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(54) Titre : FORME POSOLOGIQUE A LIBERATION IMMEDIATE DE BOSENTAN ET PROCEDE DE FABRICATION DE LADITE FORME POSOLOGIQUE

(54) Title: IMMEDIATE RELEASE DOSAGE FORM OF BOSENTAN AND PROCESS OF MANUFACTURING SUCH

(57) Abrégé/Abstract:
The present invention provides an immediate release oral pharmaceutical dosage form comprising a high dose of a poorly water soluble active ingredient, and processes for manufacturing same, wherein the in vitro dissolution rate of the dosage form provides at least 90% dissolution of the active ingredient within 30 minutes as measured by USP Paddle Method at 50 rpm at 900 ml of dissolution buffer with 1% SDS at 37°C. In particular, the immediate release oral pharmaceutical dosage forms of the present invention comprise bosentan, or pharmaceutically acceptable salts thereof, as the active ingredient.

# IMMEDIATE RELEASE DOSAGE FORM OF BOSENTAN AND PROCESS OF MANUFACTURING SUCH


## Abstract

The present invention provides an immediate release oral pharmaceutical dosage form comprising a high dose of a poorly water soluble active ingredient, and processes for manufacturing same, wherein the *in vitro* dissolution rate of the dosage form provides at least 90% dissolution of the active ingredient within 30 minutes as measured by USP Paddle Method at 50 rpm at 900 ml of dissolution buffer with 1% SDS at 37°C. In particular, the immediate release oral pharmaceutical dosage forms of the present invention comprise bosentan, or pharmaceutically acceptable salts thereof, as the active ingredient.

# IMMEDIATE RELEASE DOSAGE FORM OF BOSENTAN AND PROCESS OF MANUFACTURING SUCH

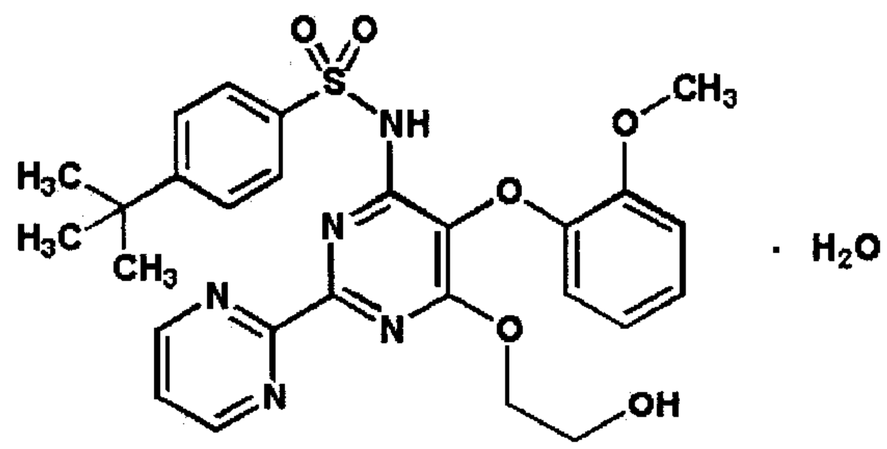
## FIELD OF THE INVENTION

The present invention relates to an immediate release oral pharmaceutical dosage form containing a high dose of a poorly water-soluble active ingredient. In particular, the present invention is directed to immediate release dosage forms containing bosentan.

## BACKGROUND OF THE INVENTION

The compound 4-tert-butyl-N-[6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-(pyrimidin-2-yl) pyrimidin-4-yl] benzenesulfonamide, also known as bosentan, is a dual endothelin receptor antagonist with affinity for both endothelin ETA and ETB receptors useful for the treatment or prevention of endothelin-receptor mediated disorders, such as pulmonary arterial hypertension ("PAH") in individuals with World Health Organization functional Class III or IV primary pulmonary hypertension and pulmonary hypertension secondary to scleroderma or congenital heart disease or human immunodeficiency virus (HIV) patients.

The bosentan monohydrate molecule has the following chemical formula:




Bosentan monohydrate is poorly soluble in water (1.0 mg/100 ml). This leads to great difficulty in the formulation of immediate release dosage forms containing such an active ingredient. Poor water solubility and high dose content make it difficult to develop a robust formulation and manufacturing process.

Poor dissolution behaviour is observed for many water-insoluble drugs. Such low solubility and poor dissolution can often result in low bioavailability, particularly given limited transit times through the gastrointestinal tract.

According to the World Standard Drug Database, the commercial available formulation of bosentan, marketed under the name Tracleer®, has the following composition: bosentan (125 or 62.5 mg), corn starch, glyceryl behenate, magnesium stearate, povidone, pregelatinized starch and sodium starch glycolate; and film coating: ethylcellulose, hydroxypropylmethylcellulose, iron oxide red, iron oxide yellow, talc, titanium dioxide and triacetin.

The preparation of bosentan is disclosed in the following patents: European Patent No. 0 526 708, Canadian Patent No. 2,071,193, United States Patent No. 5,292,740, Canadian Patent No. 2,397,258 and United States Patent No. 5,883,254.

Various techniques to prepare immediate release dosage forms of drug products such as bosentan have been described in the art.

For example, Canadian Patent Application No. 2,607,098, entitled "Dispersible tablet", discloses a dispersible tablet, wherein the monohydrate form of bosentan is used, for paediatric formulation. The tablet disintegrates completely in water at 15-22°C in 5 minutes or less. The dispersible tablets were obtained by using the method of direct compression.

International Patent Application Publication No. WO 2004/012700, entitled "Novel Dosage Form", discloses a dosage form comprising a high dose, high solubility active ingredient, as modified release and a low dose active ingredient as immediate release where the weight ratio of immediate release active ingredient and modified release active ingredient is from 1:10 to 1:15000 and the weight of modified release active ingredient per unit is from 500 mg to 1500 mg. A process for preparing the dosage form is also disclosed (bosentan is not exemplified).

The pharmaceutical industry employs various methods for compounding pharmaceutical agents into tablet formulations. Wet granulation methods are known in the art and have been described in detail by Dilip M. Parikh (*Handbook of Pharmaceutical Granulation Technology*, 2nd *ed.*, 2005 ISBN: 0824726472). Wet granulation is one of the most prevalent methods, which can be used where the flow properties of a compound such as an active pharmaceutical ingredient ("API") are poor which result in content uniformity issues when formulated as a dry blend. Wet granulation is commonly used to improve the

processing characteristics of a powder blend, including improved flowability, content uniformity and more uniform particle size.

Canadian Patent Application No. 2,326,349, entitled "Process for the manufacture of (sub)micronized particles by dissolving in compressed gas and surfactants", describes the process for manufacturing a pulverous preparation of submicronized biologically active compounds (such as bosentan) using conventional powder processing techniques.

United States Patent Application 2006/0018934 to Vaya *et al.*, issued January 26, 2006, entitled "Novel drug delivery system," discloses a novel modified release dosage form comprising a high solubility active ingredient, and optionally, another active ingredient as an immediate release form, as well as the process for preparing same.

Canadian Patent Application No. 2,603,316, entitled "Combined-step process for pharmaceutical compositions", relates to a process for the solid oral pharmaceutical formulation of the pharmaceutically active ingredient, levetiracetam. The process exemplified comprises a wet granulation of levetiracetam and simultaneous fluid bed drying such that it is simultaneously dried, thus preventing it from becoming a paste.

United States Patent Application 2008/0026062 to Farr *et al.*, issued January 31, 2008, entitled "Pharmaceutical compositions including nano-sized active agent," describes a pharmaceutical composition which comprise a water-soluble or partially water-soluble polymer matrix; and a plurality of nano-sized particles of active agent which are sparingly water-soluble to water-insoluble dispersed in the water-soluble or partially water-soluble polymer matrix. The particulate pharmaceutical composition can be micronized or in the form of a film that can be rolled up. If micronized, the individual micron-sized particles can have a plurality of nano-sized particles present in the micron-sized particles.

Similarly, United States Patent Application 2008/0026040 to Farr *et al.*, issued January 31, 2008, entitled "Active agent-releasing dosage forms," describes a pharmaceutical composition which is provided having a plurality of polymeric film layers heat sealed together as a multilayer structure and having an active agent dispersed within the multilayer structure. The multilayer structure is configured to release the active agent upon administration to a subject, either in a controlled release or immediate release manner.

International Patent Application Publication No. WO 2009/004374, entitled "Process for introduction of hydroxyethoxy side chain in bosentan", relates to an improved process for the preparation of Bosentan. In particular it relates to a process for preparing bosentan substantially free from impurities and to a pharmaceutical composition comprising bosentan and its use in the treatment of endothelin-receptor mediated disorders.

Bosentan monohydrate is currently being marketed as a tablet under the name Tracleer® for the treatment of PAH, a deadly disease if untreated.

The need to use a high dose of a poorly water soluble active ingredient, such as bosentan, with an immediate release dosage form makes it very difficult to manufacture the product to obtain reproducible results.

Therefore, a need exists for a dosage form providing a highly insoluble drug in an immediate release dosage forms.

## SUMMARY OF INVENTION

According to one aspect of the present invention, there is provided a formulation comprising a high dose of a poorly water soluble active ingredient, such as bosentan, which gives accurate dosing and immediate release dosage forms.

According to a further aspect of the present invention, there is provided a wet granulation process for preparing a novel granulate comprising a high dose of a poorly water soluble active ingredient, such as bosentan, that can be used in solid oral dosage forms such as immediate release tablets.

In a further aspect of the present invention there is provided an immediate release oral pharmaceutical dosage form comprising a high dose of a poorly water soluble active ingredient wherein the *in vitro* dissolution rate of the dosage form provides at least 90% of the active ingredient dissolved within 30 minutes as measured by USP Paddle Method at 50 rpm at 900 ml of dissolution buffer with 1% SDS at 37°C.

There is further provided a process for the manufacturing of an immediate release oral pharmaceutical dosage form comprising a high dose of poorly water soluble active ingredient, preferably bosentan monohydrate, comprising the following steps:

(1) screening the active ingredient and one or more pharmaceutically acceptable excipients;
(2) dry mixing the content of step (1);
(3) preparing a binder solution;
(4) adding the binder solution of step (3) to the dry blend of step (2);
(5) performing a granulation;
(6) drying the wet mass obtained from step (5);
(7) screening the granules obtained from step (6);
(8) adding pharmaceutically acceptable excipients to the granules of step (7);
(9) mixing the mixture of step (8) using a suitable blender;
(10) compressing the content of step (9).

The present invention is further related to the use of said dosage form for the treatment or prevention of endothelin-receptor mediated disorder, wherein the disorder is pulmonary arterial hypertension.

## DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to an immediate release oral pharmaceutical dosage form of a high dose, poorly water-soluble active ingredient. The process for manufacturing the immediate release oral pharmaceutical dosage form of the present invention utilizes a wet granulation step and a fluid bed drying step in order to prepare good granules with excellent flow properties and desired dissolution profiles.

The term "immediate release" as used herein in relation to the compositions according to the present invention, or used in any other context herein, means release which is not a modified release and releases 90%, or more, of the active ingredient within 30 minutes. The term "immediate release dosage form" as used herein can be described as a dosage form which allows the drug to dissolve in the gastrointestinal contents, with no intention of delaying or prolonging the dissolution or absorption of the drug (as per US FDA guideline for "SUPAC-MR : Modified Release Solid Oral Dosage Forms").

The term "dosage form" is intended to denote any form of the formulation that contains an amount sufficient to achieve a therapeutic effect with a single administration.

The term "active ingredient" refers to an Active Pharmaceutical Ingredients (API) which are active chemicals used in the manufacturing of drugs. The active agent can be a therapeutic, a prophylactic, or a diagnostic agent. These terms of art are well-known to the person skilled in the pharmaceutical and medicinal arts.

The term "high dose" as used herein refers to the percentage by weight of active ingredient present in the dosage form. In the preferred embodiments of the present invention, the high dose immediate release pharmaceutical dosage form comprises more than about 70% by weight of the active ingredient.

In a preferred embodiment of the present invention, the active ingredient in the dosage form is bosentan monohydrate or a pharmaceutically acceptable salt thereof.

In addition to the active ingredient, the pharmaceutical composition of the present invention contains pharmaceutically acceptable excipients added to the composition for a variety of purposes. One or more pharmaceutically acceptable excipients may be present in the composition of the present invention, such as for example, diluents, binders, lubricants, disintegrants, glidants, and acidifying agents. As understood by a person skilled in the art, these excipients are conventional excipients which are well known in the pharmaceutical art.

Suitable diluents include, for example, pharmaceutically acceptable inert fillers such as microcrystalline cellulose, lactose, pregelatinized starch, dibasic calcium phosphate, saccharides, and/or mixtures of the foregoing.

Solid pharmaceutical compositions that are compacted into a dosage form, such as a tablet, may include excipients whose functions include helping to bind the active ingredient and excipients together before compression. These excipients are referred to as binders. Suitable binders include, for example, starch, povidone, hydroxypropylmethylcellulose, pregelatinized starch, hydroxypropylcellulose and/or mixtures of the foregoing.

The preferred lubricants to be used according to the present invention, include the following: magnesium, aluminum or calcium stearate, stearic acid, sodium stearyl fumarate, talc, sodium benzoate, glyceryl mono fatty acid, glyceryl monostearate, and mixtures thereof.

The dissolution rate of a compacted solid pharmaceutical composition in the patient's stomach may be increased by the addition of a disintegrant to the composition. Suitable disintegrants according to the present invention include, for example, croscarmellose sodium, sodium starch glycolate, maize starch, CMC-Ca, CMC-Na, microcrystalline cellulose, cross-linked PVP, alginic acid, sodium alginate, pregelatinized starch and guar gum.

A composition for tabletting or capsule filling may be prepared by wet granulation. In wet granulation, the active ingredient and excipients in powder form are blended and then further mixed in the presence of a liquid, typically water, that causes the powders to clump into granules. The granules are screened and/or milled, dried and then screened and/or milled to the desired particle size. The granules may then be compressed into tablets, or other excipients may be added prior to tabletting, such as a glidant and/or a lubricant.

In a preferred embodiment of the present invention, the immediate release oral pharmaceutical dosage form comprises a high dose of bosentan monohydrate as the active ingredient (a poorly water soluble active ingredient) or a pharmaceutically acceptable salt thereof, and the following pharmaceutically acceptable excipients: pregelatinized starch, povidone K-30, sodium starch glycolate and magnesium stearate.

Oral dosage forms which may be employed with the present invention include granules, spheroids or pellets in a capsule or in any other suitable solid form. Preferably, however the oral dosage form is a tablet.

The oral dosage form preferably contains a dose of about 125 mg of bosentan monohydrate. Alternatively, the dosage form may contain molar equivalent amounts of other pharmaceutically acceptable bosentan salts.

The granules can be manufactured in accordance with conventional techniques in which the active ingredient and other pharmaceutically acceptable excipients are mixed and granulated by adding solution of binder in a low or high shear mixer or by fluidized bed granulation. The granules are then dried, preferably in a fluidized bed dryer. The dried granules are sieved and mixed with lubricants and disintegrants. Alternatively, the manufacture of granules can be made by direct mixing of the directly compressible excipients or by roller compaction.

Bosentan monohydrate is poorly soluble in water (1.0 mg/100 ml) and poorly soluble in aqueous solutions at low pH, particularly when present at a high dose. Notwithstanding this, the present invention was able to obtain an immediate release dosage form using a wet granulation process to obtain good granules and flow properties. Povidone K-30 plays a very important role as binder used in solution in order to get good granules when used in the range of about 2 to about 10 % w/w of the composition.

In one embodiment of the present invention, there is provided an immediate release oral pharmaceutical dosage form of a high dose poorly soluble active ingredient, wherein the in vitro dissolution rate of the dosage form provides at least 90% of the active ingredient dissolved within 30 minutes as measured by USP Paddle Method at 50 rpm at 900 ml of dissolution buffer with 1% SDS at 37° C.

In another embodiment of the present invention, there is provided an immediate release oral pharmaceutical dosage form of a high dose poorly soluble active ingredient, wherein said active ingredient is fully dissolved within 45 minutes as measured by USP Paddle Method at 50 rpm at 900 ml of dissolution buffer with 1% SDS at 37°C.

In one embodiment of the present invention, the process for manufacturing an oral pharmaceutical dosage form containing a high dose of a poorly water soluble active ingredient in an immediate release form comprises the following steps:

(1) screening the active ingredient and pharmaceutically acceptable excipients;
(2) dry mixing the content of step (1);
(3) preparing a binder solution;
(4) adding the binder solution of step (3) to the dry blend of step (2);

(5) performing a granulation;
(6) drying the wet mass obtained from step (5);
(7) screening the granules obtained from step (6);
(8) adding to the granules of step (7) pharmaceutically acceptable excipients;
(9) mixing the mixture of step (8) using a suitable blender; and
(10) compressing the content of step (9).

In a preferred embodiment of the present invention, the active ingredients and pharmaceutically acceptable excipients for use in step (1) are the following: bosentan or a pharmaceutically acceptable salt, such as the sodium salt (t he active ingredient) and a diluent, a binder and a disintegrant (the pharmaceutically acceptable excipients). Preferably, the bosentan is in the monohydrate form, and the diluent is pregelatinized starch, the binder is povidone K-30, and the disintegrant is sodium starch glycolate.

In one embodiment, the content of step (1) is passed through a 20 mesh manual screen and then dry mixed in small high shear for 3 minutes (step (2)). The binder solution is prepared by adding povidone K-30 to purified water and mixing for 30 minutes or until a clear solution is obtained. In step (6), the wet mass is dried in a small fluid bed dryer for a period of about 45 minutes. In step (7) the granules obtained from step (6) are passed through 0.045 inches comill screen at low speed, wherein pregelatinized starch and sodium starch glycolate are added to said granules and mixed for 2 minutes using a suitable blender (steps (8) and (9)), then a lubricant, such as magnesium stearate, is passed through a 40 mesh manual screen and added and mixed with the mixture obtained from step (9), prior to compression (step (10).

In a further embodiment, the process for preparing the immediate release oral pharmaceutical dosage form containing a high does of bosentan monohydrate comprises the following steps:

(1) screening bosentan monohydrate and pregelatinized starch, povidone K-30 and sodium starch glycolate through a 20 mesh manual screen;
(2) dry mixing the content of step (1) in a small high shear for 3 minutes;
(3) preparing a binder solution by adding povidone K-30 to a sufficient quantity of purified water and mixing for 30 minutes or until a clear solution is obtained;
(4) adding the binder solution of step (3) to the dry blend of step (2);

(5) performing a granulation;

(6) drying the wet mass obtained from step (5) in a small fluid bed for a period of about 45 minutes;

(7) screening the granules obtained from step (6);

(8) adding pregelatinized starch and sodium starch glycolate to the granules of step (7);

(9) mixing the mixture obtained from step (8) for 2 minutes using a suitable blender;

(10) screening magnesium stearate through a 40 mesh manual screen;

(11) mixing the content obtained from step (9) with the content from step (10) for 3 min using a suitable blender; and

(12) compressing the content obtained from step (11).

The following example illustrates the preferred embodiment and various aspects of the present invention.

**Example 1**

Immediate Release Dosage Form of Bosentan According to a Preferred Embodiment of the Present Invention

The required quantities of bosentan monohydrate, pregelatinized starch, povidone and sodium starch glycolate are passed through a 20 mesh manual screen and then the content is dry mixed in a small high shear for 3 minutes.

The binder solution is prepared by adding povidone K-30 to a sufficient quantity of purified water and mixing for 30 minutes or until a clear solution is obtained.

The binder solution is then added to the dry blend mixture followed by granulation. The wet mass of obtained granules are then dried in a small fluid bed for a period of about 45 minutes and then passed through 0.045 inches co-mill screen at low speed.

The required quantity of pregelatinized starch and sodium starch glycolate are added to obtain granules and mixed for 2 minutes using a suitable blender.

The granulate is then lubricated by mixing the required quantity of magnesium stearate, which is screened through a 40 mesh manual screen, then added to the obtained mixture, and mixed for 3 min using a suitable blender prior to compression.

The tablets are compressed on a suitable tabletting machine.

The formulation of Example 1 is set out in Table 1 below.

**Table 1 - Formulation According to the Preferred Embodiment**

| No. | Name of Ingredients | % w/w | mg/tablet |
|---|---|---|---|
| | **Intra-granular components** | | |
| 1. | bosentan monohydrate | 73.53 | 125.0 |
| 2. | pregelatinized starch | 9.97 | 16.949 |
| 3. | povidone K-30 | 3.0 | 5.1 |
| 4. | povidone K-30 | 3.0 | 5.1 |
| 5. | sodium starch glycolate | 5.0 | 8.5 |
| | **Extra-granular components** | | |
| 6. | pregelatinized starch | 5.0 | 8.5 |
| 7. | magnesium stearate | 0.5 | 0.85 |
| | TOTAL | 100 | 170 |

The tablets obtained from Example 1 were subsequently tested for *in vitro* dissolution rate, measured by Apparatus II (USP Paddle Method), using the following parameters:

- Speed: 50 rpm
- Media: purified with 1% SDS
- Dissolution medium (buffer) - 900ml
- Temperature: 37°C.

The dissolution results are set out in Table 2 below.

**Table 2 - Dissolution Rate of Bosentan Monohydrate Formulation of Example 1**

| Time (min) | Reference product (% dissolved) | Tablets from Example I (% dissolved) |
|---|---|---|
| 10 | 70 | 49 |
| 15 | 91 | 75 |
| 20 | 97 | 90 |
| 30 | 100 | 99 |
| 45 | 100 | 102 |
| 60 | 101 | 103 |

**CLAIMS:**

1. An immediate release oral pharmaceutical dosage form comprising:

a high dose of a poorly water soluble active ingredient; and

one or more pharmaceutically acceptable excipients;

wherein the *in vitro* dissolution rate of the dosage form provides at least 90% dissolution of the poorly water soluble active ingredient within 30 minutes as measured by USP Paddle Method at 50 rpm at 900 ml of dissolution buffer with 1% SDS at 37°C.

2. The immediate release oral pharmaceutical dosage form according to claim 1, wherein the poorly water soluble active ingredient is bosentan or a pharmaceutically acceptable salt thereof.

3. The immediate release oral pharmaceutical dosage form according to claim 2, wherein the bosentan is in monohydrate form.

4. The immediate release oral pharmaceutical dosage form according to any one of claims 2 or 3, wherein the poorly water soluble active ingredient is in the form of its sodium salt.

5. The immediate release oral pharmaceutical dosage form according to any one of claims 1 to 4, wherein the poorly water soluble active ingredient is present at an amount greater than about 70% by weight of the dosage form.

6. The immediate release oral pharmaceutical dosage form according to any one of claims 1 to 5, wherein the poorly water soluble active ingredient is present in a dose of about 125 mg.

7. The immediate release oral pharmaceutical dosage form according to any one of claims 1 to 6, for use in the treatment of pulmonary arterial hypertension.

8. The immediate release oral pharmaceutical dosage form according to any one of claims 1 to 7, wherein the pharmaceutically acceptable excipients comprise a diluent, a binder, a disintegrant and a lubricant.

9. The immediate release oral pharmaceutical dosage form according to claim 8, wherein the diluent is pregelatinized starch.

10. The immediate release oral pharmaceutical dosage form according to claim 8, wherein the binder is povidone.

11. The immediate release oral pharmaceutical dosage form according to claim 8, wherein the disintegrant is sodium starch glycolate.

12. The immediate release oral pharmaceutical dosage form according to claim 8, wherein the lubricant is magnesium stearate.

13. The immediate release oral pharmaceutical dosage form according to claim 10, wherein the povidone is present in the immediate release oral pharmaceutical dosage form at an amount ranging from about 2 to about 10 % by weight of the dosage form.

14. An immediate release oral pharmaceutical dosage form comprising:

a high dose of a poorly water soluble active ingredient; and

one or more pharmaceutically acceptable excipients;

wherein the poorly water soluble active ingredient is fully dissolved within 45 minutes as measured by USP Paddle Method at 50 rpm at 900 ml of dissolution buffer with 1% SDS at 37°C.

15. An immediate release oral pharmaceutical dosage form comprising:

a high dose of a poorly water soluble active ingredient; and

one or more pharmaceutically acceptable excipients;

wherein the poorly water soluble active ingredient is fully dissolved within 60 minutes as measured by USP Paddle Method at 50 rpm at 900 ml of dissolution buffer with 1% SDS at 37°C.

16. A process for the preparation of an immediate release oral pharmaceutical dosage form comprising a high dose of a poorly water soluble active ingredient, wherein the process comprises the following steps:

(1) screening the active ingredient and one or more pharmaceutically acceptable excipients;

(2) dry mixing the content of step (1);

(3) preparing a binder solution;

(4) adding the binder solution of step (3) to the dry blend of step (2);

(5) performing a granulation;

(6) drying the wet mass obtained from step (5);

(7) screening the granules obtained from step (6);

(8) adding pharmaceutically acceptable excipients to the granules of step (7);

(9) mixing the mixture of step (8) using a suitable blender;

(10) compressing the content of step (9).

17. The process according to claim 16, wherein the active ingredient is bosentan monohydrate.

18. The process according to any one of claims 16 and 17, wherein the pharmaceutically acceptable excipients of step (1) comprise a diluent, a binder, and a disintegrant.

19. The process according to claim 18, wherein the diluent is pregelatinized starch.

20. The process according to claim 18, wherein the binder is povidone.

21. The process according to claim 18, wherein the disintegrant is sodium starch glycolate.

22. The process according to any one of claims 16 to 21, wherein step (1) further comprises screening the active ingredient and the pharmaceutically acceptable excipients through a 20 mesh manual screen.

23. The process according to any one of claims 16 to 22, wherein step (2) further comprises dry mixing the content of step (1) in small high shear for about 3 minutes.

24. The process according to any one of claims 16 to 23, wherein step (3) further comprises preparing the binder solution by adding a binder to a sufficient quantity of purified water and mixing.

25. The process according to claim 24, wherein the binder of step (3) is povidone.

26. The process according to any one of claims 24 and 25, wherein the binder solution is prepared by mixing the binder and purified water for about 30 minutes or until a clear solution is obtained.

27. The process according to any one of claims 16 to 26, wherein step (6) further comprises drying the wet mass in a small fluid bed dryer for a period of about 45 minutes.

28. The process according to any one of claims 16 to 27, wherein step (7) further comprises screening the granules obtained from step (6) through a 0.045 inches comill screen at low speed.

29. The process according to any one of claims 16 to 28, wherein the pharmaceutically acceptable excipients added to the granules of step (7) comprise a diluent and a disintegrant.

30. The process according to claim 29, wherein the diluent is pregelatinized starch.

31. The process according to claim 29, wherein the disintegrant is sodium starch glycolate.

32. The process according to any one of claims 16 to 31, wherein step (9) further comprises mixing the mixture of step (8) for about 2 minutes using a suitable blender.

33. The process according to any one of claims 16 to 32, wherein a lubricant is added and mixed with mixture obtained from step (9), prior to step (10), compression.

34. The process according to claim 33, wherein the process further comprises screening the lubricant with a 40 mesh manual screen prior to being added to the mixture obtained from step (9), followed by mixing the lubricant and the mixture obtained from step (9) for about 3 minutes using a suitable blender, prior to step (10), compression.

35. The process according to any one of claims 33 and 34, wherein the lubricant is magnesium stearate.

36. An immediate release oral pharmaceutical dosage form comprising a high dose of a poorly water soluble active ingredient prepared according to the process claimed in any one of claims 16 to 35.

37. A process for the preparation of an immediate release oral pharmaceutical dosage form comprising a high dose of bosentan monohydrate, wherein the *in vitro* dissolution rate of the dosage form provides at least 90% of the bosentan monohydrate dissolved within 30 minutes, as measured by USP Paddle Method at 50 rpm at 900 ml of dissolution buffer with 1% SDS at 37°C, wherein said process comprises the following steps:

(1) screening bosentan monohydrate and one or more pharmaceutically acceptable excipients;

(2) dry mixing the contents of step (1);

(3) preparing a binder solution by adding a binder to a sufficient quantity of purified water and mixing;

(4) adding the binder solution of step (3) to the dry blend of step (2);

(5) performing a granulation;

(6) drying the wet mass obtained from step (5) in a fluid bed for a period of about 45 minutes;

(7) screening the granules obtained from step (6);

(8) adding a diluent and disintegrant to the granules of step (7);

(9) mixing the mixture obtained from step (8);

(10) screening a lubricant through a screen;

(11) mixing the contents obtained from step (9) and the screened lubricant from step (10); and

(12) compressing the contents obtained from step (11).

38. The process according to claim 37, wherein the pharmaceutically acceptable excipients of step (1) comprise a diluent, binder, and disintegrant.

39. The process according to claim 38, wherein the diluent is pregelatinized starch.

40. The process according to claim 38, wherein the binder is povidone.

41. The process according to claim 38, wherein the disintegrant is sodium starch glycolate.

42. The process according to any one of claims 37 to 41, wherein step (1) further comprises screening the active ingredient and the pharmaceutically acceptable excipients through a 20 mesh manual screen.

43. The process according to any one of claims 37 to 42, wherein step (2) further comprises dry mixing the content of step (1) in small high shear for about 3 minutes.

44. The process according to any one of claims 37 to 42, wherein the binder of step (3) is povidone.

45. The process according to any one of claims 37 to 44, wherein the binder solution is prepared by mixing the binder and purified water for about 30 minutes or until a clear solution is obtained.

46. The process according to any one of claims 37 to 45, wherein step (6) further comprises drying the wet mass in a small fluid bed dryer for a period of about 45 minutes.

47. The process according to any one of claims 37 to 46, wherein step (7) further comprises screening the granules obtained from step (6) through a 0.045 inches comill screen at low speed.

48. The process according to any one of claims 37 to 47, wherein step (9) further comprises mixing the mixture of step (8) for about 2 minutes using a suitable blender.

49. The process according to any one of claims 37 to 48, wherein step (10) further comprises screening the lubricant with a 40 mesh manual screen prior to being added to the mixture obtained from step (9).

50. The process according to any one of claims 37 to 49, wherein step (11) further comprises mixing the lubricant from step (10) and the mixture obtained from step (9) for about 3 minutes using a suitable blender.

51. The process according to any one of claims 37 to 50, wherein the lubricant is magnesium stearate.

52. An immediate release oral pharmaceutical dosage form comprising a high dose of a poorly water soluble active ingredient prepared according to the process claimed in any one of claims 37 to 52.

53. A process for the manufacturing of an oral pharmaceutical dosage form of a high dose of bosentan monohydrate in an immediate release form, said process comprises a wet granulation step and a fluid bed drying step.

54. Use of an immediate release oral pharmaceutical dosage form according to any one of claims 1 to 15, 36 and 52 for the treatment or prevention of an endothelin-receptor mediated disorder.

55. The use according to claim 54, wherein the endothelin-receptor mediated disorder is pulmonary arterial hypertension.