

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
30 April 2009 (30.04.2009)

PCT

(10) International Publication Number
WO 2009/053748 A2

(51) International Patent Classification:

C07D 239/69 (2006.01) **A61P 11/00** (2006.01)
A61P 9/12 (2006.01) **A61K 31/506** (2006.01)

(21) International Application Number:

PCT/GB2008/050986

(22) International Filing Date: 24 October 2008 (24.10.2008)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

2108/MUM/2007 24 October 2007 (24.10.2007) IN

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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, BR, BW, BY, BZ, CA, CH, 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, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, 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, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished upon receipt of that report

(54) Title: NOVEL CRYSTALLINE FORMS

(57) **Abstract:** The present invention relates to novel crystalline forms of bosentan and processes for their preparation. Further, the invention relates to pharmaceutical compositions comprising said crystalline forms and use of said compositions in the treatment of patients suffering from endothelin receptor mediated disorders, for example, cardiovascular disorders such as hypertension, pulmonary hypertension, ischemia, vasospasm and angina pectoris.

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Novel Crystalline Forms

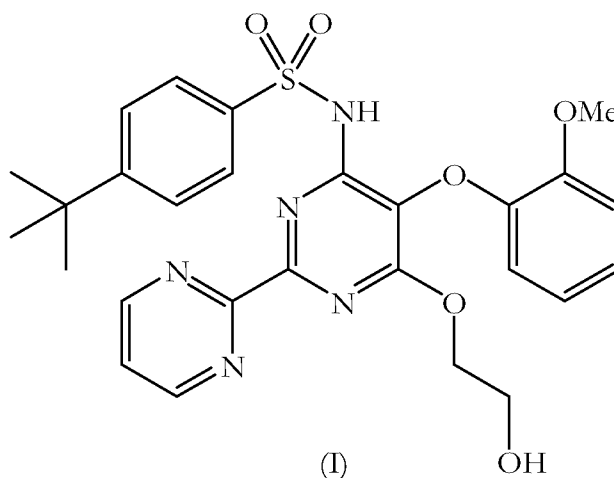
Field of the invention

5 The present invention relates to novel crystalline forms of bosentan and processes for their preparation. Further, the invention relates to pharmaceutical compositions comprising said crystalline forms and use of said compositions in the treatment of patients suffering from endothelin receptor mediated disorders, for example, cardiovascular disorders such as hypertension, pulmonary hypertension, ischemia, vasospasm and angina pectoris.

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Background of the invention

Bosentan, represented by structural formula (I) and chemically named 4-tert-butyl-N-[6-(2-hydroxyethoxy)-5-(2-methoxyphenoxy)-2-(2-pyrimidinyl)-pyrimidin-4-yl]-benzenesulfonamide, is an endothelin receptor antagonist. It is useful for the treatment of cardiovascular disorders such as hypertension, ischemia, vasospasm and angina pectoris. Bosentan is currently marketed as Tracleer[®] and indicated for the treatment of pulmonary arterial hypertension (PAH) to improve exercise capacity and symptoms in patients with grade III functional status.



20

Polymorphism is the ability of a solid material to exist in more than one form or crystal structure. Each crystalline structure is termed a polymorph and may have distinct physical properties. Therefore, a single compound may give rise to a variety of polymorphic forms (or crystalline structures) where each form can have different and distinct physical

25

properties, such as different solubility profiles, different melting point temperatures and/or different X-ray diffraction peaks. The solubility and, consequently, rates of uptake in the body may vary accordingly, leading to lower or higher biological activity than desired. In extreme cases an undesired polymorph can even show toxicity (see, for example, K.
5 Knapman, Modern Drug Discoveries, March 2000, page 53). The occurrence of an unknown polymorphic form during manufacture can have an enormous impact. Polymorphic forms of a compound can be distinguished in a laboratory by X-ray diffraction spectroscopy and by other methods such as infrared spectrometry, Differential Scanning Calorimetry, Thermo-Gravimetric Analysis and melting point analysis.
10 Additionally, the properties of different polymorphic forms of the same active pharmaceutical ingredient are well known in the pharmaceutical art to have an effect on the manufacture of drug product compositions comprising the API. For example, the solubility, stability, flowability, tractability and compressibility of the API as well as the safety and efficacy of the drug product can be dependent on the polymorphic form.

15

Understanding and controlling polymorphism, then, gives a decided advantage in bringing new drugs to the marketplace. First, predicting any possible polymorphs for a drug product can be used to diminish the possibility of contamination during a drug's manufacture or storage by other polymorphic forms. Failure to catch contamination can
20 have life-threatening consequences in some cases. Crystallizing an unintended polymorph during manufacture can mean weeks or even months of production downtime, while scientists find and correct the cause of the new crystal form or go through another round of testing to obtain approval for the new form.

25 So critical are the potential effects of different polymorphic forms in a single drug substance on the safety and efficacy of the respective drug product(s) that the United States Food and Drug Administration (FDA) requires each drug substance manufacturer, at least to control its synthetic processes such that the percentages of the various respective polymorphic forms, when present, must be controlled and consistent among batches and
30 within the drug substance/product's specification as approved by the FDA. Left uncontrolled in synthetic processes, the percentage of a given polymorph outside of an FDA approved specification could render the adulterated batches unfit for commercial sale. Accordingly, the FDA typically requires full characterization of each drug substance

used in each drug product marketed in the United States, including the identification and control of polymorphic forms. The FDA further requires robust synthetic process specifications and controls which consistently produce the respective drug substance and drug product.

5

The discovery of new polymorphic forms of a pharmaceutically useful compound provides a new opportunity to improve the performance characteristics of a pharmaceutical product. Preparation of novel polymorphic forms can also provide products having high chemical and polymorphic purity, i.e. with low levels of chemical impurities or other crystalline forms respectively. It also adds to the material that a formulation scientist has available for designing, for example, a pharmaceutical dosage form of a drug with a targeted release profile or other desired characteristics.

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Summary of the invention

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Novel crystalline forms of bosentan have been prepared and characterised, and processes for their preparation are described below. The novel crystalline forms of bosentan have been found to have advantageous properties, for example, better solubility, bioavailability, stability, flowability, tractability, compressibility, safety or efficacy.

20

Accordingly, a first aspect of the present invention provides a crystalline form 5 of bosentan comprising two or more (preferably three or more, four or more, five or more, six or more, seven or more, eight or more, nine or more, ten or more, eleven or more, twelve or more, thirteen or more, fourteen or more, or fifteen) characteristic XRPD peaks selected from peaks at 2θ values 4.02, 6.12, 8.38, 9.39, 10.04, 15.26, 17.72, 17.98, 18.81, 19.28, 20.31, 21.05, 27.57, 31.91 and $45.65 \pm 0.2^\circ$.

25

In a second aspect there is provided a crystalline form 5 of bosentan having an XRPD trace substantially as shown in figure 1.

30

In a third aspect of the invention a bosentan crystalline form 5 is characterized by a DSC trace comprising endothermic peaks at about 93°C and about 196°C , preferably at about 92.65°C and about 195.90°C , all $\pm 2^\circ\text{C}$.

In a fourth aspect there is provided a crystalline form 5 of bosentan having a DSC trace substantially as shown in figure 2.

- 5 Whilst a fifth aspect according to the invention provides a crystalline form 5 of bosentan having a TGA trace substantially as shown in figure 3.

Preferably the crystalline form 5 of bosentan of the present invention is substantially free of other polymorphic forms including amorphous bosentan. It preferably comprises less
10 than 10%, preferably less than 5%, preferably less than 3%, preferably less than 2%, preferably less than 1%, preferably less than 0.5%, preferably less than 0.1% of other polymorphic forms including amorphous bosentan.

A sixth aspect according to the invention provides a process for preparing the crystalline
15 form 5 of bosentan, comprising the steps of:

- (a) dissolving bosentan in one or more organic solvent(s);
- (b) causing a crystalline solid to precipitate from the solution obtained in step (a); and
- (c) isolating the crystalline solid obtained from step (b).

20 In a preferred embodiment the solvent comprises ethyl acetoacetate. In another embodiment the solvent is heated in step (a) until a clear solution is obtained. A further embodiment provides that the crystalline solid is precipitated by cooling the solution. A further embodiment still provides that the precipitated solid is isolated by filtration and preferably the isolated solid is dried under vacuum until a constant weight is achieved.

25

A seventh aspect provides a process for preparing the crystalline form 5 of bosentan, comprising the steps of:

- (a) heating bosentan in ethyl acetoacetate until a clear solution is obtained;
- (b) cooling the solution from step (a) until a precipitate forms; and
- 30 (c) filtering the suspension from step (b) and drying the obtained solid under vacuum at about 20-40°C, preferably at about 25°C, until a constant weight is achieved.

In an eighth aspect of the invention a crystalline form 6 of bosentan is provided characterized by an X-ray diffraction pattern comprising two or more peaks (preferably three or more, four or more, five or more, or six peaks) selected from peaks at 2θ values 3.87, 7.51, 8.84, 11.14, 18.74 and $23.30 \pm 0.2^\circ$.

5

A ninth aspect provides a crystalline form 6 of bosentan having an XRPD trace substantially as shown in figure 4.

10 A tenth aspect provides a crystalline form 6 of bosentan characterized by a DSC trace comprising endothermic peaks at about 78°C and about 134°C , preferably at about 77.57°C and about 134.08°C , all $\pm 2^\circ\text{C}$, preferably all $\pm 0.5^\circ\text{C}$.

An eleventh aspect provides a crystalline form 6 of bosentan having a DSC trace substantially as shown in figure 5.

15

A twelfth aspect provides a crystalline form 6 of bosentan having a TGA trace substantially as shown in figure 6.

20 Preferably the crystalline form 6 of bosentan of the present invention is substantially free of other polymorphic forms including amorphous bosentan. It preferably comprises less than 10%, preferably less than 5%, preferably less than 3%, preferably less than 2%, preferably less than 1%, preferably less than 0.5%, preferably less than 0.1% of other polymorphic forms including amorphous bosentan.

25 According to a thirteenth aspect of the invention there is provided a process for preparing the crystalline form 6 of bosentan, comprises the steps of:

- (a) dissolving bosentan in one or more organic solvent(s) and optionally water;
- (b) causing a crystalline solid to precipitate from the solution obtained in step (a); and
- (c) isolating the crystalline solid obtained from step (b).

30

In a preferred embodiment the solvent, each solvent or one or more of the solvent(s) is a $\text{C}_1\text{-C}_6$ alcohol. In a particularly preferred embodiment bosentan is dissolved in step (a) by heating in butan-2-ol and amyl alcohol and adding water. In another embodiment the solid

is precipitated by cooling the solution from step (a) and adding cyclohexane. Preferably, the precipitated solid is isolated by filtration, which solid is preferably dried under vacuum until a constant weight is achieved.

5 A fourteenth aspect according to the invention provides a process for preparing the crystalline form 6 of bosentan, comprising the steps of:

- (a) dissolving or suspending bosentan in a solvent system comprising one or more C₁-C₆ alcohol(s);
- (b) adding water to the solution or suspension from step (a) until a clear solution is
10 obtained;
- (c) cooling the solution from step (b) to between about 20-40°C;
- (d) adding cyclohexane to the solution from step (c) until a precipitate is formed; and
- (e) filtering the resultant precipitated solid and drying under vacuum at between about 20-30°C until a constant weight is achieved.

15

In a preferred embodiment the solvent system comprises butan-2-ol and amyl alcohol and preferably is heated in step (a) to about 80°C.

In a fifteenth aspect of the invention a crystalline form 7 of bosentan is provided
20 characterized by an X-ray diffraction pattern comprising two or more peaks (preferably three or more, four or more, five or more, six or more, seven or more, eight or more, nine or more, ten or more, eleven or more, twelve or more, thirteen or more, fourteen or more, fifteen or more, sixteen or more, or seventeen peaks) selected from peaks at 2θ values 3.64, 4.23, 4.95, 7.04, 7.68, 8.23, 9.05, 9.66, 10.48, 13.95, 15.20, 16.17, 17.37, 18.06, 20.03, 22.13
25 and $23.62 \pm 0.2^\circ$.

A sixteenth aspect provides a crystalline form 7 of bosentan having an XRPD trace substantially as shown in figure 7.

30 A seventeenth aspect provides a crystalline form 7 of bosentan characterized by a DSC trace comprising endothermic peaks at about 75°C and about 130°C, preferably at about 74.58°C and about 129.99°C, all $\pm 2^\circ\text{C}$.

An eighteenth aspect provides a crystalline form 7 of bosentan having a DSC trace substantially as shown in figure 8.

5 A nineteenth aspect of the invention provides a crystalline form 7 of bosentan having a TGA trace substantially as shown in figure 9.

Preferably the crystalline form 7 of bosentan of the present invention is substantially free of other polymorphic forms including amorphous bosentan. It preferably comprises less than 10%, preferably less than 5%, preferably less than 3%, preferably less than 2%,
10 preferably less than 1%, preferably less than 0.5%, preferably less than 0.1% of other polymorphic forms including amorphous bosentan.

A twentieth aspect provides a process for preparing the crystalline form 7 of bosentan, comprising the steps of:

- 15 (a) dissolving bosentan in one or more organic solvent(s);
(b) causing a crystalline solid to precipitate from the solution obtained in step (a); and
(c) isolating the crystalline solid obtained from step (b).

In a preferred embodiment, bosentan is dissolved in the or each solvent until a clear
20 solution is obtained. Preferably, bosentan is dissolved in step (a) by heating the or each solvent. In another preferred embodiment the, each or one or more of the solvent(s) is a C₁-C₆ alcohol. Most preferably, the solvents are a mixture of cyclohexanone and n-butanol or, alternatively, the solvents are a mixture of cyclohexanone and ethanol. In a further embodiment, the crystalline solid is precipitated by adding n-hexane to the solution from
25 step (a). Preferably, the solid is isolated by filtration, more preferably the isolated solid is dried under vacuum until a constant weight is achieved.

In a twenty-first aspect of the invention there is provided a process for preparing the crystalline form 7 of bosentan, comprising the steps of:

- 30 (a) dissolving bosentan in a mixture of cyclohexanone and a C₁-C₆ alcohol;
(b) cooling the solution from step (a) to about 30°C within about 30 minutes whilst stirring;

- (c) adding n-hexane to the solution from step (b) to form a precipitate and stirring the suspension for about 2-5 hours; and
- (d) filtering the suspension from step (c) and drying the obtained solid under vacuum at about 20-40°C, preferably at about 25°C, until a constant weight is achieved.

5

In a preferred embodiment the C₁-C₆ alcohol is n-butanol. Preferably bosentan is dissolved in step (a) by heating the mixture until a clear solution is obtained, preferably at about 50°C.

10 Alternatively, in a twenty-second aspect of the invention there is provided a process for preparing the crystalline form 7 of bosentan, comprising the steps of:

- (a) dissolving bosentan in a mixture of cyclohexanone and a C₁-C₆ alcohol;
- (b) cooling the solution from step (a) to about 30°C within about 20 minutes whilst stirring;
- 15 (c) adding n-hexane to the solution from step (b) to form a precipitate and stirring the suspension for between about 15-25 hours; and
- (d) filtering the suspension from step (c) and drying the obtained solid under vacuum at about 20-40°C, preferably at about 25°C, until a constant weight is achieved.

20 In a particularly preferred embodiment the C₁-C₆ alcohol is ethanol. Preferably bosentan is dissolved in step (a) by heating the mixture until a clear solution is obtained, preferably at about 80°C.

A twenty-third aspect according to the invention provides a crystalline form 8 of bosentan
25 characterized by an X-ray diffraction pattern comprising two or more peaks (preferably three or more, four or more, five or more, six or more, seven or more, eight or more, nine or more, ten or more, eleven or more, twelve or more, thirteen or more, fourteen or more, fifteen or more, sixteen or more, seventeen or more, or eighteen peaks) selected from peaks at 2θ values 9.47, 13.41, 14.52, 15.46, 15.73, 16.35, 16.88, 17.99, 18.87, 19.25, 20.53,
30 21.82, 23.02, 23.83, 24.61, 24.86, 25.13 and 26.03 ± 0.2 °θ

In an alternative embodiment, the twenty-third aspect according to the invention provides a crystalline form 8 of bosentan characterized by an X-ray diffraction pattern comprising

two or more peaks (preferably three or more, or four peaks) selected from peaks at 2θ values 3.73, 7.43, 14.95 and $19.78 \pm 0.2^\circ$.

5 A twenty-fourth aspect provides a crystalline form 8 of bosentan having an XRPD trace substantially as shown in figure 10.

A twenty-fifth aspect provides a crystalline form 8 of bosentan characterized by a DSC trace comprising endothermic peaks at about 58°C and about 110°C, preferably at about 58.29°C and about 109.55°C, all $\pm 2^\circ\text{C}$.

10

A twenty-sixth aspect provides a crystalline form 8 of bosentan having a DSC trace substantially as shown in figure 11.

15 A twenty-seventh aspect provides a crystalline form 8 of bosentan having a TGA trace substantially as shown in figure 12.

20 Preferably the crystalline form 8 of bosentan of the present invention is substantially free of other polymorphic forms including amorphous bosentan. It preferably comprises less than 10%, preferably less than 5%, preferably less than 3%, preferably less than 2%, preferably less than 1%, preferably less than 0.5%, preferably less than 0.1% of other polymorphic forms including amorphous bosentan.

A twenty-eighth aspect provides a process for preparing the crystalline form 8 of bosentan, comprising the steps of:

- 25 (a) mixing bosentan in one or more organic solvent(s);
(b) filtering the mixture from step (a); and
(c) isolating the crystalline solid from the filtrate obtained in step (b).

Preferably the process of the twenty-eighth aspect comprises the steps of:

- 30 (a) mixing bosentan in one or more organic solvent(s);
(b) filtering the mixture from step (a);
(c) causing a crystalline solid to precipitate from the filtrate obtained in step (b); and
(d) isolating the crystalline solid obtained in step (c).

Preferably, bosentan is heated in step (a) in a mixture of ethyl acetoacetate, octanol and n-pentyl acetate. In another embodiment in step (b) the mixture is filtered hot under vacuum. In another preferred embodiment the crystalline solid is obtained by cooling the
5 filtrate in step (c). Further preferred embodiments provide that the crystalline solid is further filtered and dried under vacuum until a constant weight is achieved.

A twenty-ninth aspect provides a process for preparing the crystalline form 8 of bosentan, comprising the steps of:

- 10 (a) heating bosentan in a mixture of ethyl acetoacetate, octanol and n-pentyl acetate to about 90-110°C, preferably about 100°C;
- (b) filtering the solution from step (a) under vacuum;
- (c) cooling the filtrate from step (b) until a precipitate forms; and
- (d) filtering the precipitate from step (c) and drying said precipitate under vacuum at
15 about 20-40°C, preferably at about 25°C, until a constant weight is achieved.

Preferably the bosentan crystalline form 5, form 6, form 7 and form 8 of the present invention is suitable for use in medicine, preferably for treating or preventing an endothelin receptor mediated disorder. In one embodiment the endothelin receptor mediated disorder
20 is a cardiovascular disorder. Preferably, the cardiovascular disorder is hypertension, pulmonary hypertension, ischemia, vasospasm or angina pectoris, most preferably pulmonary arterial hypertension.

A thirtieth aspect of the present invention provides a pharmaceutical composition
25 comprising any one or a combination of bosentan crystalline form 5, form 6, form 7 or form 8, and further comprising one or more pharmaceutically acceptable excipients. Preferably the pharmaceutical composition is suitable for treating or preventing an endothelin receptor mediated disorder. In one embodiment the endothelin receptor mediated disorder is a cardiovascular disorder. Preferably, the cardiovascular disorder is
30 hypertension, pulmonary hypertension, ischemia, vasospasm or angina pectoris, most preferably pulmonary arterial hypertension.

A thirty-first aspect of the present invention provides the use of any one or a combination of bosentan crystalline form 5, form 6, form 7 or form 8, or the use of a composition according to the thirtieth aspect of the present invention for the treatment or prevention of an endothelin receptor mediated disorder. In one embodiment the endothelin receptor mediated disorder is a cardiovascular disorder. Preferably, the cardiovascular disorder is hypertension, pulmonary hypertension, ischemia, vasospasm or angina pectoris, most preferably pulmonary arterial hypertension.

A thirty-second aspect of the present invention provides a method of treating or preventing an endothelin receptor mediated disorder, comprising administering to a patient in need thereof a therapeutically or prophylactically effective amount of any one or a combination of bosentan crystalline form 5, form 6, form 7 or form 8, or of a composition according to the thirtieth aspect of the present invention. In one embodiment the endothelin receptor mediated disorder is a cardiovascular disorder. Preferably, the cardiovascular disorder is hypertension, pulmonary hypertension, ischemia, vasospasm or angina pectoris, most preferably pulmonary arterial hypertension. Preferably the patient is a mammal, preferably a human.

Brief description of the accompanying figures

Figure 1 represents the XRPD trace of bosentan form 5. Figure 2 represents the DSC trace of bosentan form 5. Figure 3 represents the TGA trace of bosentan form 5.

Figure 4 represents the XRPD trace of bosentan form 6. Figure 5 represents the DSC trace of bosentan form 6. Figure 6 represents the TGA trace of bosentan form 6.

Figure 7 represents the XRPD trace of bosentan form 7. Figure 8 represents the DSC trace of bosentan form 7. Figure 9 represents the TGA trace of bosentan form 7.

Figure 10 represents the XRPD trace of bosentan form 8. Figure 11 represents the DSC trace of bosentan form 8. Figure 12 represents the TGA trace of bosentan form 8.

Detailed description of the invention

The present invention provides novel crystalline forms 5-8 of bosentan. The processes disclosed herein for preparing said forms are capable of providing these crystalline forms
5 of the invention with consistent polymorphic purity irrespective of the scale of preparation.

Embodiments of the invention related to the preparation of the forms 5-8 generally involve the dissolution of an amount of bosentan starting material in one or a mixture of organic solvents. It is envisaged that any form of bosentan known or unknown even any
10 amorphous forms may be used as the initial bosentan starting material.

In preferred embodiments of the processes for preparing forms 5-8 of bosentan according to the invention, the starting material is dissolved or suspended in a solvent, preferably an organic solvent. In embodiments where the bosentan starting material is dissolved, any
15 technique known to the skilled person may be employed to dissolve the bosentan. In preferred embodiments, heating the bosentan starting material in the desired solvent or solvents until a clear solution is obtained is preferred. In further embodiments, the desired crystalline form is crystallised by cooling the crystallisation solution and/or adding an appropriate anti-solvent. The skilled person will understand, of course, that the cooling of
20 the solution is performed to allow the desired crystalline form to precipitate from the solution, thus any temperature that allows such precipitation is within the scope of this invention. Preferably the crystallisation solution is then stirred. A crystallisation solution may be stirred for any of a number of reasons known to the skilled person, for example, to allow uniform dispersion of heat during cooling, or to provide a homogenous slurry. The
25 stirring may be effected by any means known in the art, for example, by a magnetic stirrer or paddle stirrer. The final stages of preparing crystalline forms 5-8 according to the invention generally involve the isolation of the desired crystalline form. In preferred embodiments this may include filtering the desired crystalline form from the crystallisation suspension. In certain embodiments, the desired isolated crystalline form according to the
30 invention is then dried. Preferably, the desired crystalline form according to the invention is dried until a constant weight is achieved. In particularly preferred embodiments the desired crystalline form is dried under vacuum at about room temperature or between 20 and 35°C.

A further embodiment of the invention provides compositions of crystalline forms 5-8 according to the invention and further comprising one or more pharmaceutically acceptable excipient(s). Another aspect of the present invention is the use of
5 pharmaceutical compositions comprising one or more of the novel forms 5-8 according to the invention to treat patients suffering from endothelin receptor mediated disorders, in particular cardiovascular disorders such as hypertension, ischemia, vasospasm, angina pectoris and pulmonary hypertension.

10 A further embodiment of the invention is a process for making a pharmaceutical composition comprising mixing a crystalline form of bosentan according to the invention and one or more pharmaceutically acceptable excipients. In one embodiment of the invention, there is provided a method for the treatment of an endothelin receptor mediated disorder comprising administering to a subject in need thereof a composition comprising a
15 therapeutically effective amount of a crystalline form of bosentan according to the invention. In a further embodiment according to the invention, there is provided the use of a crystalline form of bosentan according to the invention substantially free of other polymorphic forms, for the preparation of a medicament for treating an endothelin receptor mediated disorder. Preferably the disorder is pulmonary hypertension. In
20 preferred embodiments the purity is in the order of bosentan form 5, form 6, form 7 or form 8 comprising less than 10%, preferably less than 5%, more preferably less than 1%, most preferably less than 0.1% of any other known or unknown crystalline or amorphous forms of bosentan.

25 Illustrative of the invention is a pharmaceutical composition comprising a novel crystalline form of bosentan according to the invention and one or more pharmaceutically acceptable excipient(s). Said composition may comprise solid pharmaceutical compositions which in certain embodiments may comprise tablets including, for example, oral dispersible tablets, capsules containing pellets, mini-tablets, powders or mixtures thereof, caplets, or any of the
30 solid dosage forms that are within the repertoire of the skilled formulation scientist. These may further include immediate release forms of the above solid dosage forms or controlled release forms of the above including sustained release, delayed release and prolonged release compositions. It is also envisaged that the invention comprises liquid formulations

which may be prepared by mixing the crystalline forms according to the invention with a pharmaceutically suitable liquid carrier or solvent.

In one embodiment of the invention there is provided a method for the treatment of an endothelin receptor mediated disorder in a subject in need thereof, comprising
5 administering to the subject a composition comprising a therapeutically effective amount of a novel polymorph of bosentan according to the invention. In a further embodiment according to the invention there is provided the use of a novel polymorph of bosentan according to the invention substantially free of other crystalline and amorphous forms, for
10 the preparation of a medicament for treating an endothelin receptor mediated disorder in a subject in need thereof, preferably the purity is in the order of bosentan form 5, form 6, form 7 or form 8 comprising less than 10%, preferably less than 5%, more preferably less than 1%, most preferably less than 0.1% of other forms of bosentan.

15 In addition to the active ingredient(s), the pharmaceutical compositions of the present invention may, as alluded to above, contain one or more excipients. Excipients are added to the composition for a variety of purposes. Diluents increase the bulk of a solid pharmaceutical composition and may make a pharmaceutical dosage form containing the composition easier for the patient and care giver to handle. Diluents for solid
20 compositions include, for example, microcrystalline cellulose (e.g. Avicel[®]), microfine cellulose, lactose, starch, pregelatinized starch, calcium carbonate, calcium sulfate, sugar, dextrates, dextrin, dextrose, dibasic calcium phosphate dihydrate, tribasic calcium phosphate, kaolin, magnesium carbonate, magnesium oxide, maltodextrin, mannitol, polymethacrylates (e.g. Eudragit[®]), potassium chloride, powdered cellulose, sodium
25 chloride, sorbitol and talc.

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 other excipients together after compression. Binders for solid pharmaceutical
30 compositions include acacia, alginic acid, carbomer (e.g. Carbopol[®]), carboxymethyl cellulose sodium, dextrin, ethyl cellulose, gelatin, guar gum, hydrogenated vegetable oil, hydroxyethyl cellulose, hydroxypropyl cellulose (e.g. Klucel[®]), hydroxypropyl methyl cellulose (e.g. Methocel[®]), liquid glucose, magnesium aluminium silicate, maltodextrin,

methyl cellulose, polymethacrylates, povidone (e.g. Kollidon[®], Plasdone[®]), pregelatinized starch, sodium alginate and starch.

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. Disintegrants include alginic acid, carboxymethyl cellulose calcium, carboxymethyl cellulose sodium (e.g. Ac-Di-Sol[®], Primellose[®]), colloidal silicon dioxide, croscarmellose sodium, crospovidone (e.g. Kollidon[®], Polyplasdone[®]), guar gum, magnesium aluminium silicate, methyl cellulose, microcrystalline cellulose, polacrillin potassium, powdered cellulose, 10 pregelatinized starch, sodium alginate, sodium starch glycolate (e.g. Explotab[®]) and starch.

Glidants can be added to improve the flowability of a non-compacted solid composition and to improve the accuracy of dosing. Excipients that may function as glidants include colloidal silicon dioxide, magnesium trisilicate, powdered cellulose, starch, talc and tribasic 15 calcium phosphate.

When a dosage form such as a tablet is made by the compaction of a powdered composition, the composition is subjected to pressure from a punch and dye. Some excipients and active ingredients have a tendency to adhere to the surfaces of the punch 20 and dye, which can cause the product to have pitting and other surface irregularities. A lubricant can be added to the composition to reduce adhesion and ease the release of the product from the dye. Lubricants include magnesium stearate, calcium stearate, glyceryl monostearate, glyceryl palmitostearate, hydrogenated castor oil, hydrogenated vegetable oil, mineral oil, polyethylene glycol, sodium benzoate, sodium lauryl sulfate, sodium stearyl 25 fumarate, stearic acid, talc and zinc stearate.

Flavouring agents and flavour enhancers make the dosage form more palatable to the patient. Common flavouring agents and flavour enhancers for pharmaceutical products that may be included in the composition of the present invention include maltol, vanillin, 30 ethyl vanillin, menthol, citric acid, fumaric acid, ethyl maltol and tartaric acid.

Solid and liquid compositions may also be dyed using any pharmaceutically acceptable colorant to improve their appearance and/or facilitate patient identification of the product and unit dosage level.

- 5 In liquid pharmaceutical compositions of the present invention, the crystalline bosentan and any other solid excipients are dissolved or suspended in a liquid carrier such as water, vegetable oil, alcohol, polyethylene glycol, propylene glycol or glycerine.

10 Liquid pharmaceutical compositions may further contain emulsifying agents to disperse uniformly throughout the composition an active ingredient or other excipient that is not soluble in the liquid carrier. Emulsifying agents that may be useful in liquid compositions of the present invention include, for example, gelatin, egg yolk, casein, cholesterol, acacia, tragacanth, chondrus, pectin, methyl cellulose, carbomer, cetostearyl alcohol and cetyl alcohol.

15

Liquid pharmaceutical compositions of the present invention may also contain a viscosity enhancing agent to improve the mouth-feel or organoleptic qualities of the product and/or coat the lining of the gastrointestinal tract. Such agents include acacia, alginic acid, bentonite, carbomer, carboxymethyl cellulose calcium or sodium, cetostearyl alcohol, 20 methyl cellulose, ethyl cellulose, gelatin, guar gum, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, maltodextrin, polyvinyl alcohol, povidone, propylene carbonate, propylene glycol alginate, sodium alginate, sodium starch glycolate, starch tragacanth and xanthan gum.

- 25 Sweetening agents such as sorbitol, saccharin, sodium saccharin, sucrose, aspartame, fructose, mannitol and invert sugar may be added to improve the taste.

Preservatives and chelating agents such as alcohol, sodium benzoate, butylated hydroxytoluene, butylated hydroxyanisole and ethylenediaminetetraacetic acid may be 30 added at levels safe for ingestion to improve storage stability.

According to the present invention, a liquid composition may also contain a buffer such as gluconic acid, lactic acid, citric acid or acetic acid, sodium gluconate, sodium lactate, sodium citrate or sodium acetate.

- 5 Selection of excipients and the amounts used may be readily determined by the formulation scientist based upon experience and consideration of standard procedures and reference works in the field.

The solid compositions of the present invention include powders, granulates, aggregates
10 and compacted compositions. The dosages include dosages suitable for oral, buccal, rectal, parenteral (including subcutaneous, intramuscular, and intravenous), inhalant and ophthalmic administration. Although the most suitable administration in any given case will depend on the nature and severity of the condition being treated, the most preferred route of the present invention is oral. The dosages may be conveniently presented in unit
15 dosage form and prepared by any of the methods well-known in the pharmaceutical arts. Dosage forms include solid dosage forms like tablets, powders, capsules, suppositories, sachets, troches and lozenges, as well as liquid syrups, suspensions and elixirs.

The dosage form of the present invention may be a capsule containing the composition,
20 preferably a powdered or granulated solid composition of the invention, within either a hard or a soft shell. The shell may be made from gelatin and optionally contain a plasticizer such as glycerine and sorbitol, and an opacifying agent or colourant. The active ingredient and excipients may be formulated into compositions and dosage forms according to methods known in the art.

25 A composition for tableting or capsule filling may be prepared by wet granulation. In wet granulation, some or all of 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 granulate is screened and/or milled, dried and then screened
30 and/or milled to the desired particle size. The granulate may then be tableted, or other excipients may be added prior to tableting, such as a glidant and/or a lubricant.

A tableting composition may be prepared conventionally by dry blending. For example, the blended composition of the actives and excipients may be compacted into a slug or a sheet and then comminuted into compacted granules. The compacted granules may subsequently be compressed into a tablet.

5

As an alternative to dry granulation, a blended composition may be compressed directly into a compacted dosage form using direct compression techniques. Direct compression produces a uniform tablet without granules. Excipients that are particularly well suited for direct compression tableting include microcrystalline cellulose, spray dried lactose, dicalcium phosphate dihydrate and colloidal silica. The proper use of these and other excipients in direct compression tableting is known to those in the art with experience and skill in particular formulation challenges of direct compression tableting.

10

A capsule filling of the present invention may comprise any of the aforementioned blends and granulates that were described with reference to tableting, however, they are not subjected to a final tableting step.

15

In further embodiments, the composition of the invention may further comprise one or more additional active ingredients.

20

The details of the invention, its objects and advantages are explained hereunder in greater detail in relation to non-limiting exemplary illustrations.

Examples

25

The following examples describe specific methods for preparing crystalline forms of bosentan according to the invention. In all the examples below the starting material comprises 1g of bosentan form 1 as prepared using the procedure described in WO 01/55120.

30

Example 1: method for preparing bosentan form 5

A mixture of bosentan and ethyl acetoacetate (5 volumes, (vol)) was heated to 50°C until a clear solution was obtained. The solution was then cooled to about 30°C within about 50
5 minutes and stirred at that temperature for about 17 hours. The resulting suspension was then filtered to obtain the desired crystalline solid and said solid was dried under vacuum at 25°C for about 4 hours or until a constant weight was achieved.

XRPD and DSC analysis data confirmed that the product obtained was bosentan form 5.

Molar yield = 0.18g

10 Chemical purity > 99% (measured by HPLC)

Polymorphic purity = high (measured by DSC)

Example 2: method for preparing bosentan form 6

15 A mixture of bosentan, butan-2-ol (2.6 vol) and amyl alcohol (2.6 vol) was heated to about 80°C, resulting in a suspension of the bosentan in the solvents. Water (1 vol) was added to this suspension to effect dissolution of the bosentan and a clear solution was obtained. The solution was then cooled to 30°C within about 45 minutes. Cyclohexane (10 vol) was added to this cooled solution and stirred whilst the temperature was maintained at about
20 30°C for about 30 minutes. The resulting suspension was then filtered to obtain the desired crystalline solid and said solid was dried under vacuum at 25°C for about 2 hours or until a constant weight was achieved.

XRPD and DSC analysis data confirmed that the product obtained was bosentan form 6.

Molar yield = 0.81g

25 Chemical purity > 99% (measured by HPLC)

Polymorphic purity = high (measured by DSC)

Example 3: method for preparing bosentan form 7

30 A mixture of bosentan, cyclohexanone (2 vol) and n-butanol (2 vol) was heated to about 50°C to obtain a clear solution. This solution was cooled to about 30°C within about 30 minutes and stirred at this temperature for 30 minutes. n-Hexane (15 vol) was then added to the cooled solution resulting in a solid precipitate. The suspension was further stirred

for about 2.5 hours. The suspension was then filtered to obtain the desired crystalline solid and said solid was dried under vacuum at 25°C for about 23 hours or until a constant weight was achieved.

XRPD and DSC analysis data confirmed that the product obtained was bosentan form 7.

5 Molar yield = 0.83g

Chemical purity > 99% (measured by HPLC)

Polymorphic purity = high (measured by DSC)

Example 4: method for preparing bosentan form 7

10

A mixture of bosentan, cyclohexanone (2 vol) and ethanol (2 vol) was heated to about 80°C to obtain a clear solution. This solution was cooled to about 30°C within about 30 minutes and stirred at this temperature for 30 minutes. n-Hexane (15 vol) was then added to the cooled solution resulting in a solid precipitate. The suspension was further stirred
15 for about 21 hours. The suspension was then filtered to obtain the desired crystalline solid and said solid was dried under vacuum at 25°C for about 13 hours or until a constant weight was achieved.

XRPD and DSC analysis data confirmed that the product obtained was bosentan form 7.

Molar yield = 0.54g

20 Chemical purity > 99% (measured by HPLC)

Polymorphic purity = high (measured by DSC)

Example 5: method for preparing bosentan form 8

25 A mixture of bosentan, ethyl acetoacetate (0.8 vol), octanol (2 vol) and n-pentyl acetate (1.2 vol) was heated to about 100°C. The resultant suspension was filtered at this temperature under vacuum. The filtrate was then cooled to about 26°C within about 15 minutes, resulting in the formation of a solid precipitate, and stirred at that temperature for about 4 hours. The suspension was then filtered to obtain the desired crystalline solid and said
30 solid was dried under vacuum at 25°C for about 13 hours or until a constant weight was achieved.

XRPD and DSC analysis data confirmed that the product obtained was bosentan form 8.

Molar yield = 0.42g

Chemical purity > 99% (measured by HPLC)

Polymorphic purity = high (measured by DSC)

5 The foregoing description and examples have been set forth merely to illustrate the invention and are not intended to be limiting. Since modifications of the described embodiments incorporating the spirit and substance of the invention may occur to persons skilled in the art, the invention should be construed broadly to include all variations within the scope of the appended claims and equivalents thereof.

Claims

1. Crystalline form 5 of bosentan characterized by an X-ray diffraction pattern comprising two or more peaks selected from peaks at 2θ values 4.02, 6.12, 8.38, 9.39, 10.04,
5 15.26, 17.72, 17.98, 18.81, 19.28, 20.31, 21.05, 27.57, 31.91 and $45.65 \pm 0.2^\circ$.
2. Crystalline form 5 of bosentan having an XRPD trace substantially as shown in figure 1.
- 10 3. Crystalline form 5 of bosentan characterized by a DSC trace comprising endothermic peaks at about $93^\circ\text{C} \pm 2^\circ\text{C}$ and about $196^\circ\text{C} \pm 2^\circ\text{C}$.
4. Crystalline form 5 of bosentan having a DSC trace substantially as shown in figure
2.
15
5. Crystalline form 5 of bosentan having a TGA trace substantially as shown in figure
3.
6. A process for preparing crystalline form 5 of bosentan according to any one of
20 claims 1-5, comprising the steps of:
 - (a) dissolving bosentan in one or more organic solvent(s);
 - (b) causing a crystalline solid to precipitate from the solution obtained in step (a); and
 - (c) isolating the crystalline solid obtained from step (b).
- 25 7. A process according to claim 6, wherein the solvent in step (a) comprises ethyl acetoacetate.
8. A process according to claim 6 or 7, wherein the solvent is heated in step (a) until a clear solution is obtained.
- 30 9. A process according to any one of claims 6-8, wherein the crystalline solid is precipitated in step (b) by cooling the solution.

10. A process according to any one of claims 6-9, wherein the precipitated solid is isolated in step (c) by filtration.
11. A process according to any one of claims 6-10, wherein the isolated solid from step
5 (c) is dried under vacuum until a constant weight is achieved.
12. A process for preparing crystalline form 5 of bosentan according to any one of claims 1-5, comprising the steps of:
- (a) heating bosentan in ethyl acetoacetate until a clear solution is obtained;
 - 10 (b) cooling the solution from step (a) until a precipitate forms; and
 - (c) filtering the suspension from step (b) and drying the obtained solid under vacuum at about 20-40°C until a constant weight is achieved.
13. Crystalline form 6 of bosentan characterized by an X-ray diffraction pattern
15 comprising two or more peaks selected from peaks at 2θ values 3.87, 7.51, 8.84, 11.14, 18.74 and $23.30 \pm 0.2^\circ$.
14. Crystalline form 6 of bosentan having an XRPD trace substantially as shown in figure 4.
20
15. Crystalline form 6 of bosentan characterized by a DSC trace comprising endothermic peaks at about $78^\circ\text{C} \pm 2^\circ\text{C}$ and about $134^\circ\text{C} \pm 2^\circ\text{C}$.
16. Crystalline form 6 of bosentan having a DSC trace substantially as shown in figure
25 5.
17. Crystalline form 6 of bosentan having a TGA trace substantially as shown in figure 6.
- 30 18. A process for preparing crystalline form 6 of bosentan according to any one of claims 13-17, comprising the steps of:
- (a) dissolving bosentan in one or more organic solvent(s) and optionally water;
 - (b) causing a crystalline solid to precipitate from the solution obtained in step (a); and

(c) isolating the crystalline solid obtained from step (b).

19. A process according to claim 18, wherein the solvent, each solvent or one or more of the solvent(s) in step (a) is a C₁-C₆ alcohol.

5

20. A process according to claim 18 or 19, wherein bosentan is dissolved in step (a) by heating in butan-2-ol and amyl alcohol and adding water.

21. A process according to any one of claims 18-20, wherein the solid is precipitated in step (b) by cooling the solution from step (a) and adding cyclohexane.

10

22. A process according to any one of claims 18-21, wherein the precipitated solid from step (b) is isolated by filtration.

23. A process according to any one of claims 18-22, wherein the isolated solid from step (c) is dried under vacuum until a constant weight is achieved.

15

24. A process for preparing crystalline form 6 of bosentan according to any one of claims 13-17, comprising the steps of:

20 (a) dissolving or suspending bosentan in a solvent system comprising one or more C₁-C₆ alcohol(s);

(b) adding water to the solution or suspension from step (a) until a clear solution is obtained;

(c) cooling the solution from step (b) to between about 20-40°C;

25 (d) adding cyclohexane to the solution from step (c) until a precipitate is formed; and

(e) filtering the resultant precipitated solid and drying under vacuum at between about 20-30°C until a constant weight is achieved.

25. A process according to claim 24, wherein the solvent system in step (a) comprises butan-2-ol and amyl alcohol.

30

26. A process according to claim 24 or 25, wherein the solvents are heated in step (a) to about 80°C.

27. Crystalline form 7 of bosentan characterized by an X-ray diffraction pattern comprising two or more peaks selected from peaks at 2θ values 3.64, 4.23, 4.95, 7.04, 7.68, 8.23, 9.05, 9.66, 10.48, 13.95, 15.20, 16.17, 17.37, 18.06, 20.03, 22.13 and $23.62 \pm 0.2^\circ$.

5

28. Crystalline form 7 of bosentan having an XRPD trace substantially as shown in figure 7.

29. Crystalline form 7 of bosentan characterized by a DSC trace comprising
10 endothermic peaks at about $75^\circ\text{C} \pm 2^\circ\text{C}$ and about $130^\circ\text{C} \pm 2^\circ\text{C}$.

30. Crystalline form 7 of bosentan having a DSC trace substantially as shown in figure 8.

15 31. Crystalline form 7 of bosentan having a TGA trace substantially as shown in figure 9.

32. A process for preparing crystalline form 7 of bosentan according to any one of claims 27-31, comprising the steps of:

- 20 (a) dissolving bosentan in one or more organic solvent(s);
(b) causing a crystalline solid to precipitate from the solution obtained in step (a); and
(c) isolating the crystalline solid obtained from step (b).

33. A process according to claim 32, wherein bosentan is dissolved in step (a) in the or
25 each solvent until a clear solution is obtained.

34. A process according to claim 32 or 33, wherein bosentan is dissolved in step (a) by heating the or each solvent.

30 35. A process according to any one of claims 32-34, wherein the solvent, each solvent or one or more of the solvent(s) in step (a) is a $\text{C}_1\text{-C}_6$ alcohol.

36. A process according to any one of claims 32-35, wherein the solvents in step (a) are a mixture of cyclohexanone and n-butanol.

37. A process according to any one of claims 32-35, wherein the solvents in step (a) are
5 a mixture of cyclohexanone and ethanol.

38. A process according to any one of claims 32-37, wherein the crystalline solid is precipitated by adding n-hexane to the solution from step (a).

10 39. A process according to any one of claims 32-38, wherein the solid is isolated in step (c) by filtration.

40. A process according to any one of claims 32-39, wherein the isolated solid from step (c) is dried under vacuum until a constant weight is achieved.

15

41. A process for preparing crystalline form 7 of bosentan according to any one of claims 27-31, comprising the steps of:

- (a) dissolving bosentan in a mixture of cyclohexanone and a C₁-C₆ alcohol;
- (b) cooling the solution from step (a) to about 30°C within about 30 minutes whilst
20 stirring;
- (c) adding n-hexane to the solution from step (b) to form a precipitate and stirring the suspension for about 2-5 hours; and
- (d) filtering the suspension from step (c) and drying the obtained solid under vacuum at about 20-40°C until a constant weight is achieved.

25

42. A process according to claim 41, wherein the C₁-C₆ alcohol in step (a) is n-butanol.

43. A process according to claim 41 or 42, wherein bosentan is dissolved in step (a) by heating the mixture until a clear solution is obtained.

30

44. A process for preparing crystalline form 7 of bosentan according to any one of claims 27-31, comprising the steps of:

- (a) dissolving bosentan in a mixture of cyclohexanone and a C₁-C₆ alcohol;

(b) cooling the solution from step (a) to about 30°C within about 30 minutes whilst stirring;

(c) adding n-hexane to the solution from step (b) to form a precipitate and stirring the suspension for between about 15-25 hours; and

5 (d) filtering the suspension from step (c) and drying the obtained solid under vacuum at about 20-40°C until a constant weight is achieved.

45. A process according to claim 44, wherein the C₁-C₆ alcohol in step (a) is ethanol.

10 46. A process according to claim 44 or 45, wherein bosentan is dissolved in step (a) by heating the mixture until a clear solution is obtained.

47. Crystalline form 8 of bosentan characterized by an X-ray diffraction pattern comprising two or more peaks selected from peaks at 2θ values 9.47, 13.41, 14.52, 15.46,
15 15.73, 16.35, 16.88, 17.99, 18.87, 19.25, 20.53, 21.82, 23.02, 23.83, 24.61, 24.86, 25.13 and 26.03 ± 0.2 °θ.

48. Crystalline form 8 of bosentan having an XRPD trace substantially as shown in figure 10.

20

49. Crystalline form 8 of bosentan characterized by a DSC trace comprising endothermic peaks at about 58°C ± 2°C and about 110°C ± 2°C.

50. Crystalline form 8 of bosentan having a DSC trace substantially as shown in figure
25 11.

51. Crystalline form 8 of bosentan having a TGA trace substantially as shown in figure 12.

30 52. A process for preparing crystalline form 8 of bosentan according to any one of claims 47-51, comprising the steps of:

(a) mixing bosentan in one or more organic solvent(s);

(b) filtering the mixture from step (a);

- (c) causing a crystalline solid to precipitate from the filtrate obtained in step (b); and
- (d) isolating the crystalline solid obtained in step (c).

53. A process according to claim 52, wherein bosentan is heated in step (a) in a mixture
5 of ethyl acetoacetate, octanol and n-pentyl acetate.

54. A process according to claim 52 or 53, wherein in step (b) the mixture is filtered under vacuum whilst still hot.

10 55. A process according to any one of claims 52-54, wherein the crystalline solid is obtained by cooling the filtrate in step (c).

56. A process according to any one of claims 52-55, wherein the crystalline solid is filtered in step (d) and dried under vacuum until a constant weight is achieved.

15

57. A process for preparing crystalline form 8 of bosentan according to any one of claims 47-51, comprising the steps of:

- (a) dissolving bosentan in a mixture of ethyl acetoacetate, octanol and n-pentyl acetate;
- (b) filtering the solution from step (a) under vacuum;
- 20 (c) cooling the filtrate from step (b) until a precipitate forms; and
- (d) filtering the precipitate from step (c) and drying said precipitate under vacuum at about 20-40°C until a constant weight is achieved.

58. A process according to claim 57, wherein bosentan is dissolved in step (a) by
25 heating the mixture to about 90-110°C.

59. A crystalline form of bosentan according to any one of claims 1-5, 13-17, 27-31 or 47-51, comprising less than 10% of other forms of bosentan.

30 60. A crystalline form of bosentan according to claim 59, comprising less than 5% of other forms of bosentan.

61. A crystalline form of bosentan according to claim 60, comprising less than 1% of other forms of bosentan.

62. A crystalline form of bosentan according to claim 61, comprising less than 0.1% of other forms of bosentan.

63. A crystalline form of bosentan according to any one of claims 1-5, 13-17, 27-31, 47-51 or 59-62, for use in medicine.

64. A crystalline form of bosentan according to claim 63, for treating or preventing an endothelin receptor mediated disorder.

65. A crystalline form of bosentan according to claim 64, wherein the endothelin receptor mediated disorder is a cardiovascular disorder.

66. A crystalline form of bosentan according to claim 65, wherein the cardiovascular disorder is hypertension, pulmonary hypertension, ischemia, vasospasm or angina pectoris.

67. A crystalline form of bosentan according to claim 66, wherein the cardiovascular disorder is pulmonary arterial hypertension.

68. A pharmaceutical composition comprising one or more crystalline forms of bosentan according to any one of claims 1-5, 13-17, 27-31, 47-51 or 59-67, and one or more pharmaceutically acceptable excipients.

69. Use of one or more crystalline forms of bosentan according to any one of claims 1-5, 13-17, 27-31, 47-51 or 59-67, or use of a composition according to claim 68, for the treatment or prevention of an endothelin receptor mediated disorder.

70. Use according to claim 69, for the treatment or prevention of a cardiovascular disorder.

71. Use according to claim 70, wherein the cardiovascular disorder is hypertension, pulmonary hypertension, ischemia, vasospasm or angina pectoris.

5 72. Use according to claim 71, wherein the cardiovascular disorder is pulmonary arterial hypertension.

73. A method of treating or preventing an endothelin receptor mediated disorder, comprising administering to a patient in need thereof a therapeutically or prophylactically effective amount of one or more crystalline forms of bosentan according to any one of
10 claims 1-5, 13-17, 27-31, 47-51 or 59-67, or of a composition according to claim 68.

74. A method according to claim 73, wherein the endothelin receptor mediated disorder is a cardiovascular disorder.

15 75. A method according to claim 74, wherein the cardiovascular disorder is hypertension, pulmonary hypertension, ischemia, vasospasm or angina pectoris.

76. A method according to claim 75, wherein the cardiovascular disorder is pulmonary arterial hypertension.
20

77. A method according to any one of claims 73-76, wherein the patient is a mammal.

78. A method according to claim 77, wherein the mammal is a human.
25

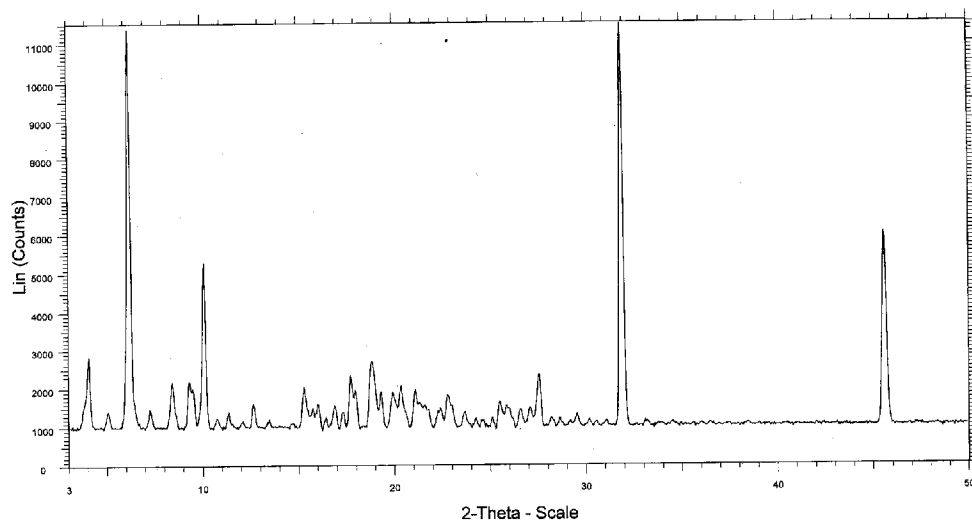


Figure 1

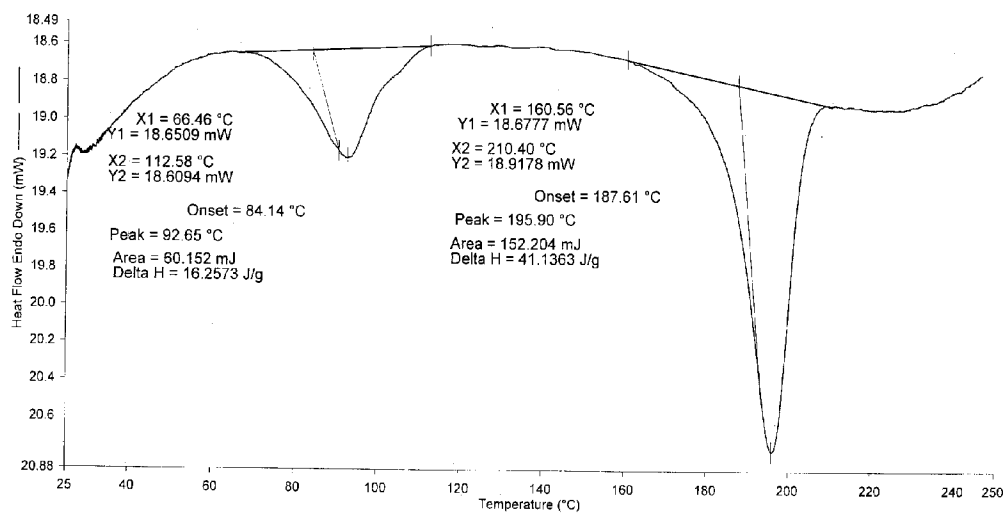


Figure 2

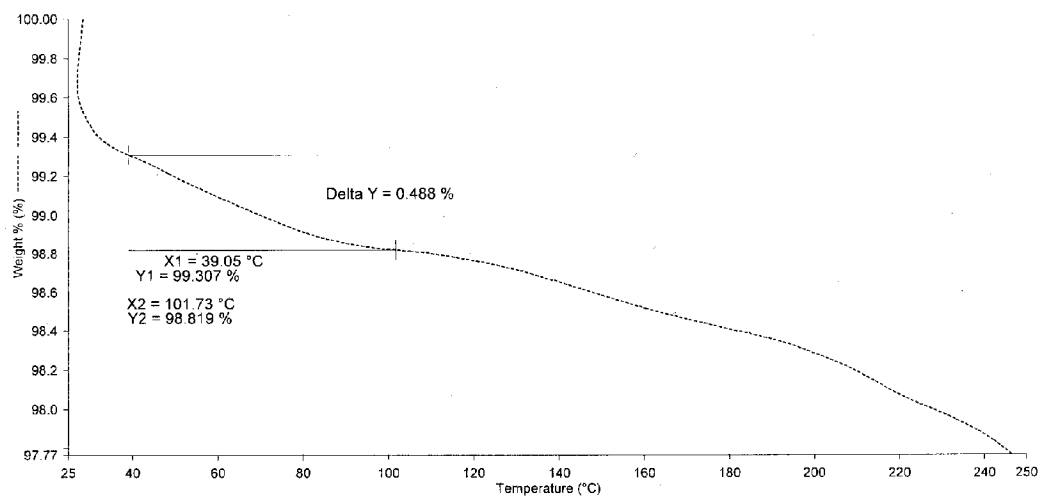


Figure 3

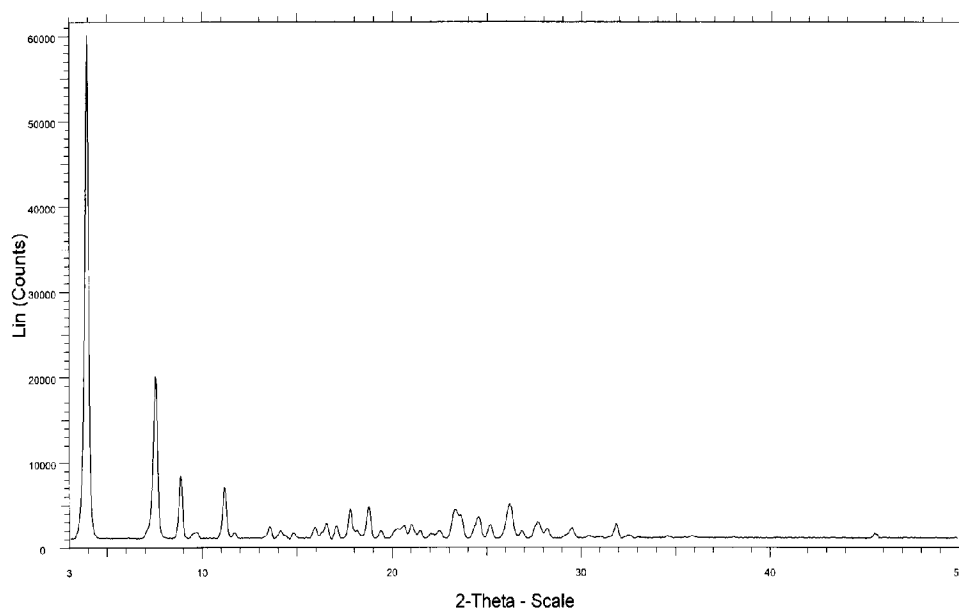


Figure 4

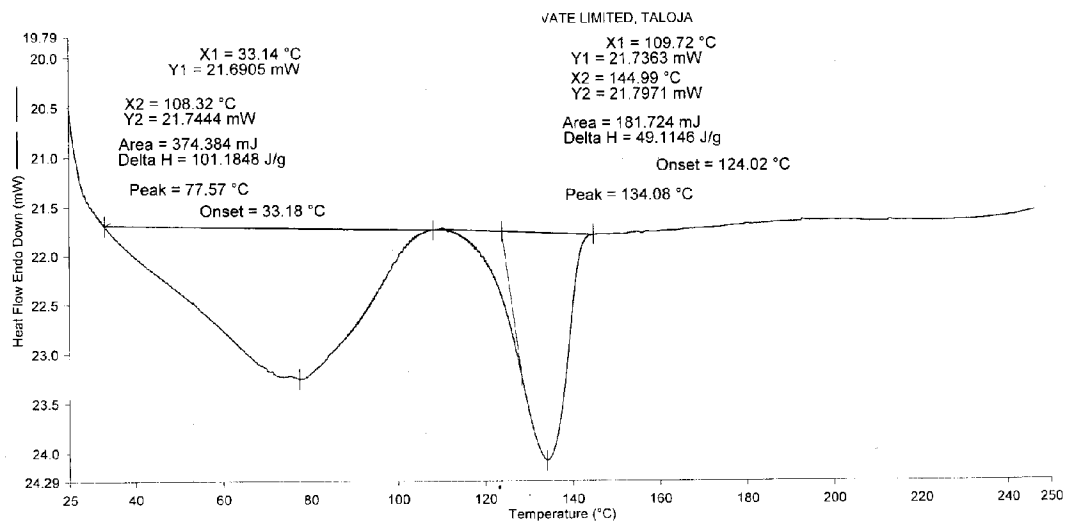


Figure 5

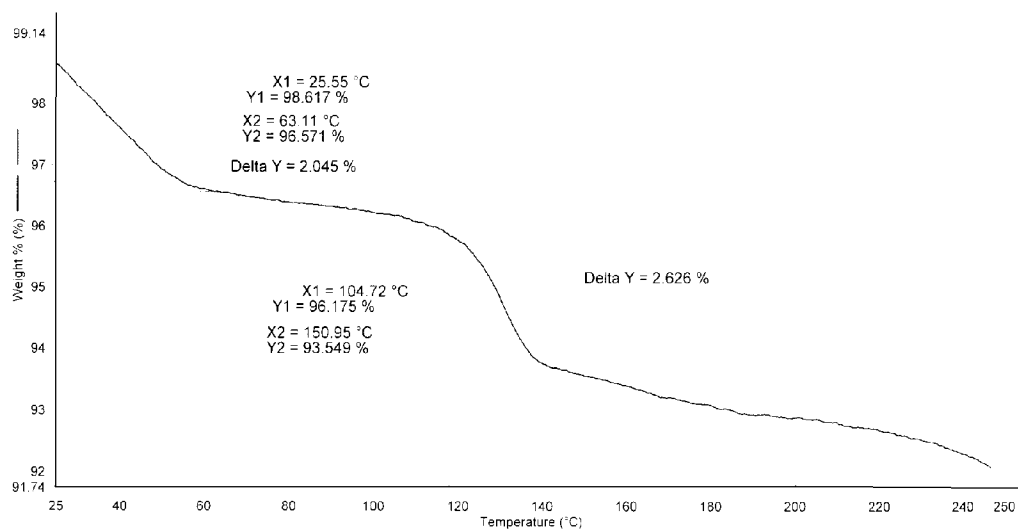


Figure 6

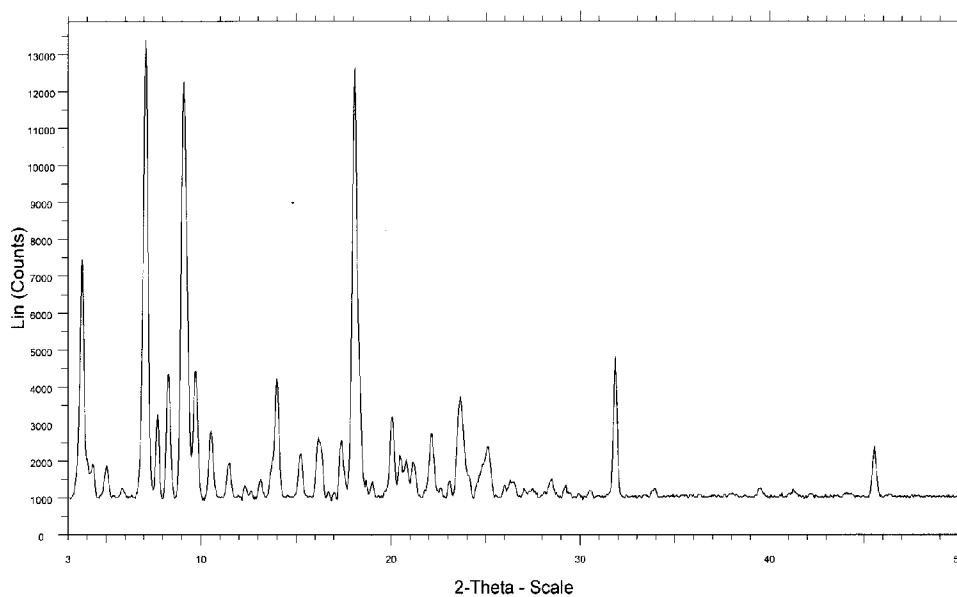


Figure 7

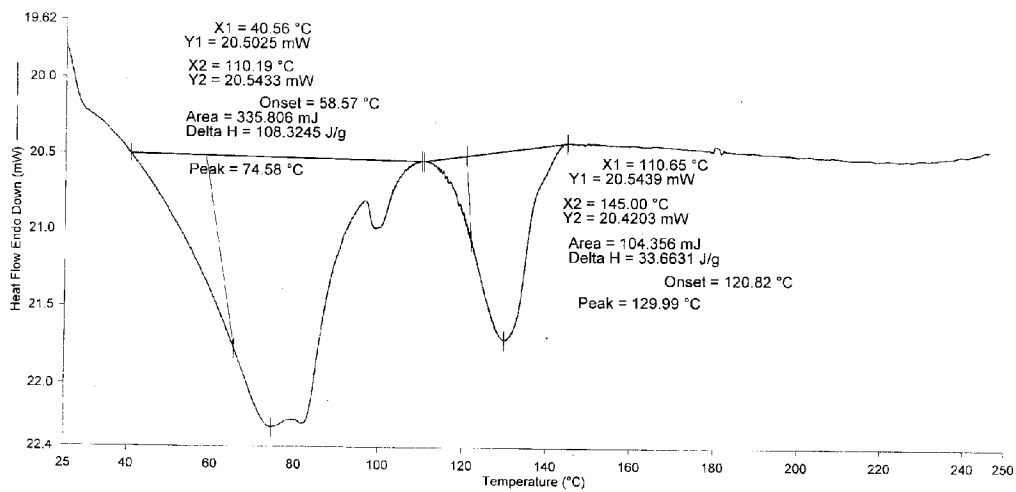


Figure 8

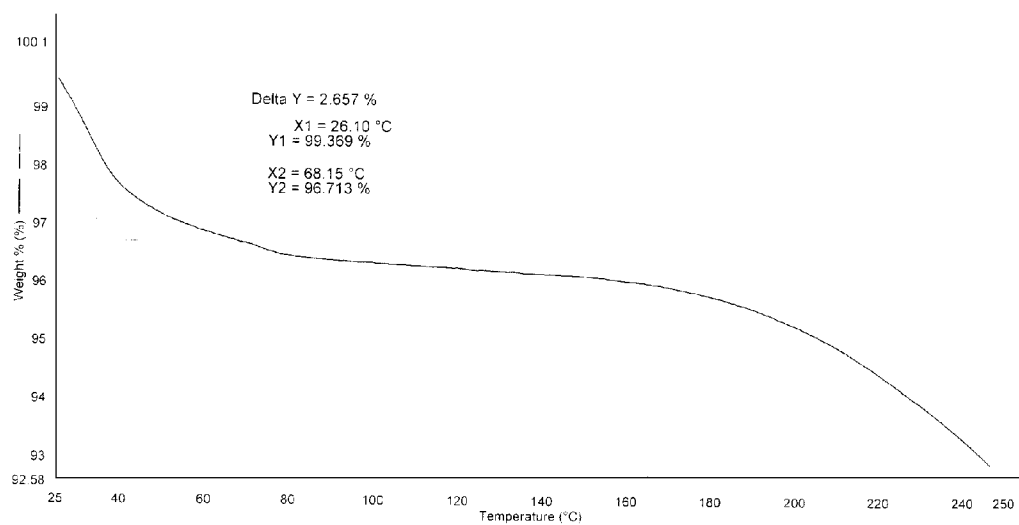


Figure 9

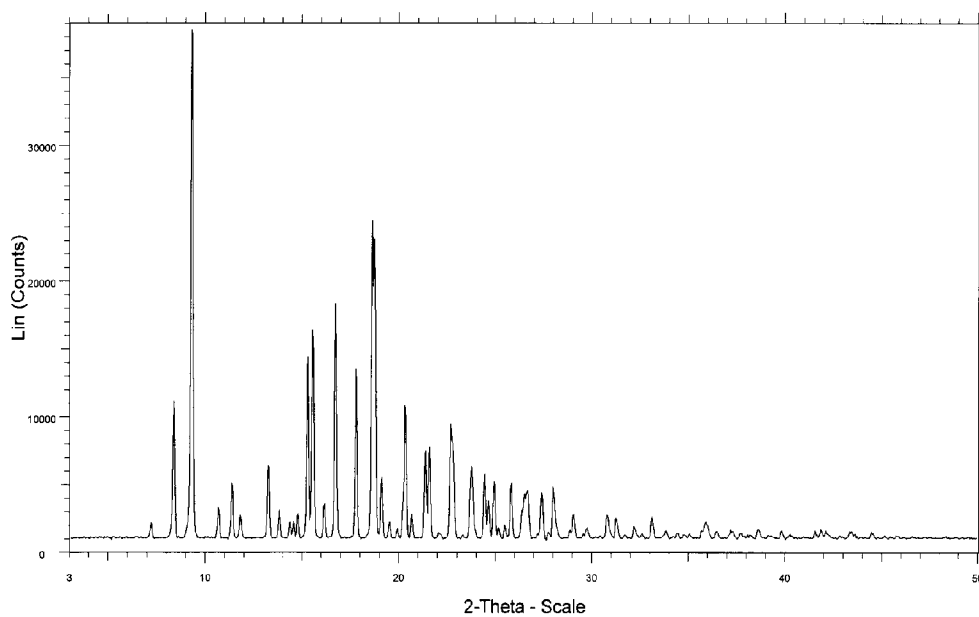


Figure 10

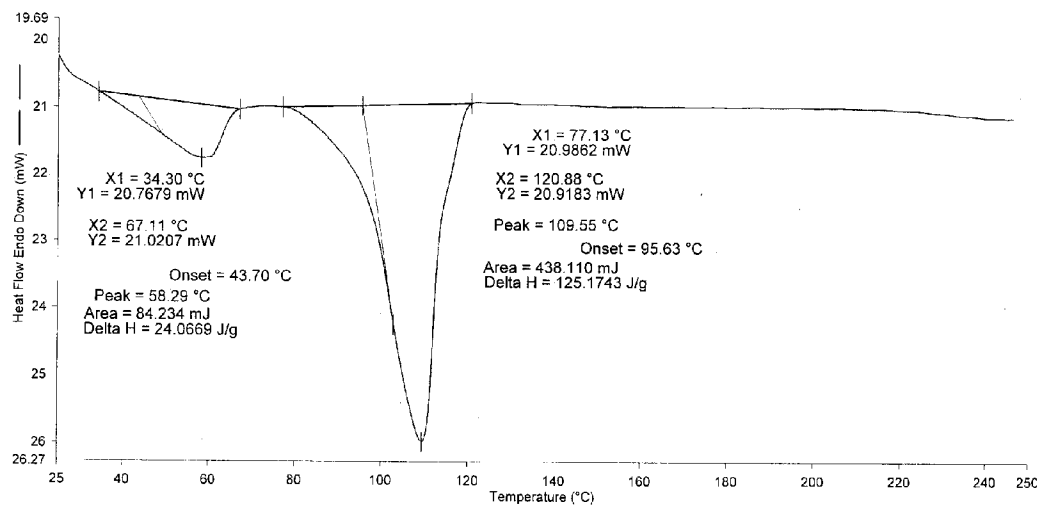


Figure 11

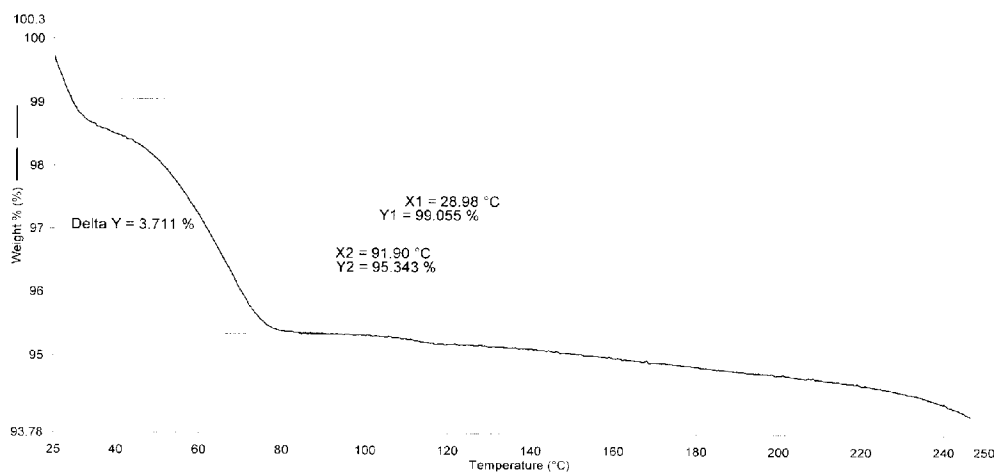


Figure 12