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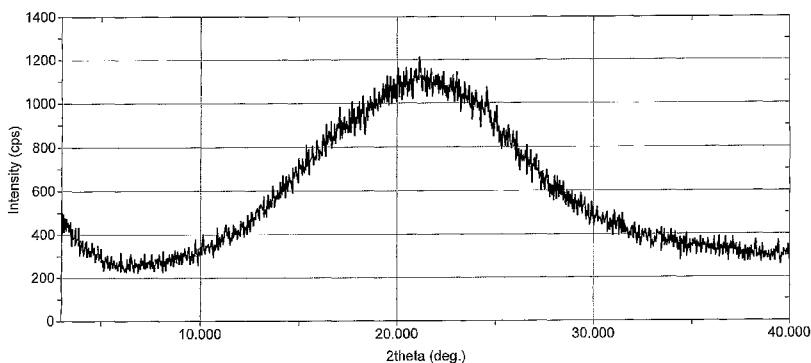


FIG. 1

(57) Abstract: The present invention provides sorafenib or a pharmaceutically acceptable salt thereof in amorphous form. The present invention also provides a complex of sorafenib or a pharmaceutically acceptable salt thereof with polyvinylpyrrolidone.

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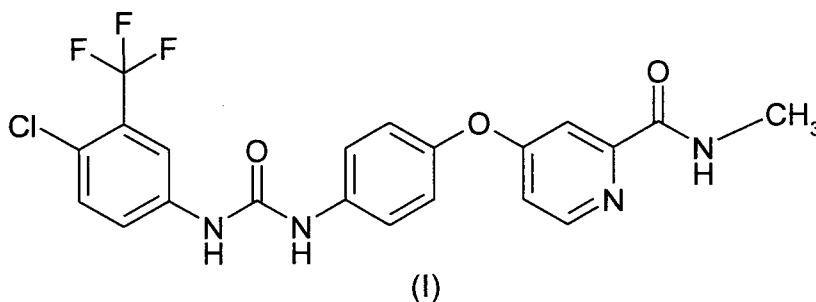
Polymorphs of Sorafenib and Salts Thereof

Technical Field of the Invention

The present invention relates to an amorphous form of 4-(4-{3-[4-chloro-3-(trifluoromethyl)phenyl]ureido}phenoxy)-*N*²-methylpyridine-2-carboxamide or its pharmaceutically acceptable salt, processes for the preparation of the amorphous form and compositions comprising it.

Background of the Invention

10 4-(4-{3-[4-chloro-3-(trifluoromethyl)phenyl]ureido}phenoxy)-*N*²-methylpyridine-2-carboxamide is commonly known as sorafenib (I). Sorafenib is generally prepared as its tosylate salt.



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Sorafenib and pharmaceutically acceptable salts thereof are disclosed in WO0042012. Sorafenib is also disclosed in WO0041698. Both these patents also disclose processes for the preparation of sorafenib.

20

WO2006034796 discloses a process for the preparation of sorafenib and its tosylate salt. WO2006034797 also describes various polymorphs of sorafenib tosylate. WO2006034796 acknowledges that sorafenib tosylate prepared by the general method disclosed in WO0042012 gives polymorphic Form II which is metastable. WO2006034796 itself
25 describes Form I, Form III, an ethanol solvate and a methanol solvate of sorafenib tosylate which are characterized by melting point, Differential Scanning Calorimetry (DSC) and thermogravimetry, X-ray diffraction, IR spectrum, Raman spectrum, NIR spectrum and FIR

spectrum. WO2006034796 also describes various methods for the preparation of Form I, Form III, the methanol solvate and the ethanol solvate. For example, WO2006034796 discloses processes for the preparation of Form I from Form II. The polymorphic form I is claimed in WO2006034797 which involves tedious reaction processes such as long
5 reaction hours, cooling the reaction mixture to very low temperatures such as -25°C. Also the process for preparation of Form I requires critical conditions like cooling at a controlled rate to get Form I.

Thus, processes given for preparation of polymorphs I & III are time consuming.

10

All these reaction conditions are very difficult to achieve at industrial level.

The majority of drugs exhibit polymorphism and different activity in different polymorphic forms. Polymorphism in general means that the drug exists in different physical forms
15 which may be crystalline or non-crystalline. Different polymorphs will have different free energies and therefore different physical properties like solubility, chemical stability, melting point, density, flow characteristics which affects the ease with which the material is handled during processing into pharmaceutical product. Another important property is rate of dissolution i.e. the rate at which drug gets dissolved in patient's stomach.

20

Unlike crystalline forms, amorphous solids do not possess a distinguishable crystal lattice. In general, amorphous solids are more stable and hence, they are preferred in formulating pharmaceutical compositions. Further, amorphous solids usually have better bioavailability.

25

WO2008008733 discloses compositions comprising a nanoparticulate sorafenib, or a salt, such as a sorafenib tosylate, or derivative thereof. According to the description, the particles can be in crystalline phase, semi-crystalline phase, amorphous phase, semi-amorphous phase, or a combination thereof. However, there is no disclosure of how the
30 various forms are prepared.

Objects of the Invention

It is the object of the present invention to provide a compound of formula (I) or pharmaceutically acceptable salts thereof in an amorphous form.

- 5 It is another object of the present invention to provide a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof in an amorphous form.

Another aspect of the present invention is to provide a process for the conversion of an
10 amorphous form of a pharmaceutically acceptable salt of compound of formula (I) to Form I thereof.

A further object of the present invention is to provide a complex of polyvinyl pyrrolidone (PVP) with a compound of formula (I) or a pharmaceutically acceptable salt thereof.

15

Another object of the present invention is to provide a process for the preparation of a complex of polyvinyl pyrrolidone (PVP) with a compound of formula (I) or a pharmaceutically acceptable salt thereof.

- 20 In yet another object of the present invention there is provided a pharmaceutical composition comprising a compound of formula (I) or pharmaceutically acceptable salt thereof in an amorphous form or a PVP complex with compound of formula (I) or a pharmaceutically acceptable salt thereof with one or more pharmaceutically acceptable carriers and/or excipients.

25

Summary of the Invention

According to a first aspect of the present invention, there is provided sorafenib or a pharmaceutically acceptable salt thereof in an amorphous form.

In an embodiment, there is provided amorphous sorafenib free base. The amorphous sorafenib free may be characterised by having the XRPD pattern as shown in Figure 1.

In another embodiment, there is provided amorphous sorafenib tosylate. The amorphous
5 sorafenib tosylate may characterised by having the XRPD pattern as shown in Figure 2.

According to another aspect of the present invention, there is provided a process for the preparation of sorafenib or a pharmaceutically acceptable salt thereof in an amorphous form, the process comprising dissolving sorafenib or a pharmaceutically acceptable salt
10 thereof in an organic solvent and recovering the amorphous material by spray drying or freeze drying. The sorafenib or salt thereof produced by the process may be as described above. The starting material in the process, i.e. the sorafenib or pharmaceutically acceptable salt thereof which is dissolved in the organic solvent may be in any crystalline or other form.

15

The organic solvent may be selected from the group consisting of a ketone, an ether, an amide, an alcohol, a hydrocarbon which may or may not be substituted, a halogenated hydrocarbon and a mixture thereof. Suitably, the solvent is selected from the group consisting of acetone, methyl isobutyl ketone, tetrahydrofuran, N,N-dimethyl formamide,
20 methanol, ethanol, isopropanol, isobutanol, n-butanol, dimethyl sulfoxide, N-methyl pyrrolidone, toluene, methylene dichloride and a mixture thereof.

According to another aspect of the present invention, there is provided a process for preparing sorafenib tosylate Form I, the process comprising: a) suspending amorphous
25 sorafenib tosylate in an organic solvent whereby a crystalline solid precipitates; and b) isolating the crystalline solid. Isolation may be by any conventional technique well known to the skilled person. For example, the isolation may be by filtration or solvent distillation, then drying in a vacuum.

The organic solvent may be selected from the group consisting of an alcohol, an ester, an ether, a ketone, an amide, a hydrocarbon which may or may not be substituted, a halogenated hydrocarbon, and a mixture thereof. Suitably, the solvent is selected from the group consisting of methanol, ethanol, isopropanol, n-butanol, isobutanol, ethyl acetate, diisopropyl ether, acetone, methyl isobutyl ketone, ethyl methyl ketone, N,N-dimethyl formamide, dimethyl sulfoxide, toluene, hexane, methylene dichloride, ethylene dichloride and a mixture thereof.

In an embodiment, the temperature during step a) ranges from around 25°C to around 40°C. More preferably from around 25°C to around 35°C.

In an embodiment, the reaction mass in step a) is stirred for a period of time ranging from around 5 hours to around 24 hours, preferably for a period of time ranging from around 12 hours to around 14 hours.

15

According to another aspect of the present invention, there is provided a complex of sorafenib or a pharmaceutically acceptable salt thereof, with polyvinyl pyrrolidone (PVP). Advantageously, the sorafenib or salt thereof is in amorphous form, which form is as described above. In an alternative embodiment, the sorafenib or salt thereof is not in amorphous form, i.e. the sorafenib or salt thereof is in crystalline form. For example, the complex may comprise crystalline Form I sorafenib tosylate and PVP.

In an embodiment, the complex comprises sorafenib free base and PVP, suitably amorphous sorafenib free base and PVP.

25

In another embodiment, the complex comprises a salt of sorafenib, suitably in amorphous form, and PVP. Suitably, the complex comprises sorafenib tosylate, suitably amorphous sorafenib tosylate, and PVP.

In an embodiment, the PVP is present in an amount of around 5% to around 50% by weight of sorafenib or its pharmaceutically acceptable salt, preferably in an amount of around 10% to around 40% by weight of sorafenib or its pharmaceutically acceptable salt, more preferably around 20% to around 30% by weight of sorafenib or its pharmaceutically acceptable salt, most preferably in an amount of around 25% by weight of sorafenib or its pharmaceutically acceptable salt.

According to another aspect of the present invention, there is provided a process for preparing a complex of sorafenib or a pharmaceutically acceptable salt thereof in amorphous form, with polyvinyl pyrrolidone (PVP), which process comprises: a) dissolving or suspending sorafenib or a pharmaceutically acceptable salt thereof in a first organic solvent; b) dissolving PVP in a second organic solvent; and c) adding the solution of PVP prepared in step b) to the solution or suspension prepared in step a), stirring the mixture and isolating the complex. Isolation may be by any conventional technique well known to the skilled person. For example, the isolation may be by filtration or concentration and then drying. Optionally, the solution or suspension in step a) is heated.

In an embodiment, the first organic solvent is selected from the group consisting of a ketone, an ether, an alcohol, an amide, or a hydrocarbon which may or may not be substituted and a mixture thereof. Suitably, the first organic solvent is selected from the group consisting of acetone, tetrahydrofuran, dioxane, a C₁-C₄ alcohol, N,N-dimethyl formamide, dimethyl sulfoxide and mixtures thereof. The C₁-C₄ alcohol may be, for example, methanol, ethanol, isopropanol, isobutanol or n-butanol.

In an embodiment, the second organic solvent is selected from the group consisting of an alcohol, an ether and a mixture thereof. Suitably, the second organic solvent is selected from the group consisting of a C₁-C₄ alcohol, tetrahydrofuran and a mixture thereof. The C₁-C₄ alcohol may be, for example, methanol, ethanol, isopropanol, isobutanol or n-butanol.

7

According to another aspect of the present invention, there is provided a pharmaceutical composition comprising sorafenib or a pharmaceutically acceptable salt thereof in amorphous form as described above, or a complex as described above, together with one or more pharmaceutically acceptable excipients.

5

The pharmaceutical compositions contain an effective amount of the amorphous form of sorafenib or its pharmaceutically acceptable salt. The "effective amount" means an amount of a compound of the present invention which is effective for prevention or treatment of the various cancers.

10

The pharmaceutical composition may be in a form suitable for administration orally, parenterally, transdermally or nasally. Suitably, the composition is in the form of a tablet, a hard or soft gelatin capsule, a sub-lingual tablet, a dry syrup, a suspension, a sachet, an aqueous or non-aqueous solution or emulsion, a spray, a patch or an aerosol delivery system.

The sorafenib or salt thereof may be in micronized form.

According to another aspect of the present invention, there is provided the use of sorafenib or a pharmaceutically acceptable salt thereof as described above, or a complex as described above or a pharmaceutical composition as described above, for use in medicine.

According to another aspect of the present invention, there is provided the use of sorafenib or a pharmaceutically acceptable salt thereof as described above, or a complex as described above or a pharmaceutical composition as described above, for use in treating cancer.

According to another aspect of the present invention, there is provided a method of treating cancer in a subject, the method comprising administering to the subject an

effective amount of sorafenib or a pharmaceutically acceptable salt thereof as described above, or a complex as described above or a pharmaceutical composition as described above.

5 Detailed Description of the Invention

In one aspect, the invention provides compound of formula (I), i.e. sorafenib, or a pharmaceutically acceptable salt thereof in an amorphous form.

In another aspect, the invention provides a process for the preparation of sorafenib or a
10 pharmaceutically acceptable salt thereof in an amorphous form.

The process involves dissolving sorafenib or a pharmaceutically acceptable salt thereof in a suitable solvent and recovering the amorphous material by suitable means.

15 The suitable means which may be used to recover the amorphous form of sorafenib or its pharmaceutically acceptable salt include spray drying, freeze drying, preferably spray drying.

The sorafenib or pharmaceutically acceptable salt thereof which is dissolved to form a
20 clear solution may be in any crystalline or other form, including the form of a solvate or hydrate.

The solvent may be selected according to the technique and conditions used. The solvent may be any organic solvent or mixture thereof and may be selected from a ketone, an
25 ether, an amide, an alcohol, a hydrocarbon which may or may not be substituted, and a halogenated hydrocarbon.

The solvent may be selected from but not limited to acetone, methyl isobutyl ketone, tetrahydrofuran, N,N-dimethyl formamide, methanol, ethanol, isopropanol, isobutanol, n-
30 butanol, dimethyl sulfoxide, N-methyl pyrrolidone, toluene, methylene dichloride.

In another aspect, the amorphous form of sorafenib or a pharmaceutically acceptable salt thereof may be micronized and used in a suitable pharmaceutical formulation.

In yet another aspect of the present invention, amorphous sorafenib tosylate may be converted to sorafenib tosylate Form I. The process for conversion of amorphous sorafenib tosylate to Form I of sorafenib tosylate comprises the following steps:

- a) amorphous sorafenib tosylate is suspended in a suitable solvent and at a suitable temperature and the suspension is then stirred to obtain a crystalline solid;
- 10 b) the crystalline solid is isolated for example by filtration or by solvent distillation and drying in a vacuum.

The solvent used in the conversion process may be any organic solvent or mixture thereof which may be selected from an alcohol, an ester, an ether, a ketone, an amide, a hydrocarbon which may or may not be substituted, and a halogenated hydrocarbon.

The solvents may be selected from but not limited to methanol, ethanol, isopropanol, n-butanol, isobutanol, ethyl acetate, diisopropyl ether, acetone, methyl isobutyl ketone, ethyl methyl ketone, N,N-dimethyl formamide, dimethyl sulfoxide, toluene, hexane, methylene dichloride, ethylene dichloride.

The temperature at which amorphous sorafenib tosylate is suspended may be range from around 25°C to around 40°C, more preferably from around 25°C to around 35°C. The suspension may be stirred for a period of time ranging from around 5 hours to around 24 hours, preferably for a period of time ranging from around 12 hours to around 14 hours.

In yet another aspect of the present invention, there is provided a complex of sorafenib or its pharmaceutically acceptable salt with polyvinyl pyrrolidone (PVP).

In a further aspect, the present invention provides a process for preparing a complex of sorafenib or a pharmaceutically acceptable salt thereof with polyvinyl pyrrolidone (PVP) which process comprises the following steps:

- 5 a) sorafenib or a pharmaceutically acceptable salt thereof is dissolved or suspended in a first suitable solvent;
- b) PVP is dissolved in a second suitable solvent;
- c) the solution of PVP is added to the solution or suspension prepared in step a) and the mixture is stirred and isolated, for example by either filtration or concentration and then drying.

10

Optionally, the solution or suspension in step a) may be heated.

The first solvent used to dissolve sorafenib or its pharmaceutically acceptable salt may be any organic solvent for example selected from a ketone, an ether, an alcohol, an amide, or
15 a hydrocarbon which may or may not be substituted. The solvent may be used either alone or as a mixture with another solvent.

The first solvent may be selected from but not limited to acetone, tetrahydrofuran, dioxane, C₁-C₄ alcohols like methanol, ethanol, isopropanol, isobutanol, n-butanol, N,N-dimethyl
20 formamide, dimethyl sulfoxide.

The second solvent used to dissolve PVP may be selected from any organic solvent selected for example selected from an alcohols or an ether. The solvent may be used either alone or as a mixture with another solvent.

25

The second solvent may be selected from but not limited to a C₁-C₄ alcohol such as methanol, ethanol, isopropanol, isobutanol or n-butanol, or tetrahydrofuran.

The percentage of PVP may be range from around 5% to around 50% by weight of sorafenib or its pharmaceutically acceptable salt. The preferred percentage is 25%.

30

In yet another aspect, the present invention provides pharmaceutical compositions which contain an effective amount of the amorphous form of sorafenib or its pharmaceutically acceptable salt together with one or more pharmaceutically acceptable carriers. The "effective amount" means an amount of a compound of the present invention which is
5 effective for prevention or treatment of the various cancers.

Pharmaceutical compositions may be prepared as medicaments to be administered orally, parenterally, transdermally or nasally.

10 Suitable forms of oral administration include tablets, hard or soft gelatin capsules, sublingual tablets, dry syrups, suspensions, sachets. Suitable forms of parenteral administration include an aqueous or non-aqueous solution or emulsion while transdermal administration includes spray, patches and other known forms. Nasal administration includes suitable aerosol delivery systems known in the art.

15

Selection of excipients and the amounts to use may be readily determined by the formulation scientist based upon experience and standard procedures available or known.

Brief Description of Accompanying Drawings

20 Figure I is an X-ray powder diffractogram (XRD) of compound of formula (I) in amorphous form.

Figure II is an X-ray powder diffractogram (XRD) of tosylate salt of compound of formula (I) in an amorphous form.

Figure III is an X-ray powder diffractogram (XRD) of Form I of tosylate salt of compound of
25 formula (I).

The present invention will now be further illustrated by the following examples, which do not limit the scope of the invention in any way.

Examples

Example 1

Sorafenib base (50 g) was dissolved in acetone (2.5 lit, 50 vol) at 25 -30°C under stirring for 1 hour. It was then fed to spray dryer unit via peristaltic pump and spray dried at 45 – 50°C. The spray dried material thus obtained was collected from the spray dryer chamber and dried in vacuum oven at 45 – 50°C for 12 – 14 hours under vacuum to obtain amorphous sorafenib (45 g).

Example 2

Sorafenib tosylate (50 g) was dissolved in N,N-Dimethyl formamide (100 ml, 2 vol.) at 25 - 30°C under stirring for 10 minutes. It was then fed carefully to spray dryer unit via peristaltic pump and spray dried at 195 – 200°C. The spray dried material thus obtained was collected from the spray dryer chamber and dried in vacuum oven at 80 – 90°C for 3 – 4 days under high capacity vacuum to get sorafenib tosylate (35 g) which is amorphous in nature.

15

Example 3

Sorafenib tosylate (100 g) was dissolved in N-methyl pyrrolidone (300 ml, 3 vol.) at 25 - 30°C under stirring for 30 minutes. It was then fed carefully to spray dryer unit via peristaltic pump and spray dried at 220 – 230°C. The spray dried material thus obtained was collected from the spray dryer chamber and dried in vacuum oven at 70 – 80°C for 5 – 6 days under high capacity vacuum to get sorafenib tosylate (70 g) which is amorphous in nature.

20

Example 4

Amorphous sorafenib tosylate (5 g) was suspended in di-isopropyl ether (50 ml) at 25 - 30°C. The suspension was then stirred at ambient temperature for 12 – 14 hours where in the yellowish pale solid turned white crystalline in nature. The obtained white solid was then filtered and vacuum dried for 12 – 14 hours at 50 – 60°C. The obtained white crystalline product (4.5 g) is Form I of sorafenib tosylate.

30

Example 5

Sorafenib base (25 g) was stirred with acetone (1300 ml) at room temperature and atmospheric pressure. The obtained clear solution was then freeze dried under high vacuum using lypholiser. The obtained solid was then dried in vacuum oven at 40 – 50°C
5 to remove solvent traces. The material obtained is amorphous sorafenib (20 g).

Example 6

Sorafenib tosylate (13 g) was stirred with N,N-Dimethyl Formamide (30 ml) at room temperature and atmospheric pressure. The obtained clear solution was then freeze dried
10 under high vacuum using lypholiser. The obtained solid was then dried in vacuum oven at 80 – 90°C to remove solvent traces which further yields amorphous form of the sorafenib tosylate (9.8 g).

Example 7

15 Sorafenib tosylate (5 g) was stirred with (1:1) mixture of N,N-Dimethyl formamide and Methanol (50 ml) at room temperature and atmospheric pressure. The obtained clear solution was then freeze dried under high vacuum using lypholiser. The obtained solid was then dried in vacuum oven at 80 – 90°C to remove solvent traces to give amorphous sorafenib tosylate (3.8 g).

20

Example 8

Sorafenib (2 g) was dissolved in tetrahydrofuran (20 ml) in a round bottom flask at 50°C to get clear solution. In another flask, PVP (0.1 g) was dissolved in methanol (2 ml). To the clear solution of sorafenib, solution of PVP was added and the mixture was stirred for half
25 an hour to one hour. After completion of reaction, the solvent was distilled off completely at 50 – 55°C. The material obtained was then dried in an oven at 60°C for 12 hours to get complex of sorafenib with PVP (1.34 g).

Example 9

Sorafenib tosylate (2 g) was suspended in ethanol (50 ml) in a round bottom flask at 25-30°C. In another flask, PVP (0.1 g) was dissolved in ethanol (2 ml). To the suspension of sorafenib tosylate, solution of PVP was added and the mixture was stirred for 16 – 20 hours. After completion of reaction, the product obtained was filtered and then dried in an oven at 60°C for 12 hours to get complex of sorafenib tosylate with PVP (0.7 g).

Example 10

Sorafenib (2 g) was dissolved in tetrahydrofuran (20 ml) in a round bottom flask at 50°C to get clear solution. In another flask, PVP (0.5 g) was dissolved in methanol (4 ml). To the clear solution of sorafenib, solution of PVP was added and the mixture was stirred for half an hour to one hour. After completion of reaction, the solvent was distilled off completely at 50 – 55°C. The material obtained was then dried in an oven at 60°C for 12 hours to get complex of sorafenib with PVP (2.5 g).

15

Example 11

Sorafenib tosylate (2 g) was suspended in ethanol (50 ml) in a round bottom flask at 25-30°C. In another flask, PVP (0.5 g) was dissolved in tetrahydrofuran (4 ml). To the suspension of sorafenib tosylate, solution of PVP was added and the mixture was stirred for 16 – 20 hours. After completion of reaction, the product obtained was filtered and then dried in an oven at 60°C for 12 hours to get complex of sorafenib tosylate with PVP (1.8 g).

Example 12

25 Tablets containing amorphous form of sorafenib or its pharmaceutically acceptable salt (active ingredient).

Ingredient	Quantities
Active ingredient	274 mg
Microcrystalline cellulose	150 mg

15

Crosscarmellose sodium	40 mg
Sodium lauryl sulphate	2 mg
Magnesium stearate	4 mg
Total	470 mg

Active ingredient, microcrystalline cellulose, crosscarmellose sodium, sodium lauryl sulphate & magnesium stearate are sifted separately through suitable sieves and then blended together. The lubricated granules are then compressed into tablets using suitable
5 compression machine.

Example 13

Tablets containing amorphous form of sorafenib or its pharmaceutically acceptable salt (active ingredient).

10

Ingredient	Quantities
Active ingredient	274 mg
Microcrystalline cellulose	140 mg
Crosscarmellose sodium	20 mg
Sodium lauryl sulphate	2 mg
Hydroxypropyl methylcellulose (6 cps)	10 mg
Water	q.s.
Crosscarmellose sodium	20 mg
Magnesium stearate	4 mg
Total	470 mg

Active ingredient, microcrystalline cellulose, crosscarmellose sodium, sodium lauryl sulphate, hydroxypropyl methylcellulose & magnesium stearate are sifted separately
15 through suitable sieve. Active ingredient, microcrystalline cellulose, crosscarmellose

16

sodium, sodium lauryl sulphate are blended together. The binder is prepared using hydroxypropyl methylcellulose in water. The dry mix is then sprayed with the binder and the blend is then sifted through suitable mesh and lubricated with magnesium stearate. The lubricated granules are then compressed into tablets using suitable compression machine.

CLAIMS

1. Sorafenib or a pharmaceutically acceptable salt thereof in an amorphous form.
- 5 2. Amorphous sorafenib free base according to claim 1.
3. Amorphous sorafenib free base according to claim 2, characterised by having the XRPD pattern as shown in Figure 1.
- 10 4. Amorphous sorafenib tosylate according to claim 1.
5. Amorphous sorafenib tosylate according to claim 4, characterised by having the XRPD pattern as shown in Figure 2.
- 15 6. A process for the preparation of sorafenib or a pharmaceutically acceptable salt thereof in an amorphous form, the process comprising dissolving sorafenib or a pharmaceutically acceptable salt thereof in an organic solvent and recovering the amorphous material by spray drying or freeze drying.
- 20 7. A process according to claim 6, wherein the sorafenib or pharmaceutically acceptable salt thereof which is dissolved in the organic solvent is in any crystalline form.
8. A process according to claim 6 or 7, wherein the organic solvent is selected from the group consisting of a ketone, an ether, an amide, an alcohol, a hydrocarbon which
25 may or may not be substituted, a halogenated hydrocarbon, and a mixture thereof.
9. A process according to claim 8, wherein the solvent is selected from the group consisting of acetone, methyl isobutyl ketone, tetrahydrofuran, N,N-dimethyl formamide, methanol, ethanol, isopropanol, isobutanol, n-butanol, dimethyl sulfoxide, N-methyl
30 pyrrolidone, toluene, methylene dichloride and a mixture thereof.

10. A process for preparing sorafenib tosylate Form I, the process comprising: a) suspending amorphous sorafenib tosylate in an organic solvent whereby a crystalline solid precipitates; and b) isolating the crystalline solid.

5

11. A process according to claim 10, wherein the organic solvent is selected from the group consisting of an alcohol, an ester, an ether, a ketone, an amide, a hydrocarbon which may or may not be substituted, a halogenated hydrocarbon, and a mixture thereof.

10 12. A process according to claim 11, wherein the solvent is selected from the group consisting of methanol, ethanol, isopropanol, n-butanol, isobutanol, ethyl acetate, diisopropyl ether, acetone, methyl isobutyl ketone, ethyl methyl ketone, N,N-dimethyl formamide, dimethyl sulfoxide, toluene, hexane, methylene dichloride, ethylene dichloride and a mixture thereof.

15

13. A process according to claim 10, 11 or 12, wherein the temperature during step a) ranges from around 25°C to around 40°C.

14. A process according to any one of claims 10 to 13, wherein the reaction mass in
20 step a) is stirred for a period of time ranging from around 5 hours to around 24 hours.

15. A complex of sorafenib or a pharmaceutically acceptable salt thereof in amorphous form according to any one of claims 1 to 5, with polyvinyl pyrrolidone (PVP).

25 16. A complex according to claim 15 comprising sorafenib free base and PVP.

17. A complex according to claim 15 comprising sorafenib tosylate and PVP.

18. A complex according to claim 15, 16 or 17, wherein the PVP is present in an amount of around 5% to around 50% by weight of sorafenib or its pharmaceutically acceptable salt

5 19. A process for preparing a complex of sorafenib or a pharmaceutically acceptable salt thereof in amorphous form, with polyvinyl pyrrolidone (PVP), which process comprises: a) dissolving or suspending sorafenib or a pharmaceutically acceptable salt thereof in a first organic solvent; b) dissolving PVP in a second organic solvent; and c) adding the solution of PVP prepared in step b) to the solution or suspension prepared in
10 step a) and isolating the complex.

20. A process according to claim 19, wherein the first organic solvent is selected from the group consisting of a ketone, an ether, an alcohol, an amide, or a hydrocarbon which may or may not be substituted and a mixture thereof.

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21. A process according to claim 19 or 20, wherein the first organic solvent is selected from the group consisting of acetone, tetrahydrofuran, dioxane, a C₁-C₄ alcohol, N,N-dimethyl formamide, dimethyl sulfoxide and mixtures thereof.

20 22. A process according to claim 19, 20 or 21, wherein the second organic solvent is selected from the group consisting of an alcohol, an ether and a mixture thereof.

23. A process according to any one of claims 19 to 22, wherein the second organic solvent is selected from the group consisting of a C₁-C₄ alcohol, tetrahydrofuran and a
25 mixture thereof.

24. A pharmaceutical composition comprising sorafenib or a pharmaceutically acceptable salt thereof in amorphous form according to any one of claims 1 to 5, or a complex according to any one of claims 15 to 18, together with one or more
30 pharmaceutically acceptable excipients.

25. A composition according to claim 24, wherein the composition is in a form suitable for administration orally, parenterally, transdermally or nasally.

5 26. A composition according to claim 24 or 25, wherein the composition is in the form of a tablet, a hard or soft gelatin capsule, a sub-lingual tablet, a dry syrup, a suspension, a sachet, an aqueous or non-aqueous solution or emulsion, a spray, a patch or an aerosol delivery system.

10 27. A composition according to claim 24, 25 or 26, wherein the sorafenib or salt thereof is in micronized form.

28. Sorafenib or a pharmaceutically acceptable salt thereof in an amorphous form substantially as herein described with reference to the examples.

15

29. A complex substantially as herein described with reference to the examples.

30. A pharmaceutical composition substantially as herein described with reference to the examples.

20

31. Form I sorafenib tosylate substantially as herein described with reference to the examples.

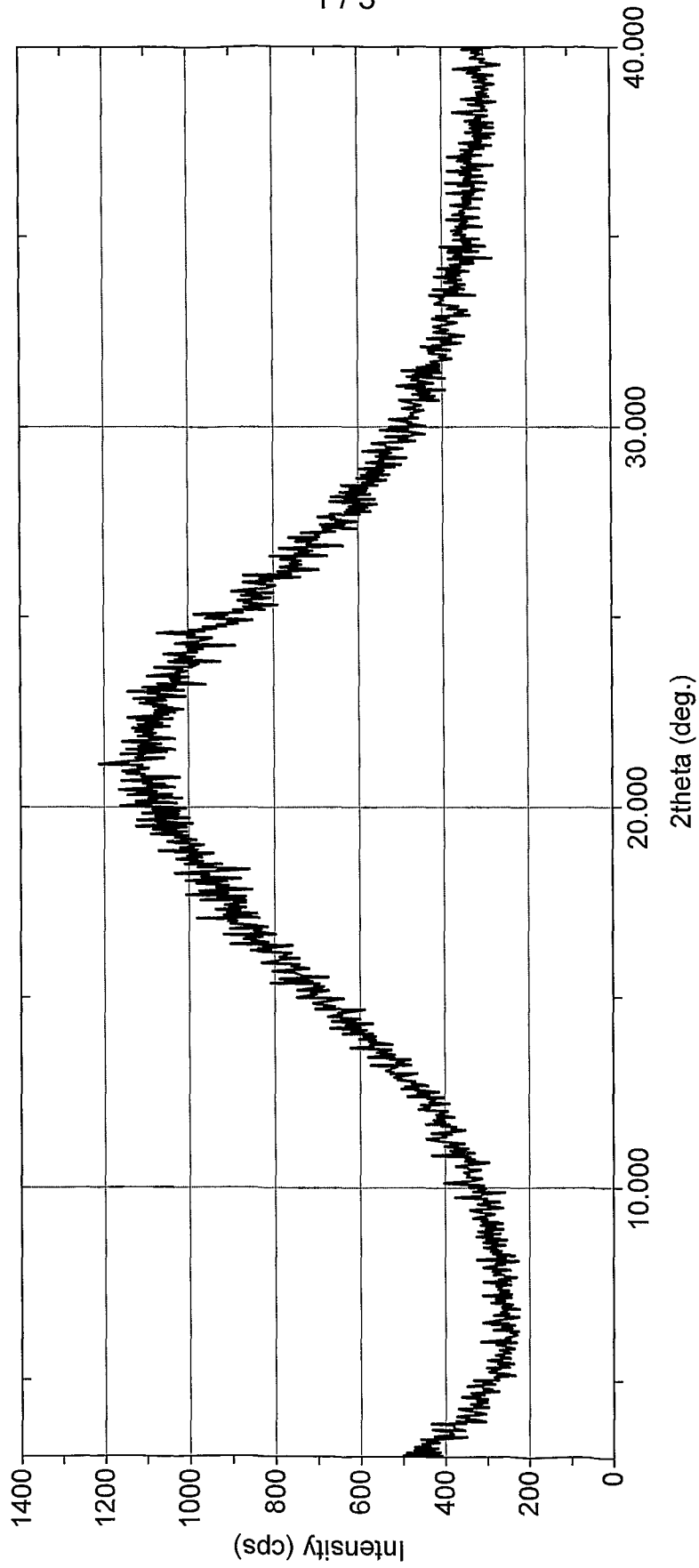


FIG. 1

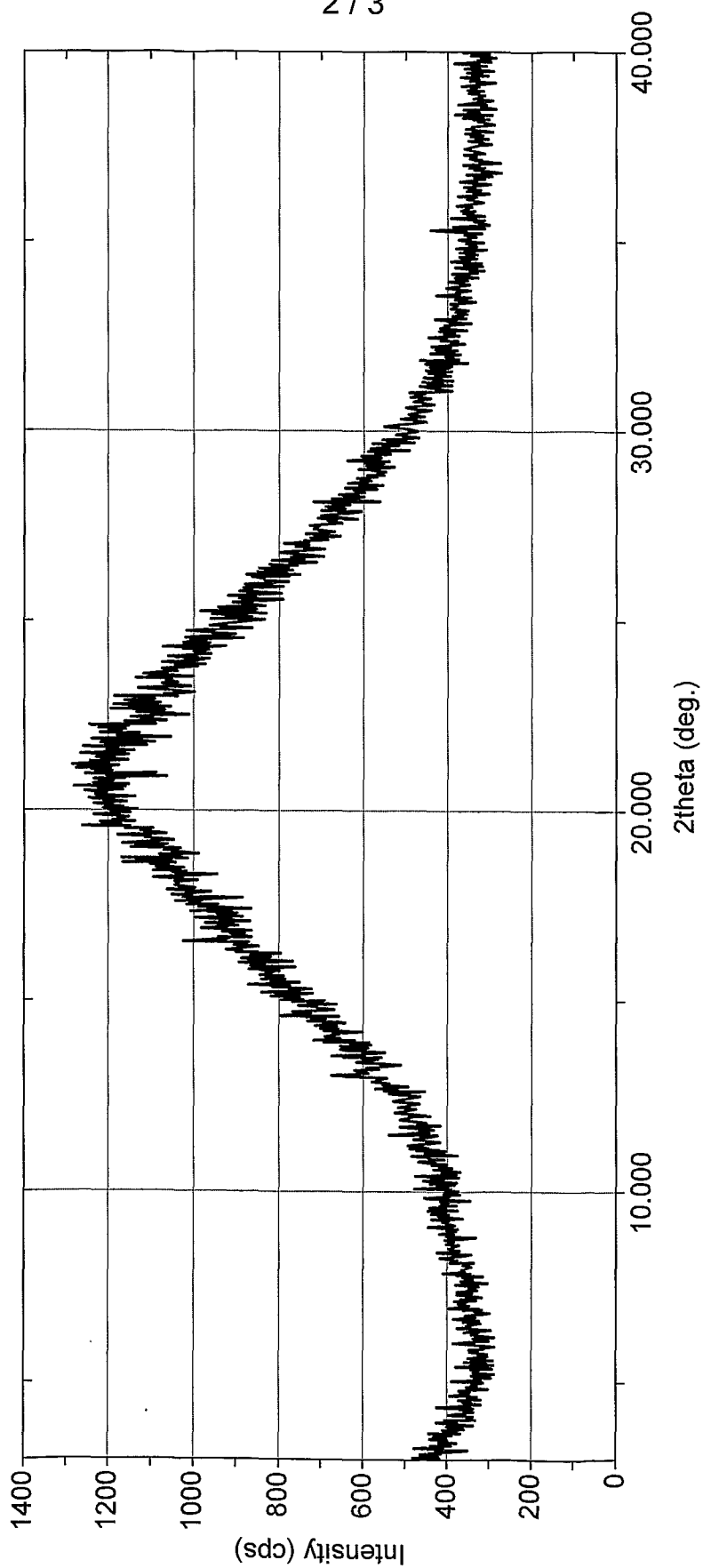


FIG. 2

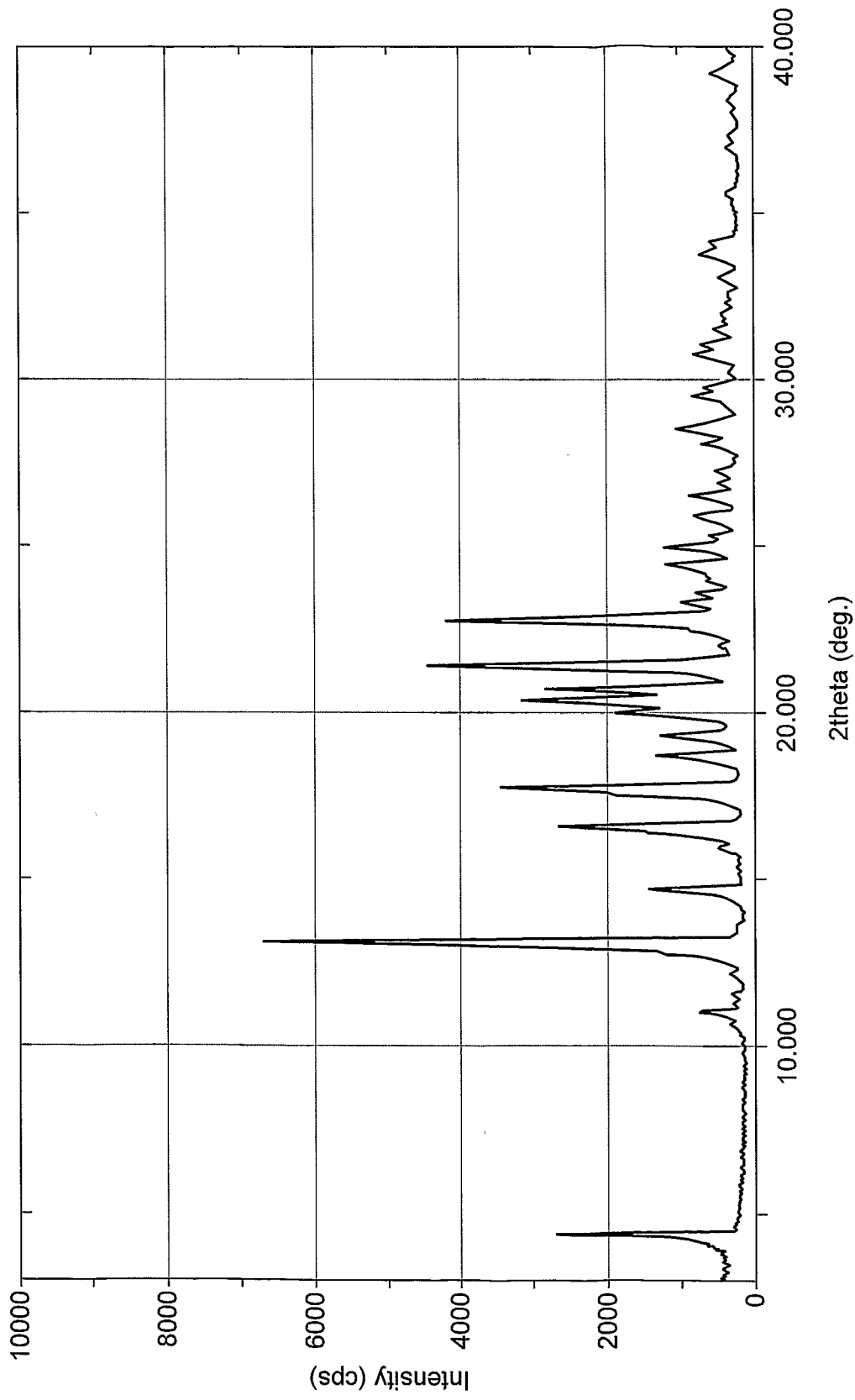


FIG. 3

INTERNATIONAL SEARCH REPORT

International application No

PCT/GB2009/000530

A. CLASSIFICATION OF SUBJECT MATTER
 INV. C07D213/89 A61K31/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2006/026501 A (BAYER PHARMACEUTICALS CORP [US]; SCHUECKLER FRITZ) 9 March 2006 (2006-03-09) claims 1,7,18; example 2	15-27, 29, 30
X	WO 2006/034797 A (BAYER HEALTHCARE AG [DE]; GRUNENBERG ALFONS [DE]; LENZ JANA [DE]) 6 April 2006 (2006-04-06) cited in the application Claims 1-22, description pages 1-3, working examples 1-2 and figures 2-6	31
Y	Claims 1-22, description pages 1-3 and working examples 1-5	1-14, 24-28, 30
A	the whole document	15-23
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Further documents are listed in the continuation of Box C.

See patent family annex.

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X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

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Date of the actual completion of the international search

29 April 2009

Date of mailing of the international search report

13/05/2009

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INTERNATIONAL SEARCH REPORT

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PCT/GB2009/000530

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
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Y	HILFIKER R. ET AL.: "Relevance of Solid-state Properties for Pharmaceutical products" 1 January 2006 (2006-01-01), POLYMORPHISM IN PHARMACEUTICAL SOLIDS, WILEY-VCH VERLAG, WEINHEIM, PAGE(S) 1-19 , XP002525043 paragraph [1.4.2]	1-14, 24-28,30

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Information on patent family members

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