The present invention relates to processes for the preparation of dasatinib and to crystalline monohydrate and anhydrous polymorphic forms of dasatinib. The invention further relates to pure polymorphs, to pharmaceutical compositions comprising said polymorphs and to uses thereof.
Processes for preparing crystalline forms

Filed of the invention

The present invention relates to processes for the preparation of dasatinib and to crystalline monohydrate and anhydrous polymorphic forms of dasatinib. The invention further relates to pure polymorphs, to pharmaceutical compositions comprising said polymorphs and to uses thereof.

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.

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.

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 presence of additional solvents can sometimes provide impurities that have at the very least to be accounted for or more likely have to be removed in an additional washing step or other impurity removal technique before the API can be approved for use in pharmaceutical preparations for human consumption.

It would thus be advantageous to provide a method for preparing crystalline dasatinib polymorphs without the excessive use of additional solvents or additional bases, preferably without the use of any additional solvents or bases or reactants.

It would also be advantageous to provide a method for preparing crystalline dasatinib monohydrate without the use or excessive use of additional solvents or additional bases, preferably having a chemical purity of greater than 99%.

It would further be advantageous to provide a method for preparing anhydrous crystalline dasatinib without the use or excessive use of additional solvents or additional bases, preferably having a chemical purity of greater than 99%.

Summary of the invention

Accordingly, in a first aspect of the invention there is provided a process for preparing dasatinib, comprising reacting an intermediate having a formula 3
with N-(2-hydroxyethyl)piperazine (HEP), characterised in that the HEP is employed as a reactant, base and solvent. It has been found that by not utilising any further solvents, bases or reactants a particularly chemically pure product can be obtained in a surprisingly high yield.

The present invention also provides dasatinib prepared by a process according to the first aspect of the invention. The present invention further provides dasatinib having a chemical purity of greater than 99%, preferably greater than 99.5%, more preferably greater than 99.8% (as measured by HLPC).

Preferably the 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%, more preferably greater than 99.7%, most preferably greater than 99.8% (as measured by HLPC). Preferably the 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).

In one embodiment of the first aspect of the invention, a process is provided wherein the dasatinib prepared is crystalline dasatinib. The crystalline dasatinib may be crystalline dasatinib monohydrate or in an alternative embodiment the crystalline dasatinib is anhydrous crystalline dasatinib.

A second aspect of the invention provides a process for preparing crystalline dasatinib monohydrate, comprising reacting an intermediate having a formula 3
with N-(2-hydroxyethyl)piperazine (HEP), characterised in that the HEP is employed as a reactant, base and solvent, wherein the molar ratio of intermediate 3:HEP is at least 1:6. Preferably the molar ratio of intermediate 3:HEP of about 1:6 to about 1:40, preferably about 1:6 to about 1:20. More preferably the molar ratio of intermediate 3:HEP is about 1:33 or in an alternative embodiment the molar ratio of intermediate 3:HEP is about 1:10.

A third aspect of the invention provides a process for preparing anhydrous crystalline dasatinib, comprising reacting an intermediate having a formula 3

with N-(2-hydroxyethyl)piperazine (HEP), characterised in that the HEP is employed as a reactant, base and solvent, wherein the molar ratio of intermediate 3:HEP is less than 1:6. Preferably the molar ratio of intermediate 3:HEP is about 1:5 or less, about 1:4 or less, about 1:3 or less, about 1:2 or less, most preferably about 1:5 or about 1:1.

In a preferred embodiment of the first, second and third aspects of the invention, no solvent other than HEP is used. In a preferred embodiment of the first, second and third aspects of the invention, no base other than HEP is used. In a preferred embodiment of the first, second and third aspects of the invention, no reactants other than intermediate 3 and HEP are used.

The following embodiments relate to any of the first, second and third aspects of the invention and deal with isolating the pure product according to each aspect.
Accordingly in a first embodiment there is provided a process comprising the steps of:

(a) heating the reaction mixture consisting of intermediate 3 and HEP, preferably to about 70-100°C, preferably to about 80-90°C, preferably to about 80-85°C;
(b) adding water as an anti-solvent to the reaction mixture;
(c) cooling the mixture, preferably to about 25-30°C; and
(d) isolating the resulting precipitated solid.

In a further preferred embodiment the precipitated solid from step (d) is:

(i) isolated by filtration;
(ii) washed with water; and
(iii) dried at between about 25-50°C for about 8-12 hours.

In preferred embodiments there is provided a process comprising further purification of the precipitated solid by recrystallisation from a polar organic solvent system. In a particularly preferred embodiment, when the isolated solid from step (d) comprises crystalline dasatinib monohydrate, the process for further purification comprises heating, preferably under reflux, the precipitated solid in a solution comprising an alcohol and allowing the reaction mixture to cool and isolating the resulting precipitated solid. Preferably the solution comprises an alcohol and water, more preferably the solution comprises ethanol and water, most preferably the ratio of ethanol : water is about 22:3. In another preferred embodiment the isolated crystalline dasatinib is further dried at between about 50-65°C for about 8-12 hours.

A fourth aspect of 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 fifth aspect according to the invention provides crystalline dasatinib monohydrate having a chemical purity of greater than 99%.
A sixth aspect provides crystalline dasatinib monohydrate having a chemical purity of greater than 99.5%.

A seventh aspect provides crystalline dasatinib monohydrate having a chemical purity of 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%, more preferably greater than 99.7%, 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).

An eighth aspect provides anhydrous crystalline dasatinib having a chemical purity of greater than 99%.

A ninth aspect provides anhydrous crystalline dasatinib having a chemical purity of greater than 99.5%.

A tenth aspect provides anhydrous crystalline dasatinib having a chemical purity of greater than 99.7%.

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%, more preferably greater than 99.7%, 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).
An eleventh aspect provides a pharmaceutical composition comprising crystalline dasatinib monohydrate prepared by a process according to the second aspect and associated embodiments or crystalline dasatinib monohydrate according to any of the fifth, sixth or seventh aspects of the invention, and one or more pharmaceutically acceptable excipients.

A twelfth aspect provides a pharmaceutical composition comprising anhydrous crystalline dasatinib prepared by a process according to the third or fourth aspects and associated embodiments or anhydrous crystalline dasatinib according to any of the eighth, ninth or tenth aspects of the invention, and one or more pharmaceutically acceptable excipients.

In a thirteenth and fourteenth aspect of the invention, use of a pharmaceutical composition according to the eleventh and twelfth aspects of the invention respectively is provided for the treatment of cancer. In particularly preferred embodiments pharmaceutical compositions are provided 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 for use in the treatment of adults with Philadelphia chromosome positive (Ph+) acute lymphoblastic leukaemia (ALL) or lymphoid blast CMT. with resistance or intolerance to prior therapy.

A fifteenth aspect provides crystalline dasatinib monohydrate prepared by a process according to the second aspect and associated embodiments or crystalline dasatinib monohydrate according to any of the fifth, sixth or seventh aspects of the invention for use in medicine, preferably 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 for use in the treatment of adults with Philadelphia chromosome positive (Ph+) acute lymphoblastic leukaemia (ALL) or lymphoid blast CML with resistance or intolerance to prior therapy.

A sixteenth aspect provides anhydrous crystalline dasatinib prepared by a process according to the third or fourth aspects and associated embodiments or anhydrous crystalline dasatinib according to any of the eighth, ninth or tenth aspects of the invention for use in medicine, preferably 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 for use in the 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 provides dasatinib prepared by a process according to the first aspect of the invention for use in medicine, preferably 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 for use in the 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 provides use of dasatinib or crystalline dasatinib monohydrate or anhydrous crystalline dasatinib 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 provides a method of treating cancer, comprising administering to a patient in need thereof a therapeutically effective amount of dasatinib or crystalline dasatinib monohydrate or anhydrous crystalline dasatinib 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 crystalline dasatinib monohydrate according to the invention.

Figure 2 shows a differential scanning calorimetry (DSC) trace of crystalline dasatinib monohydrate according to the invention.

Figure 3 shows a thermogravimetric analysis (TGA) trace of crystalline dasatinib monohydrate according to the invention.

Figure 4 shows an XRP diffractogram of anhydrous crystalline dasatinib according to the invention.

Figure 5 shows a differential scanning calorimetry (DSC) trace of anhydrous crystalline dasatinib according to the invention.

Figure 6 shows a thermogravimetric analysis (TGA) trace of anhydrous crystalline 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% and 100% as determined by HPLC. In one embodiment, crystalline dasatinib monohydrate according to the invention can be substantially pure in having a purity of greater than 99%, where the remaining less than 1% of material comprises reaction and/or processing impurities arising from its preparation. This level of consistent chemical purity has not been seen before in the prior art.

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.

In one aspect of the invention there is provided a process for preparing dasatinib comprising adding an intermediate having a formula 3 to N-(2-hydroxyethyl)piperazine (HEP), characterised in that the HEP is employed as a reactant, base and solvent. Most preferably the dasatinib comprises monohydrate or anhydrous crystalline polymorphic forms, however, the process of the first aspect may also be utilised in preparing amorphous forms or other crystalline forms apart from anhydrous and monohydrate polymorphs. The inventors found that when no other reactants or solvents or bases were employed in a process according to the invention, a particularly chemically pure product was obtained. In one embodiment there is provided a process for preparing dasatinib comprising dissolving an intermediate having a formula 3 in N-(2-hydroxyethyl)piperazine (HEP).

The inventors surprisingly found that the amount of HEP used in the reaction with intermediate 3 has an effect on the polymorphic form of the dasatinib prepared. When the amount of HEP employed in the reaction was stepwise reduced from a molar ratio of intermediate 3 : HEP of 1:33, to a molar ratio of 1:27, to a molar ratio of 1:20, to a molar ratio of 1:17, to a molar ratio of 1:10, and each time about 20 volumes of water was added as anti-solvent after 2 hours of heating, the isolated solids matched the XRPD and DSC data of the monohydrate form reported in US 2006/0004067.

Further reduction of the molar amount of HEP, for example to a molar ratio of intermediate 3 : HEP of 1:5 or 1:3.5, resulted in an anhydrous product when the amount of water added as anti-solvent was about 20 volumes. The anhydrous product exhibited an XRPD spectrum matching the anhydrous form reported in US 2006/0004067, called neat form N-6. In certain preferred embodiments the inventors found that the addition of a diluent is preferable when the intermediate 3 : HEP molar ratio is below about 1:2.

US 2006/0004076 describes the preparation of dasatinib monohydrate using intermediate 3, HEP as reactant, n-butanol as solvent and diisopropylethylamine as base, in a molar ratio
of intermediate 3 : HEP : n-butanol : DIPEA of 1 : 5 : 43 : 2. HEP at the reduced levels according to the prior art results in the formation of crystalline dasatinib monohydrate.

Thus it can be seen that the amount of HEP employed in the preparation of dasatinib surprisingly has an effect on the resulting polymorphic form. Conventional teachings would suggest that the amount of water added would have the greater effect, thus the skilled person when seeking to prepare different polymorphic forms would have varied the amount of water added and characterised the resultant polymorphs.

Illustrative of the invention is a pharmaceutical composition made by mixing crystalline dasatinib monohydrate or anhydrous crystalline dasatinib 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 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 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 crystalline dasatinib monohydrate

Example 1:
Intermediate 3 (5 g, 1 equivalent) was added to HEP (50 ml, 33 equivalents) and the reaction mixture was heated at 80-85°C for 2 hours. Water (15 volumes w.r.t. to intermediate 3) was added at 80-85°C and the reaction mixture was maintained at this temperature for 45 minutes. The reaction mixture was cooled to 25-30°C and the resultant solid filtered. The product cake was washed with water and then dried under three different conditions: (a) in a vacuum tray drier at 50°C for 8-12 hours; (b) in a rotary evaporator at 25-30°C for 8-12 hours; and (c) at ambient temperature for 2 days. The weight of solid product ranged from 4-4.7 g.

XRPD characterisation showed the isolated product to be crystalline dasatinib monohydrate according to Figure 1. Chemical Purity > 99% as measured by HPLC.

Example 2:
Intermediate 3 (5 g, 1 equivalent) was added to HEP (15 ml, 10 equivalents) and the reaction mixture was heated to 80-85°C for 2 hours. Water (20 volumes w.r.t. to intermediate 3) was added at 80-85°C and a solid precipitated out. The reaction mixture was maintained at this temperature for 45 minutes. The reaction mixture was cooled to 25-30°C and the solid filtered. The product cake was washed with water and then dried in a vacuum tray drier at 50°C for 8-12 hours. The weight of isolated product was 4.5 g.

XRPD characterisation showed the isolated product to be crystalline dasatinib monohydrate substantially matching the XRP diffractogram according to Figure 1. Chemical Purity > 99% (~ 99.2%) as measured by HPLC.

The products obtained in examples 1 and 2 were subjected to further purification recrystallisations.

Example 3:
Crystalline dasatinib monohydrate as prepared in example 1 (4.4 g) was dissolved in an ethanol (22 volumes) : water (3 volumes) mixture at 78°C for 30 minutes. Water (8 volumes) at the same temperature was added and the mixture stirred for 15 minutes. The mixture was allowed to cool to 25-30°C and the solid filtered. The product cake was washed with an ethanol (2 volumes) : water (2 volumes) mixture and dried in a vacuum tray drier at 50°C for 8-10 hours. The isolated solid weighed 3.6 g.
XRPD characterisation showed the isolated product to be crystalline dasatinib monohydrate substantially matching the XRP diffracogram according to Figure 1.

Chemical Purity > 99.7% as measured by HPLC.

**Example 4:**
Crystalline dasatinib monohydrate as prepared in example 2 (4.5 g) was dissolved in an ethanol (22 volumes) : water (3 volumes) mixture at 78°C for 30 minutes. Water (8 volumes) at the same temperature was added and the mixture stirred for 15 minutes. The mixture was allowed to cool to 25-30°C and the solid filtered. The product cake was washed with an ethanol (2 volumes) : water (2 volumes) mixture and dried in a vacuum tray drier at 50°C for 8-10 hours. The isolated solid weighed 3.45 g.

XRPD characterisation showed the isolated product to be crystalline dasatinib monohydrate substantially matching the XRP diffracogram according to Figure 1.
Chemical Purity > 99% (~ 99.6%) as measured by HPLC.

**Method for preparing anhydrous crystalline dasatinib**

**Example 5:**
Intermediate 3 (5 g, 1 equivalent) was added to HEP (5 equivalents) and the reaction mixture was heated to 85-90°C for 2 hours. Water (20 volumes w.r.t. to intermediate 3) was added at 85-90°C (when a solid precipitated out) and the reaction mixture was maintained at this temperature for 45 minutes. The reaction mixture was then cooled to 25-30°C and the solid was filtered. The product cake was washed with water and then kept in a vacuum tray drier at 50°C for 8-12 hours. The isolated solid weighed 4.9 g.

XRPD characterisation showed the isolated product to be anhydrous crystalline dasatinib substantially matching the XRP diffracogram according to Figure 4. XRPD data of three batches showed anhydrous form.
Chemical Purity > 99% as measured by HPLC.

**Methods for the conversion of dasatinib monohydrate to anhydrous dasatinib**

**Example 6:**
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 and was shown to be anhydrous dasatinib by XRPD and TGA (see Figures 4 and 6). Chemical Purity > 99.5% as measured by HPLC.

Example 7:

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 and was shown to be anhydrous dasatinib by XRPD and TGA (see Figures 4 and 6). Chemical Purity > 99.5% as measured by HPLC.

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, comprising reacting an intermediate having a formula 3

\[
\begin{align*}
\text{with } & N-(2\text{-hydroxyethyl})\text{piperazine (HEP), characterised in that the HEP is employed as a reactant, base and solvent.}
\end{align*}
\]

2. A process for preparing crystalline dasatinib monohydrate, comprising reacting an intermediate having a formula 3

\[
\begin{align*}
\text{with } & N-(2\text{-hydroxyethyl})\text{piperazine (HEP), characterised in that the HEP is employed as a reactant, base and solvent, wherein the molar ratio of intermediate 3:HEP is at least about 1:6.}
\end{align*}
\]

3. A process according to claim 2, wherein the molar ratio of intermediate 3:HEP is between about 1:6 to about 1:40.

4. A process according to claim 3, wherein the molar ratio of intermediate 3:HEP is about 1:33.

5. A process according to claim 3, wherein the molar ratio of intermediate 3:HEP is about 1:10.
6. A process for preparing anhydrous crystalline dasatinib, comprising reacting an intermediate having a formula

\[
\begin{align*}
\text{CH}_3 & \quad \text{Cl} \\
\text{N} & \quad \text{Cl} \\
\text{N} & \quad \text{N} \\
\text{N} & \quad \text{O} \\
\text{CH}_3 & \quad \text{H}
\end{align*}
\]

with N-(2-hydroxyethyl)piperazine (HEP), characterised in that the HEP is employed as a reactant, base and solvent, wherein the molar ratio of intermediate 3 : HEP is less than about 1:6.

7. A process according to claim 6, wherein the molar ratio of intermediate 3 : HEP is about 1:5.

8. A process according to claim 6, wherein the molar ratio of intermediate 3 : HEP is about 1:1.

9. A process according to any preceding claim, further comprising the steps of:

(a) heating the reaction mixture consisting of intermediate 3 and HEP;
(b) adding water as an anti-solvent to the reaction mixture;
(c) cooling the mixture; and
(d) isolating the resulting precipitated solid.

10. A process according to claim 9, wherein the precipitated solid from step (d) is:

(i) isolated by filtration;
(ii) washed with water; and
(iii) dried at between about 25-50°C for about 8-12 hours.

11. A process according to claim 9 or 10, comprising further purification of the solid isolated in step (d) by recrystallisation of the isolated solid from a polar organic solvent system.
12. A process according to claim 11, wherein when the isolated solid comprises crystalline dasatinib monohydrate, the process for further purification comprises refluxing the isolated solid in a solution comprising an alcohol and allowing the reaction mixture to cool and isolating the resulting precipitated solid.

13. A process according to claim 12, wherein the solution comprises an alcohol and water.

14. A process according to claim 13, wherein the solution comprises ethanol and water.

15. A process according to claim 14, wherein the ratio of ethanol : water is about 22:3.

16. A process according to any of claims 9-15, wherein the precipitated solid is further dried at between about 50-65°C for about 8-12 hours.

17. 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.

18. Dasatinib prepared by a process according to any of claims 1-17.

19. Dasatinib having a chemical purity of:
   (i) greater than 99%; and/or
   (ii) greater than 99.5%; and/or
   (iii) greater than 99.8%.

20. Crystalline dasatinib monohydrate prepared by a process according to any of claims 2-5 or 9-16.

21. Crystalline dasatinib monohydrate having a chemical purity of:
   (i) greater than 99%; and/or
   (ii) greater than 99.5%; and/or
(ü) greater than 99.8%.

22. Anhydrous crystalline dasatinib prepared by a process according to any of claims 6-17.

23. Anhydrous crystalline dasatinib having a chemical purity of:
   (i) greater than 99%; and/or
   (ii) greater than 99.5%; and/or
   (ü) greater than 99.8%.

24. Dasatinib according to claim 18 or 19, or crystalline dasatinib monohydrate according to claim 20 or 21, or anhydrous crystalline dasatinib according to claim 22 or 23, for use in medicine.

25. Dasatinib or crystalline dasatinib monohydrate or anhydrous crystalline dasatinib according to claim 24, for treating cancer.

26. Dasatinib or crystalline dasatinib monohydrate or anhydrous crystalline dasatinib according to claim 25, 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.

27. A pharmaceutical composition comprising dasatinib or crystalline dasatinib monohydrate or anhydrous crystalline dasatinib according to any of claims 18-26, and one or more pharmaceutically acceptable excipients.

28. A pharmaceutical composition according to claim 27, for treating cancer.

29. A pharmaceutical composition according to claim 28, 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.

30. Use of dasatinib or crystalline dasatinib monohydrate or anhydrous crystalline dasatinib according to any of claims 18-26 in the manufacture of a medicament for treating cancer.

31. Use according to claim 30, 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.

32. A method of treating cancer, comprising administering to a patient in need thereof a therapeutically effective amount of dasatinib or crystalline dasatinib monohydrate or anhydrous crystalline dasatinib according to any of claims 18-26 or a therapeutically effective amount of the pharmaceutical composition according to any of claims 27-29.

33. A method according to claim 32, 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 CMT, optionally with resistance or intolerance to prior therapy.
Figure 5