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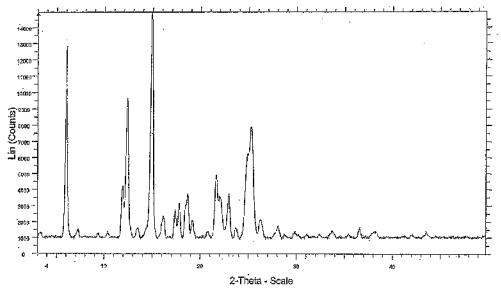
(54) Title: PROCESSES FOR PREPARING CRYSTALLINE FORMS

Figure 1



(57) Abstract: The present invention relates to intermediates and their preparation, for use in the manufacture of pure dasatinib, in particularly dasatinib monohydrate and anhydrous dasatinib. The invention also relates to pharmaceutical compositions comprising pure dasatinib and their use in the treatment of cancer.

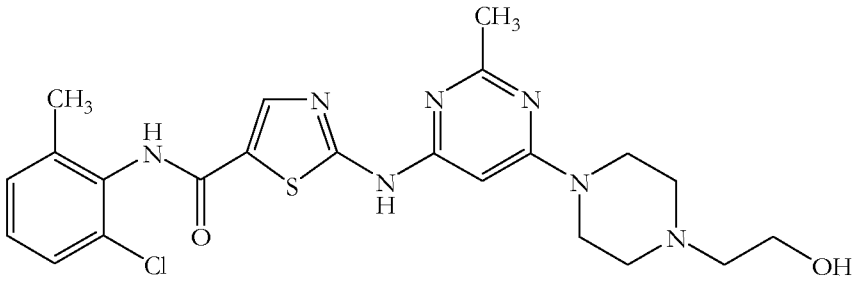
Processes for preparing crystalline forms

Field of the invention

The present invention relates to intermediates and their preparation, for use in the manufacture of pure dasatinib, in particularly dasatinib monohydrate and anhydrous dasatinib. The invention also relates to pharmaceutical compositions comprising pure dasatinib and their use in the treatment of cancer.

Background of the invention

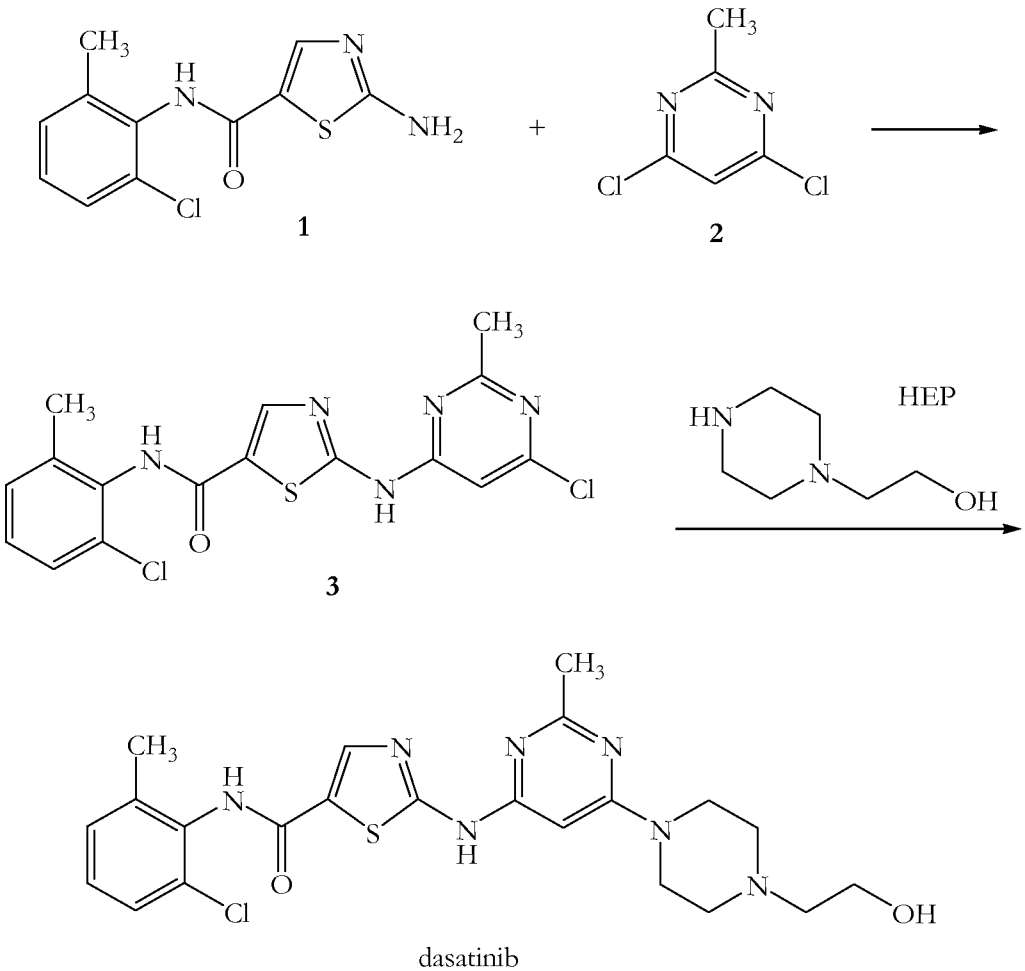
Dasatinib is an active pharmaceutical ingredient approved for the treatment of cancer, in particular treatment of adults with chronic, accelerated or blast phase chronic myeloid leukaemia (CML) with resistance or intolerance to prior therapy including imatinib mesilate. Dasatinib is also indicated for the treatment of adults with Philadelphia chromosome positive (Ph+) acute lymphoblastic leukaemia (ALL) and lymphoid blast CML with resistance or intolerance to prior therapy.



dasatinib

There is considerable interest in the development of novel polymorphs of dasatinib and processes for their preparation. The new polymorphs may be advantageous for dosage form development and enhancing bioavailability owing to the altered physicochemical properties. There is also interest in the development of novel processes for the preparation of known polymorphs of dasatinib. Such novel processes can result in polymorphs of increased and reproducible chemical and/or polymorphic purity. Further the novel processes should be robust and capable of preparing said compounds on an industrial scale.

US 2006/0004067 discloses four crystalline forms of dasatinib. A monohydrate, a 'neat' crystalline form, a butanol solvate and an ethanol solvate and processes for their preparation are described. Several salts and combinations of salts and solvates of dasatinib are reported in WO 2007/035874.



dasatinib

Scheme 1

Scheme 1 shows a general process for the preparation of dasatinib as disclosed in US 2006/0004067. Intermediate 3 and N-(2-hydroxyethyl)piperazine (HEP) are heated together in a solvent system comprising n-butanol as a solvent and diisopropylethylamine (DIPEA) as a base. On cooling of the reaction mixture, dasatinib precipitates out and is isolated by filtration.

Further processing into the monohydrate form was achieved in a number of ways, for example, forming dasatinib acetate and heating, or heating dasatinib in an aqueous ethanol solution. All the methods disclosed in US 2006/0004067 require either the intermediates to be dissolved in a solvent as in the preparation of dasatinib or for dasatinib itself to be dissolved in an aqueous solution of some sort. Further, studies by the inventors have shown that the dasatinib so prepared only has a purity of approximately 90%.

The discovery of new polymorphic forms is a continuing goal of formulators. Discovering novel processes to prepare known polymorphic forms is also a primary goal of the pharmaceutical development scientist. New processes can provide novel intermediates or synthetic pathways that result in product with increased chemical and polymorphic purity. There is thus a need to provide novel synthetic routes and intermediates that can realise these goals.

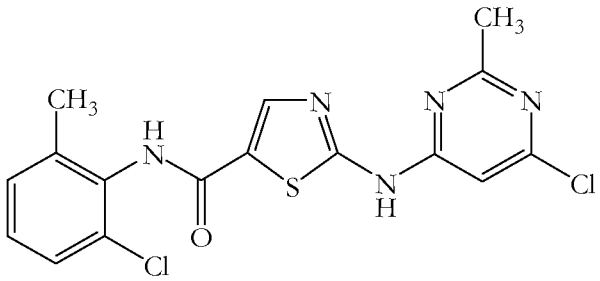
Summary of the invention

Having regard to the aforementioned need to develop novel processes and increasingly pure active pharmaceutical ingredients for use in pharmaceutical products, the object of the invention is to provide novel intermediates that can be used in the preparation of dasatinib with a purity of greater than 99.7%. In particular the intermediates may be used to prepare anhydrous dasatinib and dasatinib monohydrate.

Preparing API with increased purity is always an aim of the pharmaceutical development team. The inventors have found that preparing dasatinib monohydrate or anhydrous dasatinib using a dichloromethane (DCM) solvated dasatinib intermediate resulted in a particularly pure product with a good yield.

Accordingly, in a first aspect according to the invention a process is provided for preparing dasatinib dichloromethane solvate comprising:

(i) mixing an intermediate having structure 3



3

with N-(2-hydroxyethyl)piperazine (HEP);

(ii) adding dichloromethane as an anti-solvent; and

(iii) isolating the resulting precipitated solid dasatinib dichloromethane solvate.

Preferably, the intermediate 3 is suspended in a solvent system comprising one or more organic solvents. The inventors found that in preferred embodiments the solvent system could comprise one or more of dimethyl sulphoxide (DMSO), dimethylformamide (DMF), N-methyl-2-pyrrolidone (NMP) and dimethylacetamide (DMAC). In particularly preferred embodiments the solvent system comprises DMSO. The inventors found that when the solvent system was comprised of DMSO, a particularly pure product was prepared with high yield.

In particularly preferred embodiments of a process according to the first aspect of the invention, the inventors found that a molar ratio of intermediate 3 : HEP of about 1:2 or about 1:3 is particularly advantageous. When such a ratio is employed the HEP acting as the base serves to trap HCl that is liberated during the reaction. It has been found that this ratio is particularly advantageous and provides a particularly pure product with high yield. However the inventors have found that the invention is also enabled and high purity product is prepared in embodiments wherein the ratio of intermediate 3 : HEP is between about 1:1 to about 1:50, preferably between about 1:2 to about 1:10, or in certain embodiments between about 1:2 to about 1:5, particularly 1:2 or 1:3.

In further embodiments wherein the intermediate 3 and HEP are mixed in a solvent system, the inventors have found that dissolving the intermediate 3, either partially or completely, provides a particularly pure product. The skilled person will realise that there are a number of means by which dissolution can be effected. The mixture may be sonicated or subjected to stirring. The inventors found that in particularly preferred embodiments the

mixture may be heated until clear. The inventors also found that DMSO is the preferred solvent. In preferred embodiments the intermediate 3 / HEP mixture is heated to about 60-65°C for between about 1-24 hours, most preferably 5-10 hours. Of course the skilled person will realise that when other preferred solvents such as DMF, NMP and DMAC are used, the heating conditions may differ, but are within the skill set of the skilled person to determine. In certain embodiments the HEP is utilised as the solvent, the base and the reactant. In these embodiments further solvents are not utilised.

The skilled person will also realise that the order in which the components of the reaction are added together can be varied within the scope of the invention.

A particularly preferred embodiment comprises a process according to the first aspect of the invention, wherein the reaction mixture is allowed to cool before the anti-solvent is added, most preferably the solution is allowed to cool to about 20-30°C.

Further preferred embodiments provide a process according to the first aspect, wherein between about 10 to 50 volumes, preferably between about 15 to 30 volumes, of anti-solvent with respect to intermediate 3 are added to the reaction mixture in step (ii). Most preferably about 21 volumes of anti-solvent are added. The inventors found that this ratio of anti-solvent : intermediate 3 was particularly advantageous in preparing a pure product with good yield.

The inventors also found that adding water to the anti-solvent or to the reaction mixture was particularly advantageous. In these embodiments increased yields of dasatinib DCM solvate were noted. Accordingly in preferred embodiments the anti-solvent comprises DCM and in particularly preferred embodiments further comprises water. In particularly advantageous embodiments the water is present in a ratio of DCM : water of between about 1:4 to 4:1, most preferably the ratio is about 1:1. A ratio of about 1:1 provides a particularly pure product. The inventors determined that in certain embodiments the water can be added to the DCM before both are added to the reaction mixture or may be added to the reaction mixture independently of the DCM and the reaction still be within the spirit and scope of the invention.

Further preferred embodiments comprise a process for preparing dasatinib DCM solvate, wherein the precipitated solid from step (iii) is isolated. Of course there are a number of ways in which the precipitated solid may be isolated. Certain embodiments comprise isolating the precipitated solid by allowing the solvent to evaporate. However, in a particularly preferred embodiment the precipitated solid dasatinib DCM solvate is isolated by filtration. The filtered solid can then be allowed to dry in ambient conditions or in particularly preferred embodiments the filtered solid is further dried at between about 25-65°C for about 8-12 hours or in alternative embodiments until a constant weight is achieved. The inventors have found that drying under the preferred conditions does not cause degradation of the isolated dasatinib solvate or conversion to another polymorphic form.

The process according to the invention results in particularly pure product. In particularly preferred embodiments the chemical purity can be as high as 99.5%. However there may be some instances wherein increased purity is desired. Accordingly, there is also provided according to the invention a process for further purification of the solid dasatinib DCM solvate isolated in step (iii) by recrystallisation from an organic solvent system. In particularly preferred embodiments the solvent system comprises one of DMSO, THF, and DCM or any combination thereof. The inventors have also found that the preferred solvents may by utilised in a number of different configurations. For example in particularly preferred embodiments the sequence of addition of the solvents for further purifying the dasatinib DCM solvate comprises:

(a) mixing the precipitated solid dasatinib DCM solvate from step (iii) in DMSO;

(b) adding THF to the mixture from step (a);

(c) adding DCM to the mixture from step (b); and

(d) isolating the resultant precipitated solid dasatinib DCM solvate.

The inventors found that when the DCM solvate is fully dissolved in the DMSO, a particularly pure product is obtained. Accordingly, in certain embodiments there is provided a process wherein the precipitated solid in step (a) is dissolved in the DMSO. The skilled person will realise that the solid may be dissolved in a number of ways, which in some embodiments comprises heating or sonication, but in most preferable embodiments the solid is stirred until the DMSO is clear indicating complete dissolution of the dasatinib

DCM solvate. Preferably the solid is stirred for about 5-10 minutes at ambient temperatures, most preferably between about 20-30°C.

Further preferred embodiments comprise a process for further purifying the dasatinib DCM solvate, wherein the precipitated solid from step (d) is isolated. Of course there are a number of ways in which the precipitated solid may be isolated. Certain embodiments comprise isolating the precipitated solid by allowing the solvent to evaporate. However, in a particularly preferred embodiment the further purified precipitated solid dasatinib DCM solvate from step (d) is isolated by filtration. The filtered solid can then be allowed to dry in ambient conditions or in particularly preferred embodiments the filtered solid is further dried at between about 25-65°C for about 8-12 hours or in alternative embodiments until a constant weight is achieved. The inventors have found that drying under the preferred conditions does not cause degradation of the isolated dasatinib solvate or conversion to another polymorphic form.

In particularly preferred embodiments the further purified dasatinib DCM solvate is washed in DCM before it is dried, most preferably at between about 60-65°C for about 8-12 hours. Dasatinib DCM solvate so purified was found to be greater than 99.8% pure as determined by HPLC.

The pure dasatinib DCM solvate may be used to prepare pure anhydrous dasatinib or dasatinib monohydrate of increased purity. Accordingly there is provided in a second aspect of the invention a process for preparing anhydrous dasatinib comprising desolvating dasatinib DCM solvate. In preferred embodiments the DCM solvate is prepared by a process according to the first aspect of the invention.

In a particularly preferred embodiment the anhydrous dasatinib is prepared by heating the dasatinib DCM solvate in acetonitrile and isolating the anhydrous dasatinib. Most preferably the dasatinib DCM solvate / acetonitrile mixture is heated to between about 50-85°C for about 5-72 hours. In a particularly preferred embodiment the dasatinib DCM solvate / acetonitrile mixture is heated to between about 60-85°C or about 80-85°C for about 6-8 hours. The anhydrous dasatinib may be isolated by any of a number of means including allowing the solvent to evaporate. However, in a particularly preferred

embodiment the mixture is allowed to cool until anhydrous dasatinib precipitate is formed and the anhydrous dasatinib is isolated, preferably by filtration, and is preferably further washed in acetonitrile. The filtered anhydrous dasatinib can then be allowed to dry in ambient conditions or in particularly preferred embodiments the filtered solid is dried at between about 60-65°C for about 8-12 hours or in alternative embodiments until a constant weight is achieved. The inventors have found that drying under the preferred conditions does not cause degradation of the isolated anhydrous dasatinib or conversion to another polymorphic form.

In alternative embodiments the inventors found that using a combination of DMF (N,N-dimethylformamide) and toluene, which azeotropically removes water, also resulted in high purity anhydrous dasatinib. Accordingly in an alternative embodiment of the second aspect of the invention there is provided a process for preparing anhydrous dasatinib by recrystallising dasatinib DCM solvate from a combination of DMF (N,N-dimethylformamide) and toluene.

In a third aspect of the invention dasatinib dichloromethane solvate is provided.

A fourth aspect of the invention provides dasatinib dichloromethane solvate exhibiting an XRPD pattern substantially as shown in Figure 1. A fifth aspect provides dasatinib dichloromethane solvate exhibiting a TGA pattern substantially as shown in Figure 2. A sixth aspect provides dasatinib dichloromethane solvate exhibiting a DSC pattern substantially as shown in Figure 3.

The process of the invention for the preparation of dasatinib DCM solvate also provides pure dasatinib DCM solvate for example for use as an intermediate in preparing anhydrous dasatinib or dasatinib monohydrate. The dasatinib DCM solvate so prepared has a purity of greater than 99.5%. Accordingly there is provided in a seventh aspect of the invention, dasatinib DCM solvate having a chemical purity of greater than 99%, more preferably greater than 99.5%, most preferably greater than 99.8%.

Preferably the dasatinib DCM solvate according to the invention or prepared by a process according to the invention has a chemical purity of greater than 99%, more preferably

greater than 99.5%, most preferably greater than 99.8% (as measured by HLPC). Preferably the dasatinib DCM solvate according to the invention or prepared by a process according to the invention has a polymorphic purity of greater than 95%, more preferably greater than 98%, more preferably greater than 99%, more preferably greater than 99.5%, most preferably greater than 99.8% (as measured by XRPD).

An eighth aspect of the invention provides anhydrous dasatinib having a chemical purity of greater than 99%, more preferably greater than 99.5%, most preferably greater than 99.8%.

Preferably the anhydrous dasatinib according to the invention or prepared by a process according to the invention has a chemical purity of greater than 99%, more preferably greater than 99.5%, most preferably greater than 99.8% (as measured by HLPC). Preferably the anhydrous dasatinib according to the invention or prepared by a process according to the invention has a polymorphic purity of greater than 95%, more preferably greater than 98%, more preferably greater than 99%, more preferably greater than 99.5%, most preferably greater than 99.8% (as measured by XRPD).

A ninth aspect provides dasatinib monohydrate having a chemical purity of greater than 99%, more preferably greater than 99.5%, most preferably greater than 99.8%.

Preferably the dasatinib monohydrate according to the invention or prepared by a process according to the invention has a chemical purity of greater than 99%, more preferably greater than 99.5%, most preferably greater than 99.8% (as measured by HLPC). Preferably the dasatinib monohydrate according to the invention or prepared by a process according to the invention has a polymorphic purity of greater than 95%, more preferably greater than 98%, more preferably greater than 99%, more preferably greater than 99.5%, most preferably greater than 99.8% (as measured by XRPD).

There is also provided in a tenth aspect of the invention a process for converting anhydrous dasatinib to dasatinib monohydrate, comprising mixing anhydrous dasatinib in water and isolating the dasatinib monohydrate. Preferably anhydrous dasatinib prepared by a process according to the second aspect of the invention or anhydrous dasatinib according to the eighth aspect of the invention is used.

The anhydrous dasatinib may be dissolved in the water in any of a number of ways. In preferred embodiments the anhydrous dasatinib may only be partially dissolved with the remainder of the dasatinib in suspension or in alternative embodiments the anhydrous dasatinib is substantially completely dissolved. Dissolution may be effected in some embodiments by sonication or stirring. In particularly preferred embodiments the anhydrous dasatinib is substantially suspended in the water. The inventors found however that heating the anhydrous dasatinib and water to be most effective. Accordingly in particularly preferred embodiments the anhydrous dasatinib and water are heated to between about 90-100°C, wherein the anhydrous dasatinib remains partially dissolved, but of course the skilled person will realise that further dissolution techniques may cause the anhydrous dasatinib to dissolve completely or substantially completely. In particularly preferred embodiments the anhydrous dasatinib and water are heated until the reaction mixture is clear.

The dasatinib monohydrate may then be isolated, preferably by cooling the reaction mixture, most preferably to between about 25-30°C, until the dasatinib monohydrate precipitates from the reaction mixture. In particularly preferred embodiments the dasatinib monohydrate is formed and isolated by filtration. The filtered dasatinib monohydrate can then be allowed to dry in ambient conditions or in particularly preferred embodiments the filtered solid is dried at between about 60-65°C for about 8-12 hours or in alternative embodiments until a constant weight is achieved. The inventors have found that drying under the preferred conditions does not cause degradation of the isolated dasatinib monohydrate or conversion to another polymorphic form.

An eleventh aspect according to the invention provides a process for the conversion of dasatinib monohydrate to anhydrous dasatinib, comprising (i) heating dasatinib monohydrate in a solvent system comprising acetonitrile or (ii) heating dasatinib monohydrate in a solvent system comprising a combination of DMF and toluene and azeotropically removing the water.

A twelfth aspect of the invention provides a pharmaceutical composition comprising crystalline dasatinib monohydrate prepared by a process according to the tenth aspect of

the invention or crystalline dasatinib monohydrate according to the ninth aspect of the invention and one or more pharmaceutically acceptable excipients.

A thirteenth aspect of the invention provides the use of a pharmaceutical composition according to the twelfth aspect of the invention in the treatment of cancer, most preferably in the treatment of adults with chronic, accelerated or blast phase chronic myeloid leukaemia (CML) with resistance or intolerance to prior therapy including imatinib mesilate or treatment of adults with Philadelphia chromosome positive (Ph+) acute lymphoblastic leukaemia (ALL) or lymphoid blast CML with resistance or intolerance to prior therapy.

A fourteenth aspect of the invention provides crystalline dasatinib monohydrate prepared by a process according to tenth aspect of the invention or crystalline dasatinib monohydrate according to the ninth aspect of the invention for use in the treatment of cancer, most preferably for use in the treatment of adults with chronic, accelerated or blast phase chronic myeloid leukaemia (CML) with resistance or intolerance to prior therapy including imatinib mesilate or treatment of adults with Philadelphia chromosome positive (Ph+) acute lymphoblastic leukaemia (ALL) or lymphoid blast CML with resistance or intolerance to prior therapy.

A fifteenth aspect of the invention provides a pharmaceutical composition comprising anhydrous dasatinib prepared by a process according to the second or eleventh aspect of the invention or anhydrous dasatinib according to the eighth aspect of the invention and one or more pharmaceutically acceptable excipients.

A sixteenth aspect of the invention provides the use of a pharmaceutical composition according to the fifteenth aspect of the invention in the treatment of cancer, most preferably in the treatment of adults with chronic, accelerated or blast phase chronic myeloid leukaemia (CML) with resistance or intolerance to prior therapy including imatinib mesilate or treatment of adults with Philadelphia chromosome positive (Ph+) acute lymphoblastic leukaemia (ALL) or lymphoid blast CML with resistance or intolerance to prior therapy.

A seventeenth aspect of the invention provides anhydrous dasatinib prepared by a process according to the second or eleventh aspect of the invention or anhydrous dasatinib according to the eighth aspect of the invention for use in the treatment of cancer, most preferably for use in the treatment of adults with chronic, accelerated or blast phase chronic myeloid leukaemia (CML) with resistance or intolerance to prior therapy including imatinib mesilate or treatment of adults with Philadelphia chromosome positive (Ph+) acute lymphoblastic leukaemia (ALL) or lymphoid blast CML with resistance or intolerance to prior therapy.

An eighteenth aspect of the invention provides use of anhydrous dasatinib or crystalline dasatinib monohydrate according to the invention in the manufacture of a medicament for treating cancer. Preferably the medicament is for treating adults with chronic, accelerated or blast phase chronic myeloid leukaemia (CML) with resistance or intolerance to prior therapy including imatinib mesilate or for treating adults with Philadelphia chromosome positive (Ph+) acute lymphoblastic leukaemia (ALL) or lymphoid blast CML with resistance or intolerance to prior therapy.

A nineteenth aspect of the invention provides a method of treating cancer, comprising administering to a patient in need thereof a therapeutically effective amount of anhydrous dasatinib or crystalline dasatinib monohydrate according to the invention or a therapeutically effective amount of the pharmaceutical composition according to the invention. Preferably the method is for treating adults with chronic, accelerated or blast phase chronic myeloid leukaemia (CML) with resistance or intolerance to prior therapy including imatinib mesilate or for treating adults with Philadelphia chromosome positive (Ph+) acute lymphoblastic leukaemia (ALL) or lymphoid blast CML with resistance or intolerance to prior therapy. Preferably the patient is a mammal, preferably a human.

Brief description of the drawings

Figure 1 shows an XRP diffractogram of dasatinib DCM solvate according to the invention.

Figure 2 shows a thermogravimetric analysis (TGA) trace of dasatinib DCM solvate according to the invention.

Figure 3 shows a differential scanning calorimetry (DSC) trace of dasatinib DCM solvate according to the invention.

Figure 4 shows an XRP diffractogram of dasatinib DMSO solvate according to the invention.

Figure 5 shows a thermogravimetric analysis (TGA) trace of dasatinib DMSO solvate according to the invention.

Figure 6 shows a differential scanning calorimetry (DSC) trace of dasatinib DMSO solvate according to the invention.

Figure 7 shows an XRP diffractogram of crystalline dasatinib monohydrate according to the invention.

Figure 8 shows a thermogravimetric analysis (TGA) trace of crystalline dasatinib monohydrate according to the invention.

Figure 9 shows a differential scanning calorimetry (DSC) trace of crystalline dasatinib monohydrate according to the invention.

Figure 10 shows an XRP diffractogram of anhydrous dasatinib according to the invention.

Figure 11 shows a thermogravimetric analysis (TGA) trace of anhydrous dasatinib according to the invention.

Figure 12 shows a differential scanning calorimetry (DSC) trace of anhydrous dasatinib according to the invention.

Detailed description of the invention

As used herein, reference to chemical purity refers to a compound having a purity of greater than 95%, including greater than 96%, greater than 97%, greater than 98%, greater than 99%, greater than 99.5%, and greater than 99.8% as determined by HPLC.

The term "anhydrous" as used herein does not exclude the possibility of the presence of some water on or in the salt (e.g. a crystal of the salt). For example, there may be some water present on the surface of the salt (e.g. salt crystal), or minor amounts within the body of the salt (e.g. salt crystal). Typically, an anhydrous form contains fewer than 0.4 molecules of water per molecule of compound, and more preferably contains fewer than 0.1 molecules of water per molecule of compound, for example 0 molecules of water.

Illustrative of the invention is a pharmaceutical composition made by mixing crystalline dasatinib monohydrate according to the invention and one or more pharmaceutically acceptable excipients.

Solid pharmaceutical compositions of the present invention include powders, granulates, aggregates 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 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, 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.

A composition for tabletting 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 and/or milled to the desired particle size. The granulate may then be tabletted or other excipients may be added prior to tabletting, such as a glidant and/or a lubricant.

A tabletting composition may be prepared conventionally by dry granulation. 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.

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 tabletting include microcrystalline cellulose, spray dried lactose, dicalcium phosphate dihydrate and colloidal silica. The proper use of these and other excipients in direct compression tabletting is known to those in the art with experience and skill in particular formulation challenges of direct compression tabletting.

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

In further embodiments the pharmaceutical compositions of the invention may further comprise one or more additional active ingredients.

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

Examples

Methods for the preparation of dasatinib DCM solvate

In the following examples 1-3, the relative values relate to molar equivalents with respect to intermediate 3.

Example 1:

A suspension of intermediate 3 (40 g, 1 equivalent) in DMSO (280 ml, 7 volumes) was heated to 60-65°C. To this solution, HEP (39.6 g, 3 equivalents) was added until the reaction mass became clear. Heating was continued at the same temperature for 4 hours (reaction was monitored by TLC and HPLC). Then the reaction mixture was allowed to cool to 25-30°C and dichloromethane (840 ml, 21 volumes) was added and stirred for 1 hour until a white precipitate formed. The precipitate was separated by filtration, washed with DCM (200 ml, 5 volumes) and dried in a vacuum oven at 60-65°C for 8-12 hours. The white solid obtained weighed 44.5 g and had a purity (by HPLC) of 99.6%. The solid was determined by XRPD analysis to be dasatinib DCM solvate (see Figure 1).

Example 2:

A suspension of intermediate 3 (40 g, 1 equivalent) in DMSO (280 ml, 7 volumes) was heated to 60-65°C. To this solution, HEP (39.6 g, 3 equivalents) was added until the reaction mixture became clear. Heating was continued at the same temperature for 6 hours (reaction was monitored by TLC and HPLC). Then the reaction mixture was allowed to cool to 25-30°C and dichloromethane (840 ml, 21 volumes) was added and stirred for 1 hour until a white precipitate formed. The precipitate was separated by filtration and dried under suction for 15-20 minutes. The solid was dried in a vacuum oven at 60-65°C for 8-12 hours. The white solid obtained weighed 30.2 g and had a purity (by HPLC) of 99.7%. The solid was determined by XRPD analysis to be dasatinib DCM solvate (see Figure 1).

Example 3:

A suspension of intermediate 3 (90 g, 1 equivalent) in DMSO (630 ml, 7 volumes) was heated to 60-65°C. To this solution, HEP (89 g, 3 equivalents) was added until the reaction mixture became clear. Heating was continued at the same temperature for 6 hours (reaction

was monitored by TLC and HPLC). Then the reaction mixture was allowed to cool to 25-30°C and dichloromethane (1890 ml, 21 volumes) was added, followed by the addition of water (1800 ml, 20 volumes). The mixture was stirred for 1 hour until a white precipitate appeared. The white solid was separated by filtration and dried under suction for 15-20 minutes. The solid was dried in a vacuum oven at 60-65°C for 8-12 hours. The white solid obtained weighed 125 g and had a purity (by HPLC) of 99.6%. The solid was determined by XRPD analysis to be dasatinib DCM solvate (see Figure 1).

Example 4: Further purification

Dasatinib DCM solvate (40 g, 1 equivalent) obtained in example 2 was suspended in DMSO (200 ml, 5 volumes) and stirred at 25-30°C for 5-10 minutes until the solid completely dissolved. THF (80 ml, 2 volumes) was added at the same temperature and stirred for 5-10 minutes. Finally, DCM (500 ml, 12.5 volumes) was added at 25-30°C and the reaction mixture was stirred for 2 hours at 25-30°C. A white solid progressively precipitated out. The solid was separated by filtration, washed with DCM (200 ml, 5 volumes) and dried in a vacuum oven at 60-65°C for 8-12 hours. The white solid obtained weighed 30.2 g and had a purity (by HPLC) of 99.7%. The solid was determined by XRPD analysis to be dasatinib DCM solvate (see Figure 1).

Method for the desolvation of dasatinib DCM solvate to prepare anhydrous dasatinib

Example 5:

Dasatinib DCM solvate (28 g, 1 equivalent) obtained in example 3 was suspended in acetonitrile (280 ml, 10 volumes) and heated to 80-85°C for 6-8 hours. Then the suspension was cooled to 25-30°C, the resultant solid precipitate was filtered, washed with acetonitrile (56 ml, 2 volumes) and dried in a vacuum oven at 60-65°C for 8-12 hours. The white solid obtained weighed 24 g, had a purity of 99.7% (as measured by HPLC) and was shown to be anhydrous dasatinib by XRPD and TGA (see Figures 10 and 11).

Method for the conversion of anhydrous dasatinib to dasatinib monohydrate

Example 6:

Anhydrous dasatinib (5 g, 1 equivalent) was suspended in water (50 ml, 10 volumes). The suspension was heated to 98-100°C for 4 hours. On cooling to 25-30°C, a slurry formed which was filtered and dried in a vacuum oven at 60-65°C for 8-12 hours. The white solid obtained weighed 4.7 g, had a purity of 99.5% (as measured by HPLC) and was shown to be dasatinib monohydrate by XRPD and TGA (see Figures 7 and 8).

Method for the conversion of anhydrous dasatinib to dasatinib DMSO solvate

Example 7:

Anhydrous dasatinib (5 g, 1 equivalent) was suspended in DMSO (10 ml, 2 volumes). The suspension was heated to 45-50°C. A clear solution was observed. This clear solution was stirred at 45-50°C for 4-12 hours. On cooling to 25-30°C, a solid precipitate formed which was filtered and dried in a vacuum oven at 60-65°C for 8-12 hours. The white solid obtained weighed 4.53 g, had a purity of 99.5% (as measured by HPLC) and was shown to be a DMSO solvate of dasatinib by XRPD and TGA (see Figures 4 and 5).

Method for the conversion of anhydrous dasatinib to dasatinib DCM solvate

Example 8:

Anhydrous dasatinib (3 g, 1 equivalent) was suspended in DCM (45 ml, 15 volumes). The suspension was heated to 38-40°C and was further stirred at 38-40°C for 8-12 hours. On cooling to 5-10°C, a slurry formed which was filtered, washed with DCM (6 ml, 2 volumes) and dried in a vacuum oven at 60-65°C for 8-12 hours. The white solid obtained weighed 2.8 g, had a purity of 99.5% (as measured by HPLC) and was shown to be a dasatinib DCM solvate by XRPD and TGA (see Figures 1 and 2).

Methods for the conversion of dasatinib monohydrate to anhydrous dasatinib

Example 9:

Dasatinib monohydrate (10 g, 1 equivalent) was suspended in acetonitrile (150 ml, 15 volumes) and heated to 78-82°C for 8-12 hours. The suspension was cooled to 25-30°C. The resultant solid was filtered, washed with acetonitrile (20 ml, 2 volumes) and dried in a vacuum oven at 60-65°C for 8-12 hours. The white solid weighed 8.5 g, had a purity of

99.5% (as measured by HPLC) and was shown to be anhydrous dasatinib by XRPD and TGA (see Figures 10 and 11).

Example 10:

Dasatinib monohydrate (5 g, 1 equivalent) was suspended in DMF (100 ml, 20 volumes) and toluene (100 ml, 20 volumes) was added. The suspension was heated to 135-140°C on a Dean-Stark apparatus until the solution cleared. Water was collected over 24 hours. On cooling to 25-30°C, the resultant solid precipitate was filtered and dried in a vacuum oven at 60-65°C for 8-12 hours. The white solid weighed 4.2 g, had a purity of 99.5% (as measured by HPLC) and was shown to be anhydrous dasatinib by XRPD and TGA (see Figures 10 and 11).

All products obtained were characterised as follows.

The XRPDs were recorded on a Bruker D8 Advance Instrument (BRUKER AXS), using copper radiation as the X-ray source and LynxEye as the detector. Samples were placed on a silica background holder.

The DSCs were recorded on a Perkin Elmer Pyris 1. The DSC sample chamber was purged with 40 ml/min of ultra high purity indium. The accuracy of the measured sample temperature with this method is within about ± 1°C. The sample was placed into a closed aluminium DSC pan with pinhole. At least 2 mg of sample powder was placed in the pan and sealed. The instrument was programmed to heat at a rate of 10°C per minute in the temperature range between 25°C and 350°C.

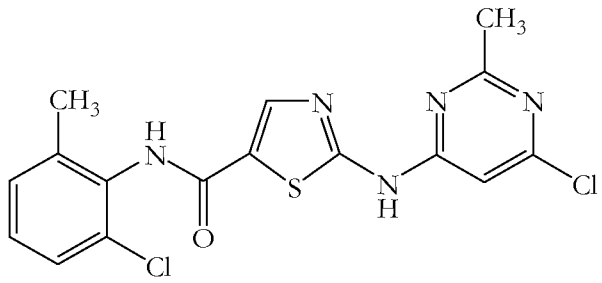
The TGAs were recorded on a Perkin Elmer Pyris 1. Samples of at least 10 mg were analysed at a heating rate of 10°C per minute in the temperature range between 25°C and about 350°C.

It will be understood that the present invention has been described above by way of example only. The examples are not intended to limit the scope of the invention. Various modifications and embodiments can be made without departing from the scope and spirit of the invention, which is defined by the following claims only.

Claims

1. A process for preparing dasatinib dichloromethane solvate comprising:

(i) mixing an intermediate having structure 3



3

with N-(2-hydroxyethyl)piperazine (HEP);

(ii) adding dichloromethane; and

(iii) isolating the resulting precipitated solid.

2. A process according to claim 1, wherein the intermediate 3 is suspended in a solvent system comprising one or more organic solvents.

3. A process according to claim 2, wherein the solvent system comprises one or more of dimethyl sulphoxide (DMSO), dimethylformamide (DMF), N-methyl-2-pyrrolidone (NMP) and dimethylacetamide (DMAC).

4. A process according to claim 3, wherein the solvent system comprises DMSO.

5. A process according to any of claims 1-4, wherein the molar ratio of intermediate 3 : HEP is:

(i) between about 1:1 to about 1:50; and/or

(ii) between about 1:2 to about 1:10; and/or

(iii) between about 1:2 to about 1:5; and/or

(iv) about 1:2 or about 1:3.

6. A process according to any of claims 1-5, wherein a mixture of intermediate 3 / DMSO / HEP is heated until clear.

7. A process according to claim 6, wherein the mixture is heated to about 60-65°C for between about 1-24 hours or about 5-10 hours.

8. A process according to any of claims 1-7, wherein the reaction mixture is allowed to cool before the DCM is added.

9. A process according to claim 8, wherein the reaction mixture is allowed to cool to about 20-30°C.

10. A process according to any of claims 1-9, wherein between about 10 to 50 volumes of DCM with respect to intermediate 3 are added to the reaction mixture in step (ii).

11. A process according to claim 10, wherein about 21 volumes of DCM are added.

12. A process according to any of claims 1-11, wherein the DCM further comprises water.

13. A process according to claim 12, wherein the ratio of DCM : water is between about 1:4 to 4:1 or wherein the ratio of DCM : water is about 1:1.

14. A process according to any of claims 1-13, wherein the precipitated solid from step (iii) is isolated by filtration.

15. A process according to claim 14, wherein the filtered solid is further dried at between about 25-65°C for about 8-12 hours.

16. A process according to any of claims 1-15, comprising further purification of the solid isolated in step (iii) by recrystallisation of the isolated solid from an organic solvent system.

17. A process according to claim 16, wherein the solvent system comprises one of DMSO, THF, and DCM or any combination thereof.

18. A process according to claim 17, wherein the further purification comprises:

(a) mixing the isolated solid from step (iii) in DMSO;

(b) adding THF to the mixture from step (a);

(c) adding DCM to the mixture from step (b); and

(d) isolating the resultant precipitated solid.

19. A process according to claim 18, wherein in step (a) the isolated solid is dissolved in the DMSO.

20. A process according to claim 18 or 19, wherein the precipitated solid from step (d) is isolated by filtration.

21. A process according to any of claims 18-20, wherein the isolated solid from step (d) is further washed with DCM.

22. A process according to any of claims 18-21, wherein the isolated solid from step (d) is dried at between about 60-65°C for about 8-12 hours.

23. Dasatinib dichloromethane solvate.

24. Dasatinib dichloromethane solvate exhibiting an XRPD pattern substantially as shown in Figure 1.

25. Dasatinib dichloromethane solvate exhibiting a thermogravimetric analysis (TGA) trace substantially as shown in Figure 2.

26. Dasatinib dichloromethane solvate exhibiting a differential scanning calorimetry (DSC) trace substantially as shown in Figure 3.

27. Dasatinib dichloromethane solvate prepared by a process according to any of claims 1-22.

28. Dasatinib dichloromethane solvate having a chemical purity of:

(i) greater than 99%; and/or

(ii) greater than 99.5%; and/or

(iii) greater than 99.8%.

29. A process for preparing anhydrous dasatinib comprising desolvating dasatinib DCM solvate according to any of claims 23-28.

30. A process according to claim 29, wherein the anhydrous dasatinib is prepared by heating the dasatinib DCM solvate in acetonitrile and isolating the anhydrous dasatinib.

31. A process according to claim 30, wherein the dasatinib DCM solvate / acetonitrile mixture is heated to between about 50-85°C for about 5-72 hours or to between about 60-85°C for about 6-8 hours or to between about 80-85°C for about 6-8 hours.

32. A process according to claim 30 or 31, wherein the anhydrous dasatinib is isolated by:

(i) cooling the reaction mixture until a precipitate is formed; and

(ii) isolating the precipitate from step (i).

33. A process according to claim 32, wherein the isolated precipitate is further washed with acetonitrile.

34. A process according to claim 32 or 33, wherein the isolated precipitate is dried at between about 60-65°C for about 8-12 hours.

35. A process according to claim 29, wherein the anhydrous dasatinib is prepared by recrystallising dasatinib DCM solvate from a combination of N,N-dimethylformamide and toluene.

36. A process for converting anhydrous dasatinib to dasatinib monohydrate, comprising mixing anhydrous dasatinib in water and isolating the dasatinib monohydrate.

37. A process according to claim 36, wherein the anhydrous dasatinib is partially dissolved in the water.

38. A process according to claim 36 or 37, wherein the anhydrous dasatinib / water mixture is heated to between about 90-100°C.

39. A process according to any of claims 36-38, wherein the dasatinib monohydrate is caused to precipitate by cooling the reaction mixture until the dasatinib monohydrate precipitate is formed and wherein the precipitated dasatinib monohydrate is isolated.

40. A process for converting dasatinib monohydrate to anhydrous dasatinib, comprising (i) heating dasatinib monohydrate in a solvent system comprising acetonitrile or (ii) heating dasatinib monohydrate in a solvent system comprising a combination of DMF and toluene and azeotropically removing the water.

41. Anhydrous dasatinib prepared by a process according to any of claims 29-35 or 40.

42. Anhydrous dasatinib having a chemical purity of:

(i) greater than 99%; and/or

(ii) greater than 99.5%; and/or

(iii) greater than 99.8%.

43. Anhydrous dasatinib according to claim 41 or 42, for use in medicine.

44. Anhydrous dasatinib according to claim 43, for treating cancer.

45. Anhydrous dasatinib according to claim 44, for treating adults with chronic, accelerated or blast phase chronic myeloid leukaemia (CML) optionally with resistance or intolerance to prior therapy including imatinib mesilate or for treating adults with Philadelphia chromosome positive (Ph+) acute lymphoblastic leukaemia (ALL) or lymphoid blast CML optionally with resistance or intolerance to prior therapy.

46. Crystalline dasatinib monohydrate prepared by a process according to any of claims 36-39.

47. Crystalline dasatinib monohydrate having a chemical purity of:

(i) greater than 99%; and/or

(ii) greater than 99.5%; and/or

(iii) greater than 99.8%.

48. Crystalline dasatinib monohydrate according to claim 46 or 47, for use in medicine.

49. Crystalline dasatinib monohydrate according to claim 48, for treating cancer.

50. Crystalline dasatinib monohydrate according to claim 49, for treating adults with chronic, accelerated or blast phase chronic myeloid leukaemia (CML) optionally with resistance or intolerance to prior therapy including imatinib mesilate or for treating adults with Philadelphia chromosome positive (Ph+) acute lymphoblastic leukaemia (ALL) or lymphoid blast CML optionally with resistance or intolerance to prior therapy.

51. A pharmaceutical composition comprising anhydrous dasatinib according to any of claims 41-45 or crystalline dasatinib monohydrate according to any of claims 46-50, and one or more pharmaceutically acceptable excipients.

52. A pharmaceutical composition according to claim 51, for treating cancer.

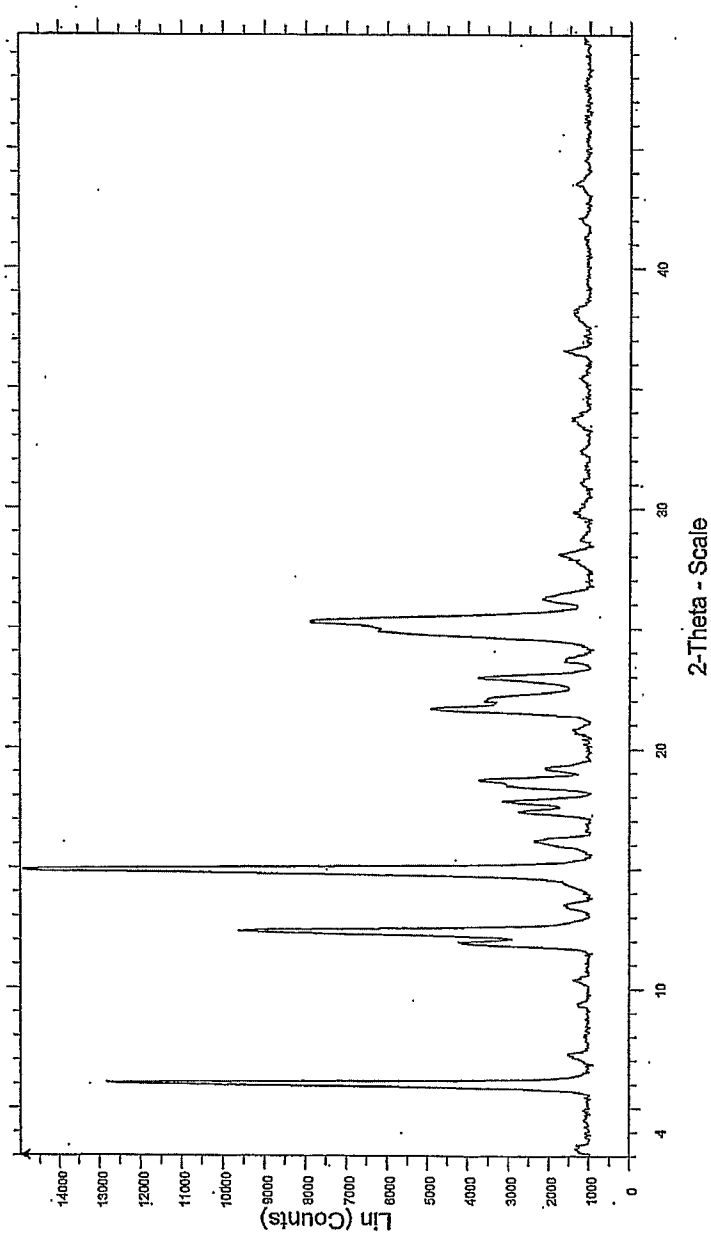
53. A pharmaceutical composition according to claim 52, for treating adults with chronic, accelerated or blast phase chronic myeloid leukaemia (CML) optionally with resistance or intolerance to prior therapy including imatinib mesilate or for treating adults with Philadelphia chromosome positive (Ph+) acute lymphoblastic leukaemia (ALL) or lymphoid blast CML optionally with resistance or intolerance to prior therapy.

54. Use of anhydrous dasatinib according to any of claims 41-45 or crystalline dasatinib monohydrate according to any of claims 46-50, in the manufacture of a medicament for treating cancer.

55. Use according to claim 54, wherein the medicament is for treating adults with chronic, accelerated or blast phase chronic myeloid leukaemia (CML) optionally with resistance or intolerance to prior therapy including imatinib mesilate or for treating adults with Philadelphia chromosome positive (Ph+) acute lymphoblastic leukaemia (ALL) or lymphoid blast CML optionally with resistance or intolerance to prior therapy.

56. A method of treating cancer, comprising administering to a patient in need thereof a therapeutically effective amount of anhydrous dasatinib according to any of claims 41-45, or a therapeutically effective amount of crystalline dasatinib monohydrate according to any of claims 46-50, or a therapeutically effective amount of the pharmaceutical composition according to any of claims 51-53.

57. A method according to claim 56, wherein the method is for treating adults with chronic, accelerated or blast phase chronic myeloid leukaemia (CML) optionally with resistance or intolerance to prior therapy including imatinib mesilate or for treating adults with Philadelphia chromosome positive (Ph+) acute lymphoblastic leukaemia (ALL) or lymphoid blast CML optionally with resistance or intolerance to prior therapy.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12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
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20
30
40
2-Theta - Scale

Figure 1

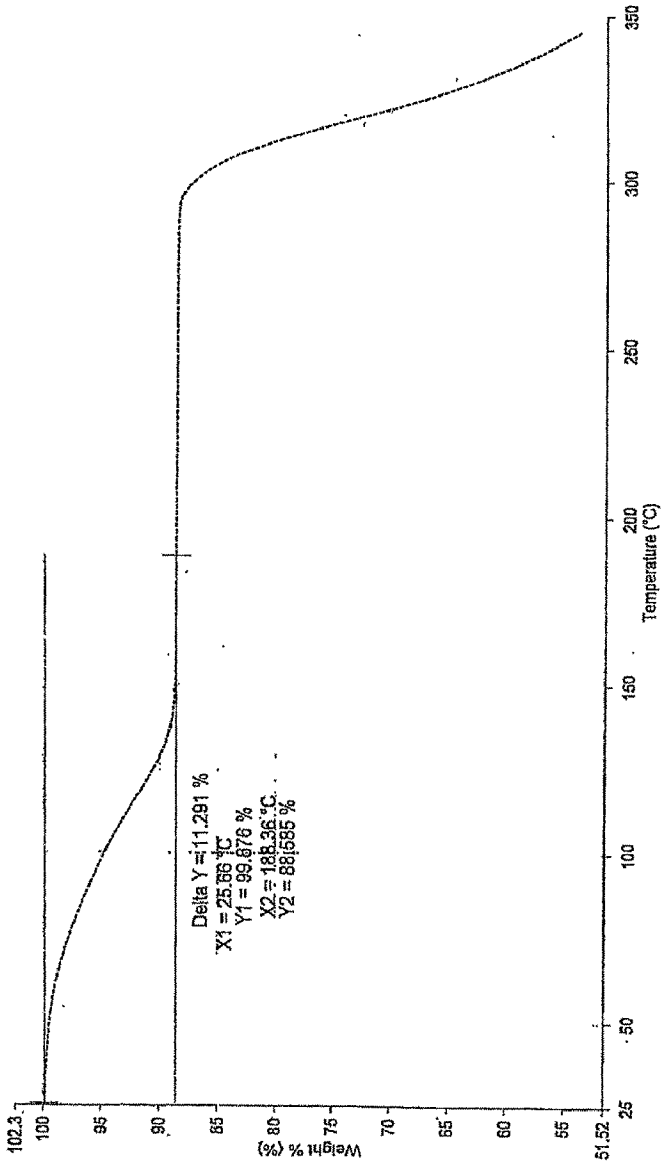
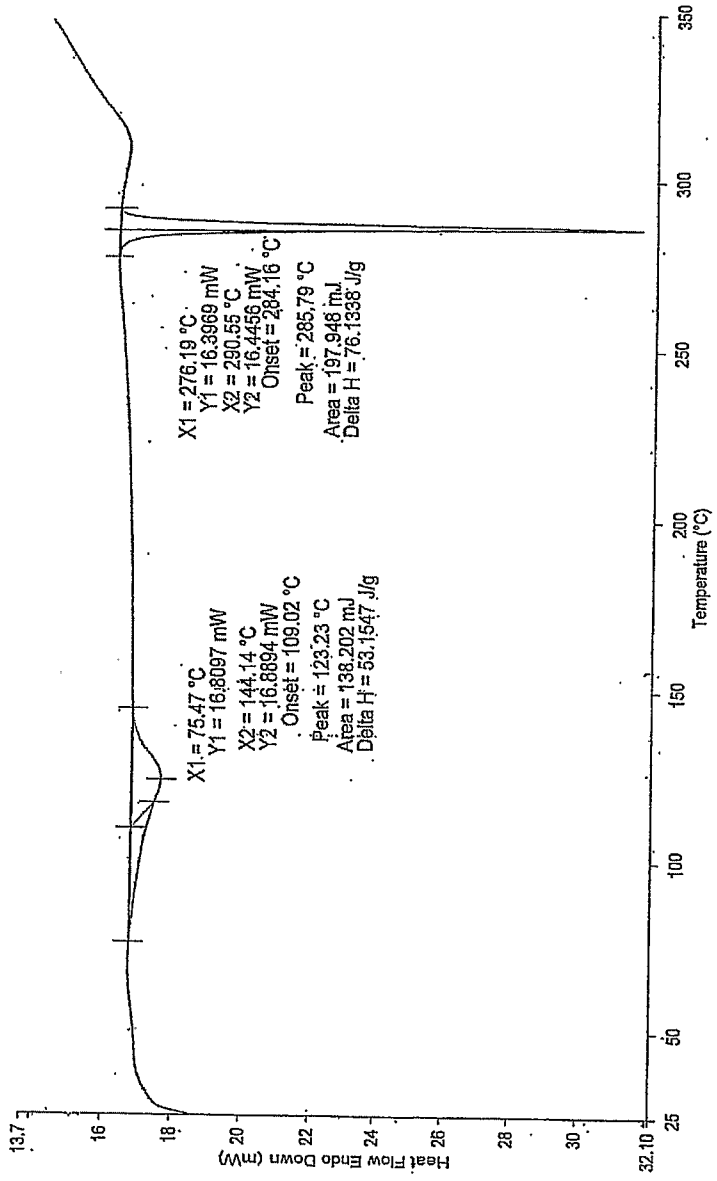

Delta Y = -11.291 %
X1 = 25.66 °C
Y1 = 99.876 %
X2 = 188.36 °C
Y2 = 88.585 %
Weight % (%)
Temperature (°C)
102.3
100
95
90
85
80
75
70
65
60
55
51.52
25
50
100
150
200
250
300
350

Figure 2


X1 = 276.19 °C
Y1 = 16.3969 mW
X2 = 290.55 °C
Y2 = 16.4456 mW
Onset = 284.16 °C
Peak = 285.79 °C
Area = 197.948 mJ
Delta H = 76.1338 J/g
X1 = 75.47 °C
Y1 = 16.8097 mW
X2 = 144.14 °C
Y2 = 16.8894 mW
Onset = 109.02 °C
Peak = 123.23 °C
Area = 138.202 mJ
Delta H = 53.1547 J/g
Heat Flow Endo Down (mW)
Temperature (°C)
13.7
16
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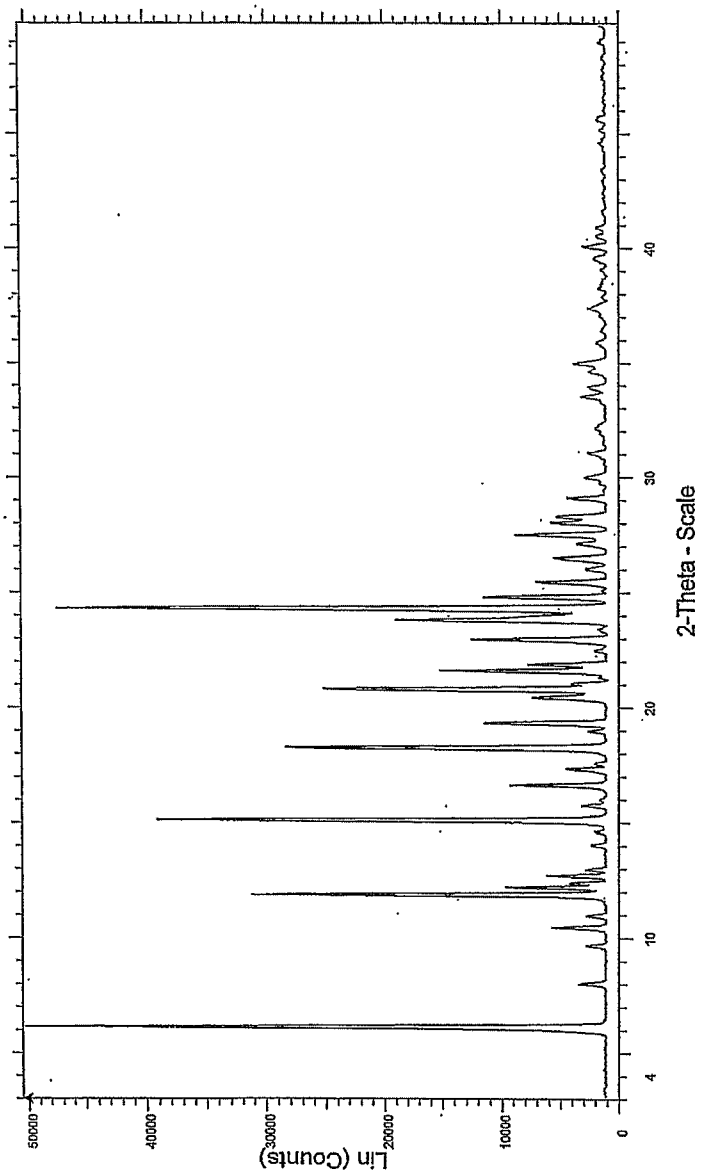
20
22
24
26
28
30
32.10
25
50
100
150
200
250
300
350

Figure 3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50000
4
10
20
30
40
2-Theta - Scale

Figure 4

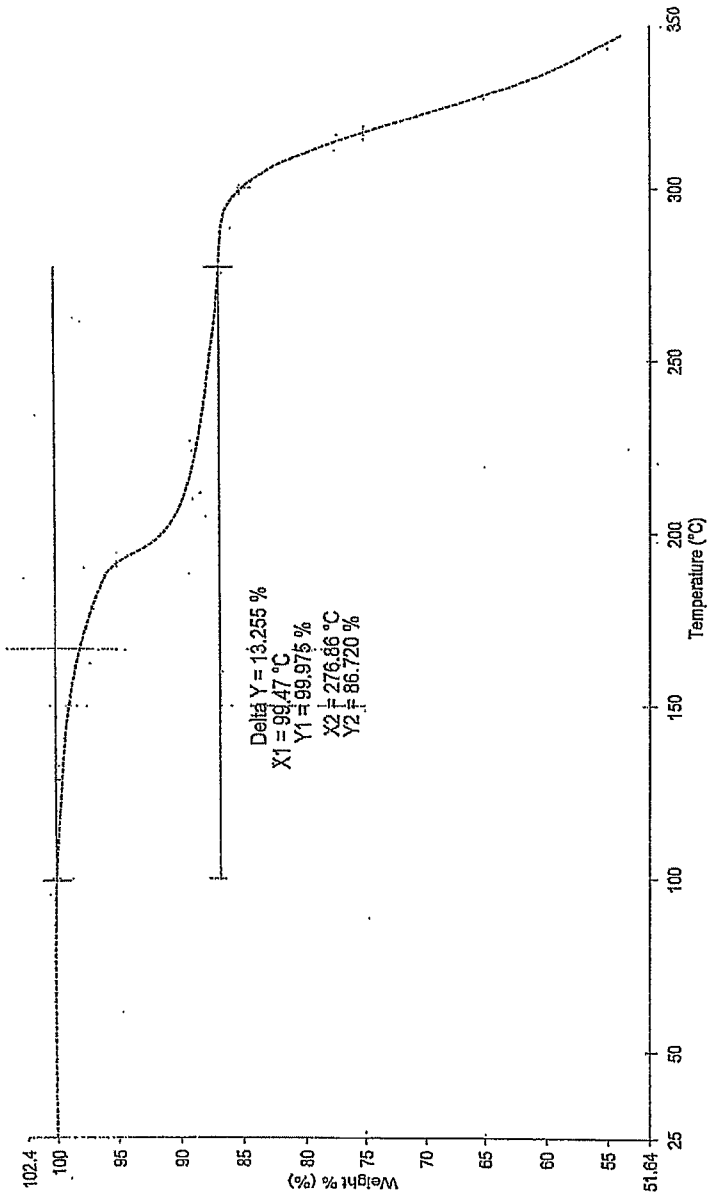

Delta Y = 13.255 %
X1 = 98.47 °C
Y1 = 99.975 %
X2 = 276.66 °C
Y2 = 86.720 %
Weight % (%)
Temperature (°C)
102.4
51.64
100
95
90
85
80
75
70
65
60
55
25
50
100
150
200
250
300
350

Figure 5

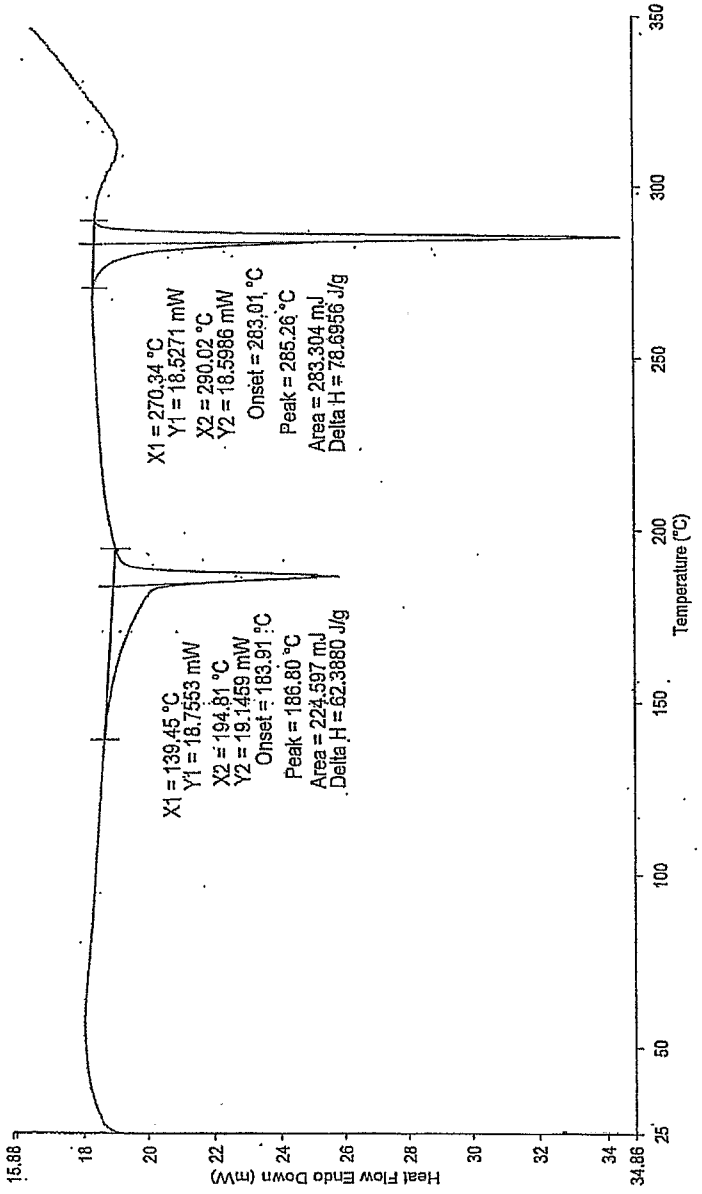
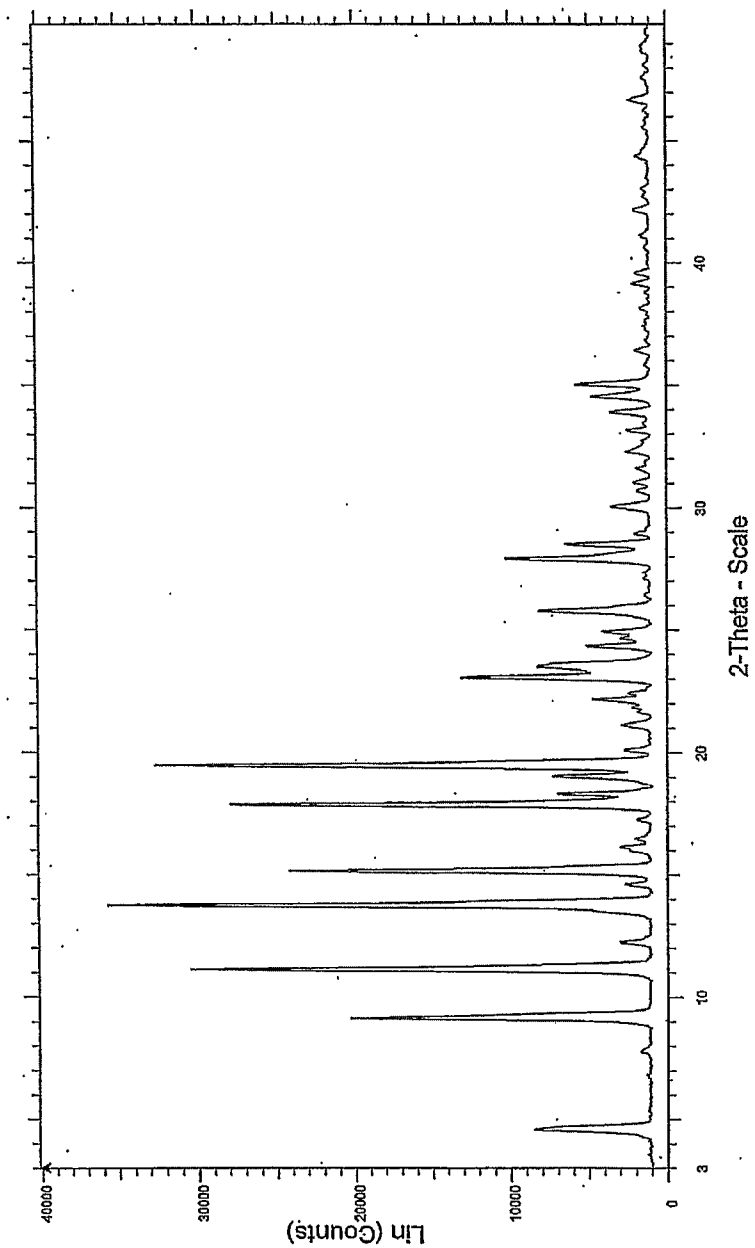

X1 = 270.34 °C
Y1 = 18.5271 mW
X2 = 290.02 °C
Y2 = 18.5986 mW
Onset = 283.01 °C
Peak = 285.26 °C
Area = 283.304 mJ
Delta H = 78.6956 J/g
X1 = 139.45 °C
Y1 = 18.7553 mW
X2 = 194.81 °C
Y2 = 19.1459 mW
Onset = 183.91 °C
Peak = 186.80 °C
Area = 224.597 mJ
Delta H = 62.3880 J/g
Heat Flow Endo Down (mW)
Temperature (°C)
15.88
18
20
22
24
26
28
30
32
34
34.86
25
50
100
150
200
250
300
350

Figure 6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3
10
20
30
40
2-Theta - Scale

Figure 7

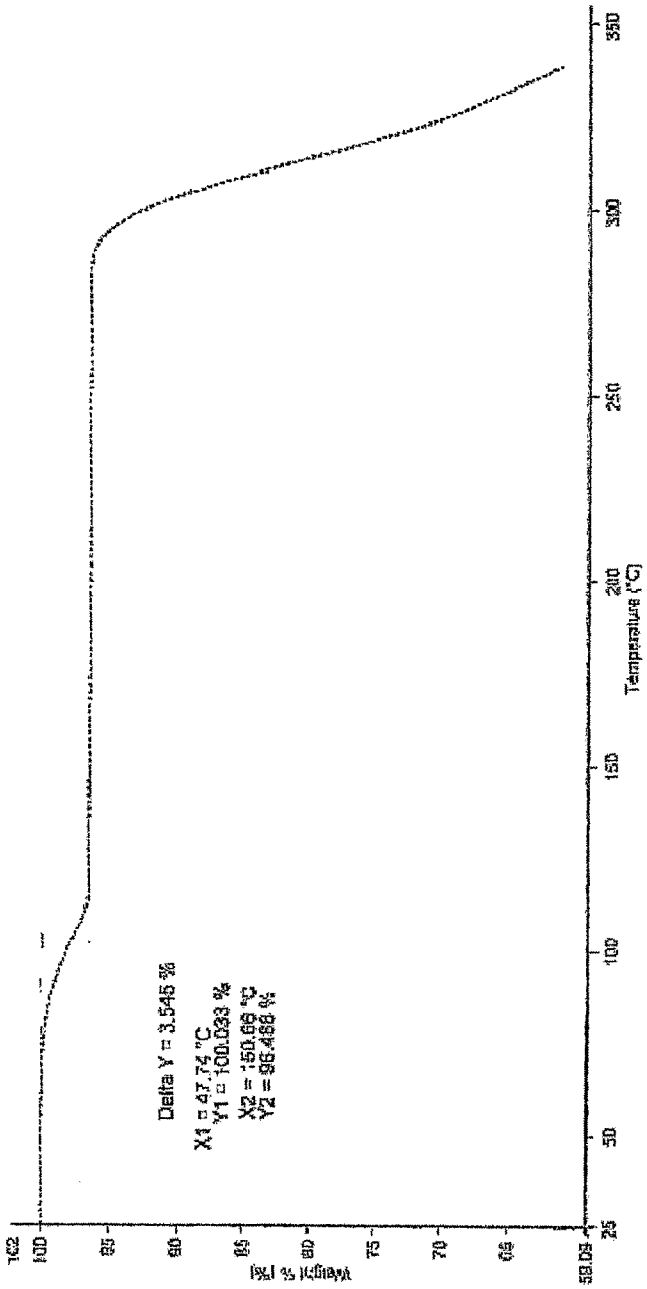

Delta Y = 3.545 %
X1 = 47.74 °C
Y1 = 100.033 %
X2 = 150.66 °C
Y2 = 96.488 %
Température (°C)

Figure 8

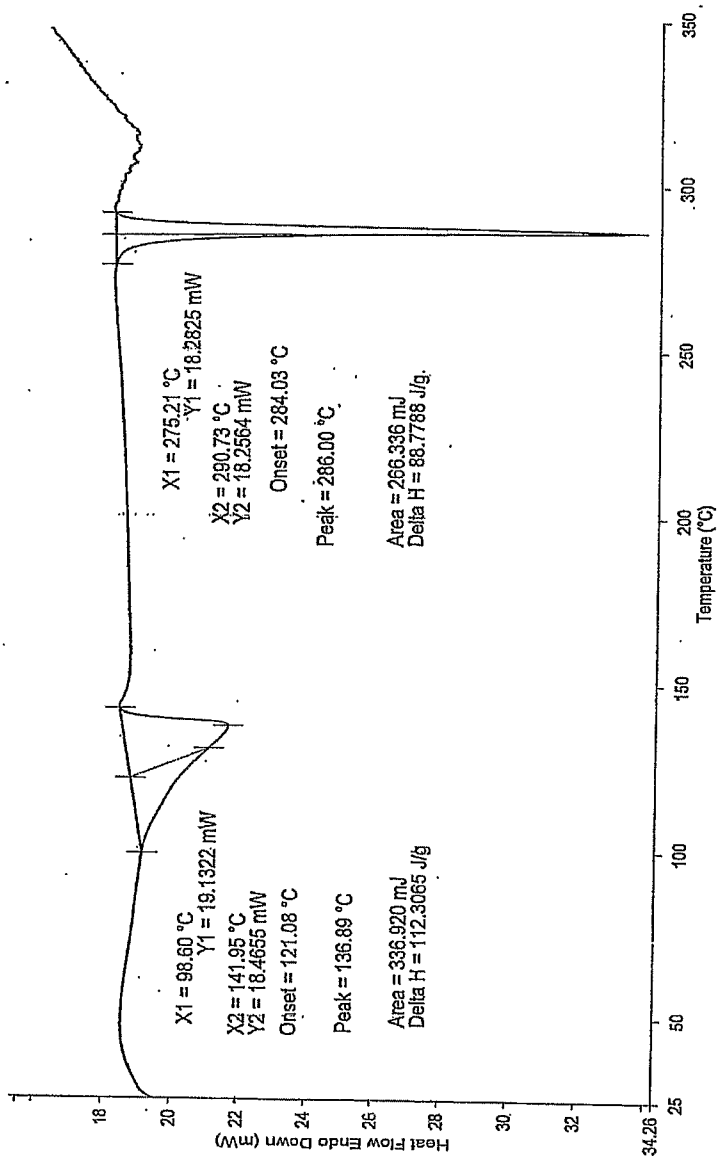
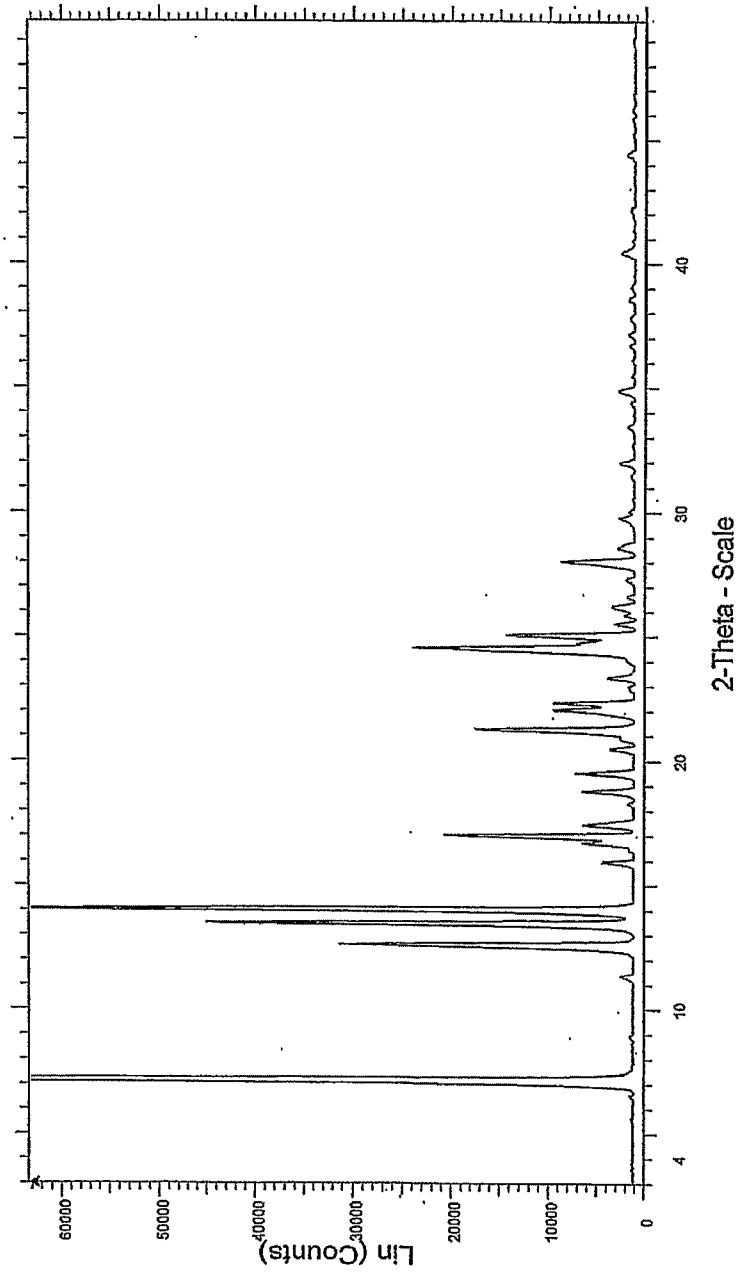

X1 = 98.60 °C
Y1 = 19.1322 mW
X2 = 141.95 °C
Y2 = 18.4655 mW
Onset = 121.08 °C
Peak = 136.89 °C
Area = 336.920 mJ
Delta H = 112.3065 J/g
X1 = 275.21 °C
Y1 = 18.2825 mW
X2 = 290.73 °C
Y2 = 18.2564 mW
Onset = 284.03 °C
Peak = 286.00 °C
Area = 266.336 mJ
Delta H = 88.7788 J/g
Heat Flow Endo Down (mW)
Temperature (°C)
18
20
22
24
26
28
30
32
34.26
25
50
100
150
200
250
300
350

Figure 9


Lin (Counts)
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30000
40000
50000
60000
4
10
20
30
40
2-Theta - Scale

Figure 10

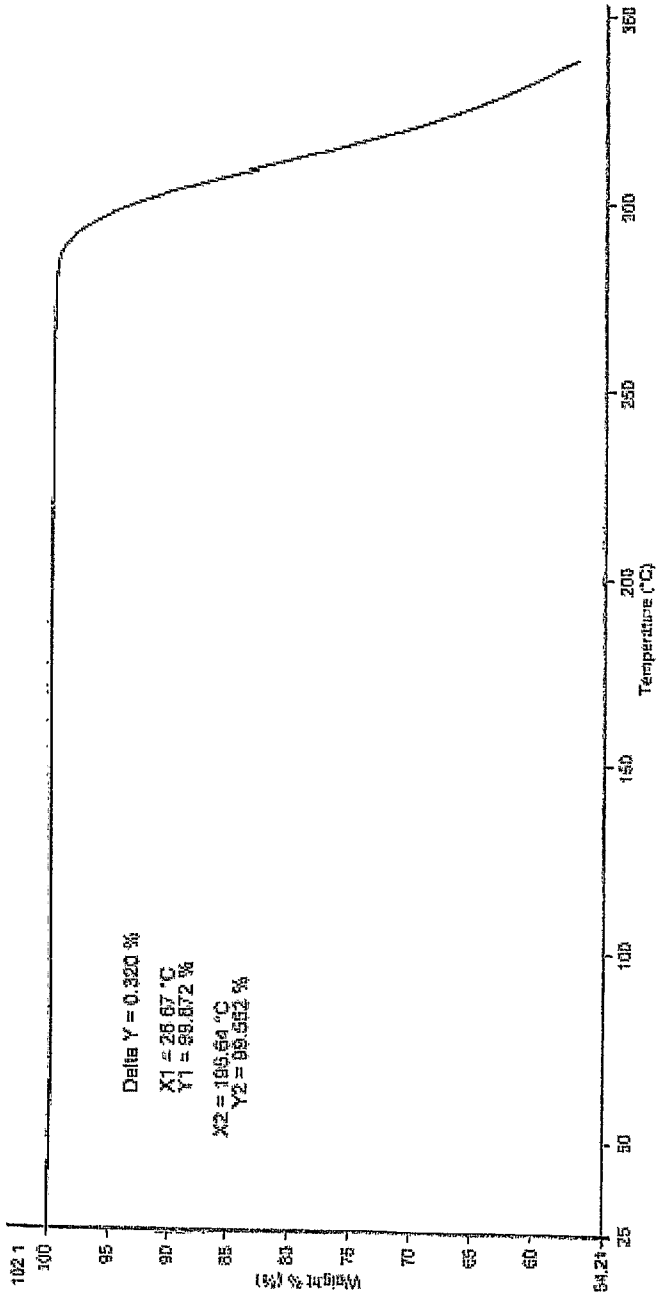
Delta Y = 0.320 %
X1 = 28.67 °C
Y1 = 99.872 %
X2 = 195.64 °C
Y2 = 99.552 %
Weight % (%)
Temperature (°C)
102.1
54.21
100
95
90
85
80
75
70
65
60
25
50
100
150
200
250
300

Figure 11

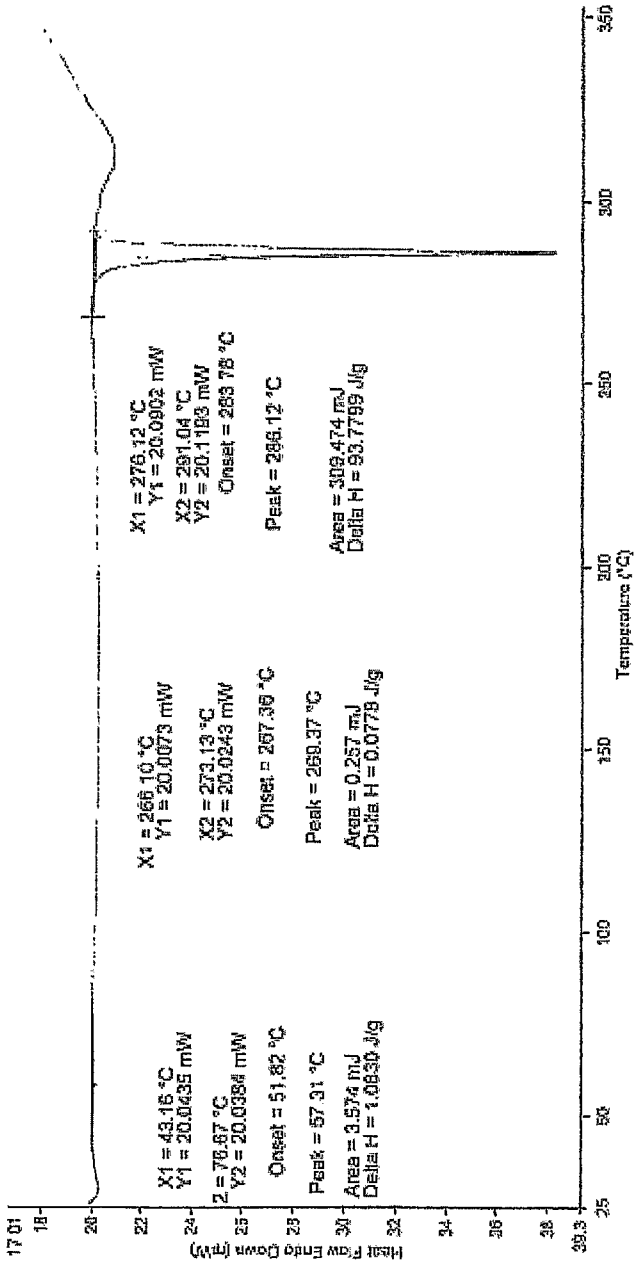
X1 = 43.16 °C
Y1 = 20.0435 mW
Z = 76.67 °C
Y2 = 20.0384 mW
Onset = 51.82 °C
Peak = 57.31 °C
Area = 3.574 mJ
Delta H = 1.0830 J/g
X1 = 266.10 °C
Y1 = 20.0075 mW
X2 = 273.13 °C
Y2 = 20.0243 mW
Onset = 267.39 °C
Peak = 269.37 °C
Area = 0.257 mJ
Delta H = 0.0778 J/g
X1 = 276.12 °C
Y1 = 20.0902 mW
X2 = 291.04 °C
Y2 = 20.1183 mW
Onset = 283.78 °C
Peak = 286.12 °C
Area = 309.474 mJ
Delta H = 93.7799 J/g
Heat Flow Endo Down (mW)
Temperature (°C)

Figure 12