and preparation methods thereof; yet the subject of the present invention cannot be limited to these examples.

EXAMPLES

Example I:

Component	% of amount in unit dose
Tadalafil	27
Effervescent Acid	33
Effervescent Base	28
Lubricant	2.5
Other excipients	9.5
Total	100,0

The effervescent formulation given above is produced according to any methods in the prior art explained in detail in the description and the formulation is presented for use in the dosage form required.

CLAIMS

1. A pharmaceutical formulation comprising tadalafil as active agent, characterized in that said formulation is in effervescent form.
2. The formulation according to claim 1, characterized in that tadalafil is in the form of its pharmaceutically acceptable salts, hydrates, solvates, esters, enantiomers, diastereomers or combinations thereof; in amorphous form or crystalline form or a combination thereof in terms of polymorphic structure.
3. The formulation according to claims 1-2, characterized in that the amount of tadalafil comprised in the formulation is in the range of 1% to 90% by weight.
4. The formulation according to claims 1-3, characterized in that the amount of tadalafil comprised in the formulation is in the range of 1% to 85% by weight.
5. The formulation according to claims 1-4, characterized in that the amount of tadalafil comprised in the formulation is in the range of 1% to 80% by weight.
6. The formulation according to any preceding claims, characterized in that the formulation is in effervescent powder, tablet and granule forms.
7. The formulation according to any preceding claims, characterized in that the average particle size of tadalafil comprised in the formulation is less than 50 μm.
8. The formulation according to claim 7, characterized in that the average particle size of tadalafil comprised in the formulation is in the range of 1 μm to 50 μm.
9. The formulation according to claims 7-8, characterized in that the average particle size of tadalafil comprised in the formulation is in the range of 1 μm to 45 μm.
10. The formulation according to any preceding claims, characterized in that said formulation comprises at least one pharmaceutically acceptable excipient.
11. The formulation according claim 10, characterized in that the excipients comprised in the formulation are selected from a group comprising binders, disintegrants, viscosity enhancing components, filling agents, drying agents, surfactants, stabilizing agents, oiling agent, lubricants, diluents, glidants, wetting agents, oiling agent, pH regulating agents, effervescent acids, effervescent bases, gelling agents, flavoring agent, sweeteners, taste regulating agents, emulsifying agents, antifoaming agents, antioxidants, preservatives, solvent or solvent mixtures, coloring agents and complexing agents or combinations thereof.
12. The formulation according to claim 11, characterized in that the excipients that can be comprised in the formulation are selected from a group comprising binders, lubricants,

effervescent acids, effervescent bases, flavoring agents, sweeteners and/or taste regulating agents, solvent, coloring agent, antifoaming agents or combinations thereof.

13. The formulation according to claim 12, characterized in that the effervescent acids that can be comprised in the formulation are selected from a group comprising organic acids such as citric acid and acetic acid, tartaric acid, fumaric acid, adipic acid, malic acid or their pharmaceutically acceptable hydrates, anhydrates and similar forms or combinations thereof.
14. The formulation according to claims 12-13, characterized in that said formulation comprises a combination of organic acid and its acceptable hydrate used as effervescent acid.
15. The formulation according to claims 12-14, characterized in that said formulation comprises a combination of citric acid and monosodium citrate used as effervescent acid.
16. The formulation according to claim 12, characterized in that effervescent bases that can be comprised in the formulation are selected from a group comprising alkaline or earth alkaline metal carbonates or bicarbonates or combinations thereof.
17. The formulation according to claim 16, characterized in that effervescent bases that can be comprised in the formulation are selected from a group comprising potassium carbonate, potassium bicarbonate, potassium citrate, potassium hydroxide, sodium carbonate and sodium bicarbonate or combinations thereof.
18. The formulation according to claims 12-17, characterized in that said formulation comprises an effervescent couple composed of at least one pharmaceutically acceptable effervescent acid and effervescent base in the range of 10% to 95% in proportion to total weight of formulation.
19. The formulation according to claim 18, characterized in that said formulation comprises an effervescent couple composed of at least one pharmaceutically acceptable effervescent acid and effervescent base in the range of 15% to 95% in proportion to total weight of formulation.
20. The formulation according to claims 18-19, characterized in that said formulation comprises at least one pharmaceutically acceptable effervescent acid and effervescent base in the range of 20% to 95% in proportion to total weight of formulation.

21. The formulation according to claims 18-20, characterized in that the ratio of at least one pharmaceutically acceptable effervescent acid to effervescent base comprised in the formulation is in the range of 0.1 to 10.
22. The formulation according to claims 12-21, characterized in that said formulation comprises a combination comprising the first taste regulating agent, second taste regulating agent and the third taste regulating agent.
23. The formulation according to claims 12-22, characterized in that said formulation comprises a combination of three different taste regulating agents and wherein the first taste regulating agent is sucralose, the second taste regulating agent is aspartame and the third taste regulating agent is sodium chloride.
24. A method for production of a formulation according to any preceding claims, characterized in that said method comprises the steps of wet granulation, dry granulation, dry blending or combinations thereof.
25. The method according to claim 24, characterized in that said method comprising the steps of obtaining the granulation solution comprising tadalafil active agent, a solvent and effervescent acid; granulating the effervescent acid, the effervescent base and the binder with the granulation solution; drying and sieving the granules obtained; adding flavouring agent, coloring agent, anti foaming agent, the taste regulating agent and lubricant into the granules and obtaining the final mixture and optionally compressing the final mixture into tablet form.
26. The tablet form comprising tadalafil as the active agent, characterized in that said tablet form
    a. is in effervescent form
    b. comprises tadalafil in the range of 1% to 90% and
    c. is compressed with a compression force in the range of 3 kN to 50 kN.

INTERNATIONAL SEARCH REPORT

International application No
PCT/TR2013/000043

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/46 A61K31/4985
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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2007/104792 A1 (JENKINS SCOTT [US]) 10 May 2007 (2007-05-10) paragraph [0002] paragraph [0019] - paragraph [0040] paragraph [0110] - paragraph [0128] claims 1-7 -----	1-26
X	US 2011/263606 A1 (ZERBE HORST [CA] ET AL) 27 October 2011 (2011-10-27) paragraph [0002] - paragraph [0009] paragraph [0027] - paragraph [0031]; examples 2, 3 claims 1, 3 ----- -/--	1,6, 10-12, 16,17,24

[X] Further documents are listed in the continuation of Box C.

[X] 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 application or patent but published on or after the international filing date

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Date of the actual completion of the international search	Date of mailing of the international search report
5 June 2013	12/06/2013

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No
PCT/TR2013/000043

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2009/052421 A1 (INNOZEN INC [US]; DUSSIA ELYSE [US]; THOMAS BENJAMIN [US]; DAVIDSON RO) 23 April 2009 (2009-04-23) paragraph [0104] - paragraph [0109] paragraph [0126] - paragraph [0128]; example 5 paragraph [0137]; example 10 -----	1,10-13, 16,17
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