Abrégé/Abstract:
The present invention provides an immediate release oral pharmaceutical dosage form of a high dose poorly soluble active ingredient, wherein the in vitro dissolution rate of the said 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; and a process for manufacturing the said dosage form.
IMMEDIATE RELEASE DOSAGE FORM OF BOSENTAN
AND PROCESS OF MANUFACTURING SUCH

ABSTRACT

The present invention provides an immediate release oral pharmaceutical dosage form of a high dose poorly soluble active ingredient, wherein the in vitro dissolution rate of the said 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; and a process for manufacturing the said dosage form.
IMMEDIATE RELEASE DOSAGE FORM OF BOSENTAN
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FIELD OF THE INVENTION

The present invention relates to an immediate release oral pharmaceutical dosage form containing a high dose poorly soluble active ingredient, more specifically the present invention is directed to dosage forms containing Bosentan.

BACKGROUND OF THE INVENTION

Bosentan is used for the treatment or prevention of endothelin-receptor mediated disorder, as pulmonary arterial hypertension (PAH).

Bosentan monohydrate being a poorly water soluble drug (1mg/100ml), leads to the great difficulty in the formulation of immediate release dosage form containing such. Poor water solubility and high dose content makes it difficult to develop a robust formulation and manufacturing process.

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

The Bosentan molecule has the following chemical formula:

![Chemical Structure]

BOSENTAN (Tracleer®) is a dual endothelin receptor antagonist important in the treatment of pulmonary artery hypertension (PAH, functional class III or IV), accordingly to World Health Organisation (WHO) and secondary to congenital heart disease and to human immunodeficiency virus (HIV).

Accordingly to the World Standard Drug Database, the commercial available formulation of Tracleer has the following composition: Bosentan (the API) (125 or 62.5mg) and tablet contents: 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 various techniques to make immediate release dosage form of drugs as described in prior art are as follows:

CA 2,607,098 disclosed a dispersible tablet, wherein Bosentan monohydrate form is used for pediatric formulation, which disintegrates completely in water at 15-22°C in no more than 5 minutes. The dispersible tablets were obtained by using the method of direct compression.

WO 2004/012700 discloses a dosage form comprising of 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, but bosentan is not exemplified).

The pharmaceutical industry employs various methods for compounding pharmaceutical agents in 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). In particular, 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.

CA 2,326,349 describes the process for manufacturing a pulverous preparation of a submicronized biologically active compounds (such as bosentan) using conventional powder processing techniques.
US 2006018934 discloses a novel modified release dosage form comprising of a high solubility active ingredient and optionally comprise another active ingredient as an immediate release form and process for preparing.

CA 2603316 relates to a process for the solid oral pharmaceutical formulation of a pharmaceutically active ingredient, levetiracetam, which is exemplified, comprising a wet granulation of levetiracetam and simultaneous fluid bed drying such that it is simultaneously dried, thus preventing it from becoming a paste.

US 20080026062 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, US 20080026040 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.

WO 2009/004374 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 for the treatment of PAH, a deadly disease if untreated. The need to use active ingredients with different mechanisms of action, especially with immediate release dosage form, since the dose of Bosentan is very high it makes it very difficult to manufacture the product to obtain reproducible results.

Therefore, accordingly a need exists for a dosage form providing a highly insoluble drug in an immediate release dosage forms.
An object of the present invention is a formulation, which gives accurate dosing and is prepared by advantageous and simple process.

A further object of the present invention is to provide a wet granulation process for making such a novel granulate that may be used in solid oral dosage forms as immediate release tablets.

**SUMMARY OF THE INVENTION**

An object of the present invention provides for an immediate release oral pharmaceutical dosage form of a high dose poorly soluble active ingredient, wherein the in vitro dissolution rate of the said 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.

Preferably, the poorly soluble active ingredient is Bosentan or a pharmaceutically acceptable salt thereof.

More preferably, wherein said active ingredient is in monohydrate form, which is present in a high dose about of 125 mg.

Preferably, the process used to make the immediate release oral pharmaceutical dosage form is a wet granulation process which allows to get good granules and flow properties.

Another object of the present invention provides for 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.

USP Paddle Method is the Paddle Method described, e.g., in U.S. Pharmacopoeia XXII (1990).

An object of the present invention provides an immediate release oral pharmaceutical dosage form of a high dose poorly soluble active ingredient, wherein said 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.
Yet another object of the present invention also provides a process for the preparation of an immediate release oral pharmaceutical dosage form containing a high dose of a poorly soluble active ingredient, wherein said process comprises the following steps:

(1) - screening the active ingredient and pharmaceutical 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;
(10) - compressing the content of step (9).

Preferably, the poorly soluble active ingredient is Bosentan monohydrate and according to the process, wherein the content from step1 comprises: as active pharmaceutical ingredient - Bosentan monohydrate and as pharmaceutically acceptable excipients: pregelatinized starch, Povidone-K30, Sodium starch glycolate and magnesium stearate.

Also, preferably the content of step (1) is passed through a 20 mesh manual screen and then dry mixed in small high shear for 3 minutes, wherein the binder solution is prepared by adding Povidone K30 to purified water and mixing for 30 minutes or until a clear solution is obtained, wherein the drying of the wet mass is carried out in a small fluid bed dryer for a period of about 45 minutes and wherein the granules obtained from step (7), are passed through 0.045 inches comill screen at low speed, wherein a pregelatinized starch and sodium starch glycolate are added to said granules and mixed for 2 minutes using a suitable blender, then a lubricant is added and mixed with mixture obtained from step (9), prior to compression, such as Magnesium stearate which is passed through a 40 mesh manual screen, added to the mixture obtained from step (9) and mixed for 3 minutes using a suitable blender, prior to compression.

An object of the present invention also provides a process for the preparation of an immediate release oral pharmaceutical dosage form containing high dose of a poorly soluble active ingredient, wherein the in vitro dissolution rate of the said 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, wherein said process comprising wet granulation step and fluid bed drying step as follows:

(1) - screening Bosentan monohydrate and pregelatinized starch, povidone 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 K30 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 (6) in small fluid bed for a period of about 45 minutes;
(7) - screening the granules obtained from step (6);
(8) - adding to the granules of step (7) pregelatinized starch and sodium starch glycolate;
(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;
(12) - compressing the content obtained from step (11).

The present invention is further related to a process for the manufacturing of an oral pharmaceutical dosage form of a high dose of Bosentan monohydrate in an immediate release form, comprising a wet granulation step and a fluid bed drying step.

The present invention is further related to 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 soluble active ingredient, using in the process of manufacturing the wet granulation step and a fluid bed drying step in order to get good granules with excellent flow properties and desired dissolution profiles.

The term "immediate release" as used herein in relation to composition according to the invention or used in any other context means release which is not modified release and releases more than
90% of the active ingredient within 30 minutes. The term "immediate release dosage form" as used herein can be described as 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 refers to the % with respect to total dosage form of weight.

In a preferred embodiment of the invention, the present invention provides a dosage form wherein the said active ingredient 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.

Preferably, according to the present invention 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 referred to as binders and other excipients together before the compression.

Preferably, according to the present invention suitable binders include for example starch, povidone, hydroxypropylmethylcellulose, pregelatinized starch, hydroxypropylcellulose and/or mixtures of the foregoing.
Preferably, according to the present invention for suitable lubricants are selected from the group consisting of: Mg-, Al- or Ca-stearate, stearic acid, sodium stearyl fumarate, talc, sodium benzoate, glyceryl mono fatty acid, glyceryl monostearate and mixtures thereof.

5 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.

Preferably, according to the present invention suitable disintegrants 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.

10 A composition for tabletting or capsule filling may be prepared by wet granulation step. 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.

15 In a preferred aspect of the invention, an immediate release oral pharmaceutical dosage form of a high dose poorly soluble active ingredient comprises as active ingredient Bosentan monohydrate or a pharmaceutically acceptable salt thereof and as pharmaceutically acceptable excipients: pregelatinized starch, povidone-K30, sodium starch glycolate and magnesium stearate.

20 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.

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

30 The granules can be manufactured in accordance with usual 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. Alternately, the manufacture of granules can be made by direct mixing of the directly compressible excipients or by roller compaction.

Since Bosentan monohydrate is poorly soluble in water (1mg/100ml) and in aqueous solutions at low pH, and especially in high dose, it was an achievement to obtain an immediate release dosage form, using wet granulation process to get 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 (2-10) % w/w in the composition.

According to an object of the present invention, the process for the manufacturing of an oral pharmaceutical dosage form of a high dose of Bosentan monohydrate in an immediate release form comprises the following steps:

(1) - screening the active ingredient and pharmaceutical 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;
(10) - compressing the content of step (9).

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 dry mixed the content in a small high shear for 3 minutes;
The binder solution is prepared by adding Povidone K30 to a sufficient quantity of purified water and mixing for 30 minutes or until a clear solution is obtained.

Then adding the binder solution to the dry blend mixture performing a granulation. The wet mass of obtained granules are then dried in small fluid bed for a period of about 45 minutes and then passed through 0.045 inches comill 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 screening through a 40 mesh manual screen, then added to the obtained mixture mixing 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**

<table>
<thead>
<tr>
<th>No.</th>
<th>Name of ingredients</th>
<th>% w/w</th>
<th>mg/tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Bosentan monohydrate</td>
<td>73.53</td>
<td>125.0</td>
</tr>
<tr>
<td>2.</td>
<td>Pregelatinized starch</td>
<td>9.97</td>
<td>16.949</td>
</tr>
<tr>
<td>3.</td>
<td>Povidone-K30</td>
<td>3.0</td>
<td>5.1</td>
</tr>
<tr>
<td>4.</td>
<td>Povidone-K30</td>
<td>3.0</td>
<td>5.1</td>
</tr>
<tr>
<td>5.</td>
<td>Sodium starch glycolate</td>
<td>5.0</td>
<td>8.5</td>
</tr>
<tr>
<td></td>
<td><strong>Extra-granular components</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.</td>
<td>Pregelatinized starch</td>
<td>5.0</td>
<td>8.5</td>
</tr>
<tr>
<td>7.</td>
<td>Magnesium stearate</td>
<td>0.5</td>
<td>0.85</td>
</tr>
<tr>
<td></td>
<td><strong>TOTAL</strong></td>
<td>100</td>
<td>170</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Reference product (%) dissolved</th>
<th>Tablets from Example 1 (%) dissolved</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>70</td>
<td>49</td>
</tr>
<tr>
<td>15</td>
<td>91</td>
<td>75</td>
</tr>
<tr>
<td>20</td>
<td>97</td>
<td>90</td>
</tr>
<tr>
<td>30</td>
<td>100</td>
<td>99</td>
</tr>
<tr>
<td>45</td>
<td>100</td>
<td>102</td>
</tr>
<tr>
<td>60</td>
<td>101</td>
<td>103</td>
</tr>
</tbody>
</table>
CLAIMS:

1. An immediate release oral pharmaceutical dosage form of a high dose of a poorly soluble active ingredient, wherein the in vitro dissolution rate of the said dosage form provides at least 95% 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.

2. A dosage form according to claim 1, wherein the poorly soluble active ingredient is Bosentan or pharmaceutically acceptable salts.

3. A dosage form according to claim 2, wherein said active ingredient is in monohydrate form.

4. A dosage form according to claim 2 or 3, wherein said active ingredient is in the form of its sodium salt.

5. A dosage form according to any one of claims 1 to 4, wherein said active ingredient is present in a dose about of 125 mg.

6. A dosage form according to any one of claims 1 to 5, used in the treatment of pulmonary arterial hypertension (PAH).

7. A dosage form according to claims 1-6, wherein the pharmaceutically acceptable excipients comprise pregelatinized starch, povidone-K30, sodium starch glycolate and magnesium stearate.

8. 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.

9. An immediate release oral pharmaceutical dosage form of a high dose poorly soluble active ingredient, wherein said 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.

10. A process for the preparation of an immediate release oral pharmaceutical dosage form containing a high dose of a poorly soluble active ingredient, wherein said process comprises the following steps.
(1) - screening the active ingredient and pharmaceutical 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;
(10) - compressing the content of step (9).

11. A process for the preparation of an immediate release oral pharmaceutical dosage form containing a high dose of a poorly soluble active ingredient, wherein the in vitro dissolution rate of the said dosage form provides at least 95% 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, wherein said process comprises the following steps:

(1) - screening Bosentan monohydrate and pregelatinized starch, povidone 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 K30 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 small fluid bed for a period of about 45 minutes;
(7) - screening the granules obtained from step (6);
(8) - adding to the granules of step (7) pregelatinized starch and sodium starch glycolate;
(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).
12. The process according to claim 10, wherein said poorly soluble active ingredient is Bosentan monohydrate.

13. The process according to claim 10, wherein the content from step 1 comprises: as active ingredient - Bosentan monohydrate and as pharmaceutically acceptable excipients: pregelatinized starch, Povidone-K30 and sodium starch glycolate.

14. The process according to claim 10, wherein said content of step (1) is passed through a 20 mesh manual screen and then dry mixed in small high shear for 3 minutes.

15. The process according to claim 10, wherein the binder solution is prepared by adding Povidone to a sufficient quantity of purified water and mixing.

16. The process according to claim 10, wherein said binder solution is prepared by adding Povidone K30 to purified water and mixing for 30 minutes or until a clear solution is obtained.

17. The process according to claim 10, wherein the drying of the wet mass is carried out in a small fluid bed dryer for a period of about 45 minutes.

18. The process according to claim 10, wherein the granules obtained from step (7) are passed through 0.045 inches comill screen at low speed.

19. The process according to claim 10, wherein a pregelatinized starch and sodium starch glycolate are added to said granules and mixed for 2 minutes using a suitable blender.

20. The process according to claim 10, wherein a lubricant is added and mixed with mixture obtained from step (9), prior to compression.

21. The process according to claim 10, wherein magnesium stearate is passed through a 40 mesh manual screen, added to the mixture obtained from step (9) and mixed for 3 minutes using a suitable blender, prior to the compression step.

22. The 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.
23. Use of a dosage form according to any one of claims 1-9 for the treatment or prevention of endothelin-receptor mediated disorder.

24. A use according to claim 23, wherein the disorder is pulmonary arterial hypertension.