Sunitinib Malate and Related Compositions

Such polymorphs and compositions are useful, for example, in preparing pharmaceutical compositions.

**Title:** POLYMORPHS OF SUNITINIB SALTS

**Abstract:** Polymorphs of Sunitinib malate and other salts have been prepared. Compositions comprising Sunitinib base, L-malic acid and another carboxylic acid are also described. Such polymorphs and compositions are useful, for example, in preparing pharmaceutical compositions.
POLYMORPHS OF SUNITINIB SALTS

CROSS-REFERENCE TO RELATED APPLICATIONS


FIELD OF THE INVENTION

[0002] The present invention relates to polymorphs of Sunitinib malate; certain other salts of Sunitinib; compositions comprising Sunitinib base, L-malic acid and another carboxylic acid; the preparation thereof and pharmaceutical compositions thereof.

BACKGROUND OF THE INVENTION

[0003] Sunitinib base, N-[2-(diethylamino) ethyl]-5-[(Z)-(5-fluoro-1, 2-dihydro-2-oxo-3H-indol-3-ylidine) methyl]-2, 4-dimethyl-1H-pyrrole-3-carboxamide, of the following formula:

\[
\begin{aligned}
&\text{H}_3\text{C} \\
&\text{F} \\
&\text{N} \\
&\text{O} \\
&\text{H} \\
&\text{N} \\
&\text{CH}_3 \\
&\text{CH}_3 \\
&\text{CH}_3
\end{aligned}
\]

can be used as an intermediate in the preparation of sunitinib salts, such as sunitinib malate of the following formula:
Sunitinib malate is a multi-kinase inhibitor marketed in the United States under the trade name SUTENT® by Pfizer, Inc. SUTENT® is approved by the FDA for the treatment of gastrointestinal stromal tumor after disease progression or on intolerance to imatinib mesylate, and for the treatment of advanced renal cell carcinoma. SUTENT® is available as hard-shell capsules containing an amount of sunitinib malate that is equivalent to 12.5 mg, 25 mg, or 50 mg of sunitinib. The capsules contain sunitinib malate together with the inactive ingredients mannitol, croscarmellose sodium, povidone (K-25) and magnesium stearate.

U.S. patent No. 6,573,293 ("'293 patent") refers to the preparation of sunitinib base and salts thereof, as well as the use of these salts. The '293 patent refers to the synthesis of sunitinib base by condensing 5-formyl-2,4-lH-pyrrole-3-carboxylic acid (2-diethylaminoethyl)amide with 5-fluoro-1,3-dihydro-indol-2-one in ethanol in the presence of pyrrolidine. See '293 patent, col. 204, 11: 33-50 (example 80, alternative synthesis). The sunitinib base thus prepared is isolated from the reaction mixture by filtration, washed with ethanol, slurried in ethanol, isolated from the slurry by filtration, washed with ethanol, and dried under vacuum to give an orange solid. Id.


Polymorphism, the occurrence of different crystal forms, is a property of some molecules and molecular complexes. A single molecule, like Sunitinib, may
give rise to a variety of polymorphs having distinct crystal structures and physical properties like melting point, thermal behaviours (e.g. measured by thermogravimetric analysis - "TGA", or differential scanning calorimetry - "DSC"), x-ray diffraction pattern, infrared absorption fingerprint, and solid state NMR spectrum. One or more of these techniques may be used to distinguish different polymorphic forms of a compound.

[0008] Discovering new polymorphic forms and solvates of a pharmaceutical product can provide materials having desirable processing properties, such as ease of handling, ease of processing, storage stability, and ease of purification or as desirable intermediate crystal forms that facilitate conversion to other polymorphic forms. New polymorphic forms and solvates of a pharmaceutically useful compound or salts thereof can also provide an opportunity to improve the performance characteristics of a pharmaceutical product. It enlarges the repertoire of materials that a formulation scientist has available for formulation optimization, for example by providing a product with different properties, e.g., better processing or handling characteristics, improved dissolution profile, or improved shelf-life. For at least these reasons, there is a need for additional polymorphs of Sunitinib and Sunitinib salts.

[0009] The present invention provides solid state physical properties of racemic Sunitinib malate; other salts of Sunitinib; and compositions comprising Sunitinib base, L-malic acid and other carboxylic acid.

SUMMARY OF THE INVENTION

[0010] According to one embodiment the present invention encompasses Sunitinib fumarate, Sunitinib hydrochloride and compositions comprising Sunitinib base, L-malic acid and another carboxylic acid.

[0011] In another embodiment, the present invention encompasses crystalline forms of racemic Sunitinib malate, Sunitinib fumarate, Sunitinib hydrochloride and of compositions comprising Sunitinib base, L-malic acid and another carboxylic acid.

[0012] In another embodiment, the present invention encompasses the use of the above described salts and crystalline forms for the preparation of formulations.

[0013] In yet another embodiment, the present invention encompasses a pharmaceutical composition comprising the above described salts and crystalline forms, and at least one pharmaceutically acceptable excipient.
In another embodiment, the present invention encompasses the use of the above described salts and crystalline forms for the preparation sunitinib malate.

BRIEF DESCRIPTION OF THE DRAWINGS:

Figure 1 provides a characteristic X-ray powder diffraction of crystalline racemic sunitinib malate form A1.

Figure 2 provides a characteristic X-ray powder diffraction of crystalline racemic sunitinib malate form A2.

Figure 3 provides a characteristic X-ray powder diffraction of composition comprising Sunitinib base, L-malic acid and fumaric acid in molar ratio 1:1:1 (form Gamma 1).

Figure 4 provides a characteristic X-ray powder diffraction of composition comprising Sunitinib base, L-malic acid and succinic acid in molar ratio 1:1:1 (form Gamma 2).

Figure 5 provides a characteristic X-ray powder diffraction of composition comprising Sunitinib base, L-malic acid and L-tartric acid in molar ratio 1:1:1 (form Gamma 3).

Figure 6 provides a characteristic X-ray powder diffraction of composition comprising Sunitinib base, L-malic acid and D-tartric acid in molar ratio 1:1:1 (form Gamma 4).

Figure 7 provides a characteristic X-ray powder diffraction composition comprising Sunitinib base, L-malic acid and malonic acid in molar ratio 1:1:1 (form Gamma 5).

Figure 8 provides a characteristic X-ray powder diffraction of composition comprising Sunitinib base, L-malic acid and adipic acid in molar ratio 1:1:1 (form Gamma 6).

Figure 9 provides a characteristic X-ray powder diffraction of composition comprising Sunitinib base, L-malic acid and fumaric acid in molar ratio 1:1:1 (form Gamma 7).

Figure 10 provides a characteristic X-ray powder diffraction of composition comprising Sunitinib base, L-malic acid and fumaric acid in molar ratio 1:1:1 (form Gamma 8).
Figure 11 provides a characteristic X-ray powder diffraction of crystalline Sunitinib fumarate form Delta.

Figure 12 provides a detailed view of a solid state $^{13}$C NMR spectrum of Sunitinib fumarate form Delta.

Figure 13 provides a full-width solid state $^{13}$C NMR spectrum of Sunitinib fumarate form Delta.

Figure 14 provides a characteristic X-ray powder diffraction of sunitinib D,L-malate form B prepared according to Example 12.

Figure 15 provides a characteristic X-ray powder diffraction of sunitinib D,L-malate form B prepared according to Example 13.

Figure 16 provides a characteristic X-ray powder diffraction of sunitinib D,L-malate form B prepared according to Example 14.

Figure 17 provides a characteristic X-ray powder diffraction of sunitinib D,L-malate form B prepared according to Example 15.

Figure 18 provides a characteristic X-ray powder diffraction of sunitinib hydrochloride form Epsilon.

**DETAILED DESCRIPTION OF THE INVENTION**

As used herein, the term "racemic" refers to a mixture that contains an approximately equal amount of enantiomers.

As used herein, the term "Room temperature" refers to a temperature between about 20 °C and about 30 °C. Usually, room temperature ranges from about 20°C to about 25 °C.

As used herein, the term "Overnight" refers to a period of between about 15 and about 20 hours, typically between about 16 to about 20 hours.

A crystal form may be referred to herein as being characterized by graphical data substantially "as depicted in" a Figure. Such data include, for example, powder X-ray diffractograms and solid state NMR spectra. The skilled person will understand that such graphical representations of data may be subject to small variations, e.g., in peak relative intensities and peak positions due to factors such as variations in instrument response and variations in sample concentration and purity, which are well known to the skilled person. Nonetheless, the skilled person would readily be capable of comparing the graphical data in the Figures herein with

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**Note:** The document is a patent application, focusing on the characterization of Sunitinib in various forms, including X-ray powder diffraction, NMR spectra, and solid state characterizations. It explains the terms used and the conditions under which measurements were taken, providing a detailed description of the invention's use and properties. This includes understanding the data through graphical representations and considering the factors that influence these representations. The skilled person is assumed to be capable of comparing such data.
graphical data generated for an unknown crystal form and confirm whether the two sets of graphical data are characterizing the same crystal form or two different crystal forms.

[00037] Crystalline forms of racemic Sunitinib malate, Sunitinib fumarate, Sunitinib hydrochloride and of compositions comprising Sunitinib base, L-malic acid and another carboxylic acid have advantageous properties selected from at least one of: chemical purity, flowability, solubility, morphology or crystal habit, stability - such as storage stability, stability to dehydration, stability to polymorphic conversion, low hygroscopicity, and low content of residual solvents.

[00038] The present invention provides solid state forms of racemic Sunitinib malate; other salts of Sunitinib; and compositions comprising Sunitinib base, L-malic acid and other carboxylic acid.

[00039] The present invention includes embodiments that are Sunitinib salts containing two different carboxylate components wherein the ratio between Sunitinib base, a first carboxylic acid and a second carboxylic acid is "about 1:1:1 (mole: mole: mole)." It will be understood that the molar ratio variation contemplated by the term "about" is ± 5 %.

[00040] In one embodiment the present invention encompasses a crystalline form of racemic sunitinib malate, designated herein as form A1. Form A1 can be characterized by data selected from: an X-ray powder diffraction pattern having peaks at 3.8, 6.4, 7.4, 11.7 and 16.3 degrees 2-theta ± 0.2 degrees 2-theta; an X-ray powder diffraction pattern substantially as depicted in Figure 1; and combinations thereof. Racemic sunitinib malate Form A1 can be further characterized by additional X-ray powder diffraction peaks at 12.8, 13.5, 24.5 and 25.4 degrees 2-theta ± 0.2 degrees 2-theta.

[00041] In another embodiment the present invention encompasses a crystalline form of racemic sunitinib malate, designated herein as form A2. Form A2 can be characterized by data selected from: an X-ray powder diffraction pattern having peaks at 3.2, 6.8, 21.2, 25.1 and 25.6 degrees 2-theta ± 0.2 degrees 2-theta; an X-ray powder diffraction pattern substantially as depicted in Figure 2; and combinations thereof. Racemic sunitinib malate Form A2 can be further characterized by additional X-ray powder diffraction peaks at 8.2, 13.2, 16.3 and 24.2 degrees 2-theta ± 0.2 degrees 2-theta.
In one embodiment, the present invention encompasses a sunitinib salt selected from a group consisting of Sunitinib fumarate; Sunitinib hydrochloride; and compositions comprising Sunitinib base, L-malic acid and another carboxylic acid.

In a preferred embodiment, the above described salts are provided in an isolated form. Preferably, the isolated Sunitinib salt is a solid, more preferably, it is crystalline.

As used herein, the term "isolated" in reference to Sunitinib salt corresponds to Sunitinib salt that is physically separated from the reaction mixture where it is formed.

Reported herein are crystalline forms of the above described Sunitinib salts.

In one embodiment the present invention encompasses a crystalline composition comprising Sunitinib base, L-malic acid and fumaric acid; wherein the ratio between Sunitinib base, L-malic acid and fumaric acid is about 1:1:1 (mole: mole: mole), designated herein as form Gamma 1. Form Gamma 1 can be characterized by data selected from: an X-ray powder diffraction pattern having peaks at 3.3, 6.8, 8.2, 10.0 and 15.3 degrees 2-theta ± 0.2 degrees 2-theta; an X-ray powder diffraction pattern substantially as depicted in Figure 3; and combinations thereof. Form Gamma 1 can be further characterized by additional powder XRD peaks at 11.0, 13.2, 16.4, 23.3 and 26.7 degrees 2-theta ± 0.2 degrees 2-theta.

In another embodiment the present invention encompasses a crystalline composition comprising Sunitinib base, L-malic acid and succinic acid; wherein the ratio between Sunitinib base, L-malic acid and succinic acid is about 1:1:1 (mole: mole: mole), designated herein as form Gamma 2. Form Gamma 2 can be characterized by data selected from: an X-ray powder diffraction pattern having peaks at 3.0, 20.0, 26.1 and 31.5 degrees 2-theta ± 0.2 degrees 2-theta; an X-ray powder diffraction pattern substantially as depicted in Figure 4; and combinations thereof. Form Gamma 2, can be further characterized by additional powder XRD peaks at 12.0, 22.6, 27.2 and 38.0 degrees 2-theta ± 0.2 degrees 2-theta.

In another embodiment the present invention encompasses a crystalline composition comprising Sunitinib base, L-malic acid and L-tartaric acid; wherein the ratio between Sunitinib base, L-malic acid and L-tartaric acid is about 1:1:1 (mole:mole:mole), designated herein as form Gamma 3. Form Gamma 3 can be
characterized by data selected from: an X-ray powder diffraction pattern having peaks at 11.3, 14.8, 23.1, 24.0 and 27.1 degrees 2-theta ± 0.2 degrees 2-theta; an X-ray powder diffraction pattern substantially as depicted in Figure 5; and combinations thereof.

[00049] In another embodiment the present invention encompasses a crystalline composition comprising Sunitinib base, L-malic acid and D-tartaric acid; wherein the ratio between Sunitinib base, L-malic acid and D-tartaric acid is about 1:1:1 (mole:mole:mole), designated herein as form Gamma 4. Form Gamma 4 can be characterized by data selected from: an X-ray powder diffraction pattern having peaks at 11.3, 14.8, 23.1, 24.0 and 27.1 degrees 2-theta ± 0.2 degrees 2-theta; an X-ray powder diffraction pattern substantially as depicted in Figure 6; and combinations thereof.

[00050] In another embodiment the present invention encompasses a crystalline composition comprising Sunitinib base, L-malic acid and malonic acid; wherein the ratio between Sunitinib base, L-malic acid and malonic acid is about 1:1:1 (mole:mole:mole), designated herein as form Gamma 5. Form Gamma 5 can be characterized by data selected from: an X-ray powder diffraction pattern having peaks at 11.5, 14.5, 22.8, 23.9 and 26.9 degrees 2-theta ± 0.2 degrees 2-theta; an X-ray powder diffraction pattern substantially as depicted in Figure 7; and combinations thereof.

[00051] In another embodiment the present invention encompasses a crystalline composition comprising Sunitinib base, L-malic acid and adipic acid; wherein the ratio between Sunitinib base, L-malic acid and adipic acid is about 1:1:1 (mole:mole:mole), designated herein as form Gamma 6. Form Gamma 6 can be characterized by data selected from: an X-ray powder diffraction pattern having peaks at 21.5, 25.2, 25.7, 31.1 and 37.2 degrees 2-theta ± 0.2 degrees 2-theta; an X-ray powder diffraction pattern substantially as depicted in Figure 8; and combinations thereof.

[00052] Form Gamma 6, can be further characterized by additional X-ray powder diffraction peaks at 12.1, 12.9, 14.5, 14.9 and 38.3 degrees 2-theta ± 0.2 degrees 2-theta.

[00053] In another embodiment the present invention encompasses a crystalline composition comprising Sunitinib base, L-malic acid and fumaric acid; wherein the ratio between Sunitinib base, L-malic acid and fumaric acid is about 1:1:1 (mole:
mole: mole), designated herein as form Gamma 7. Form Gamma 7 can be characterized by data selected from: an X-ray powder diffraction pattern having peaks at 2.9, 20.0, 26.0 and 31.4 degrees 2-theta ± 0.2 degrees 2-theta; an X-ray powder diffraction pattern substantially as depicted in Figure 9; and combinations thereof. Form Gamma 7, can be further characterized by additional X-ray powder diffraction peaks at 11.9, 22.5, 27.2 and 38.0 degrees 2-theta ± 0.2 degrees 2-theta.

[00054] In another embodiment the present invention encompasses a crystalline composition comprising Sunitinib base, L-malic acid and fumaric acid; wherein the ratio between Sunitinib base, L-malic acid and fumaric acid is about 1:1:1 (mole: mole: mole), designated herein as form Gamma 8. Form Gamma 8 can be characterized by data selected from: an X-ray powder diffraction pattern having peaks at 3.0, 9.1, 12.1, 27.0 and 28.5 degrees 2-theta ± 0.2 degrees 2-theta; an X-ray powder diffraction pattern substantially as depicted in Figure 10; and combinations thereof.

[00055] In another embodiment the present invention encompasses a crystalline Sunitinib fumarate, designated herein as form Delta. Form Delta can be characterized by data selected from: an X-ray powder diffraction pattern having peaks at 6.7, 6.9, 17.8, 18.4 and 20.6 degrees 2-theta ± 0.2 degrees 2-theta; an X-ray powder diffraction pattern substantially as depicted in Figure 11; a solid-state $^{13}$C NMR spectrum with signals at 173.1, 139.8, 135.5 and 113.0 ± 0.2 ppm, a solid-state $^{13}$C NMR spectrum having chemical shifts differences between the signal exhibiting the lowest chemical shift and another in the chemical shift range of 100 to 180 ppm of 66.4, 33.1, 28.8 and 6.3 ± 0.1 ppm; a $^{13}$C NMR spectrum substantially as depicted in Figure 12, and a solid-state $^{13}$C NMR spectrum substantially as depicted in Figure 13 and combinations thereof. Sunitinib fumarate form Delta, can be further characterized by data selected from: an additional X-ray powder diffraction peaks at 13.6, 20.0, 20.3, 23.1 and 25.4 degrees 2-theta ± 0.2 degrees 2-theta; a solid-state $^{13}$C NMR spectrum having signals at 167.1, 166.7, 128.4 and 110.1 ± 0.2 ppm; and a solid-state $^{13}$C NMR spectrum having chemical shifts differences between the signal exhibiting the lowest chemical shift and another in the chemical shift range of 100 to 180 ppm of 60.7, 60.0, 21.7 and 3.4 ± 0.1 ppm and combination thereof.

[00056] Typically, the signal exhibiting the lowest chemical shift in the chemical shift area of 100 to 180 ppm is at 106.7 ± 1 ppm.
[00057] In another embodiment the present invention encompasses a crystalline Sunitinib hydrochloride, designated herein as form Epsilon. Form Epsilon can be characterized by data selected from: an X-ray powder diffraction pattern having peaks at 6.5, 11.1, 15.2, 18.4 and 26.2 degrees 2-theta ± 0.2 degrees 2-theta; and an X-ray powder diffraction pattern substantially as depicted in Figure 18; and combinations thereof. Sunitinib hydrochloride form Epsilon, can be further characterized by data selected from an additional X-ray powder diffraction peaks at 16.0, 16.5, 20.6, 25.1 and 30.0 degrees 2-theta ± 0.2 degrees 2-theta.

[00058] The present invention further encompasses 1) a pharmaceutical composition comprising the above described salts and crystalline forms and at least one pharmaceutically acceptable excipient; 2) the use of any one or combination of the above described salts and crystalline forms and another carboxylic acid in the manufacture of a pharmaceutical composition, and 3) a method of treating gastrointestinal stromal tumor after disease progression or intolerance to imatinib mesylate and for the treatment of advanced renal cell carcinoma, comprising administering a pharmaceutically effective amount of at least one of the above described salts and crystalline forms to a subject in need of the treatment. The pharmaceutical composition can be useful for preparing a medicament. The present invention also provides at least one of the above described salts and crystalline forms for use as a medicament.

[00059] In another embodiment, the present invention encompasses the use of the above described salts and crystalline forms for the preparation sunitinib malate.
Analytical techniques

1. X-ray powder diffraction:

X-ray powder diffraction was performed on an X-Ray powder diffractometer: Philips X'pert Pro powder diffractometer, CuKa radiation, $\lambda = 1.5418$ Å. X'Celerator detector active length (2 theta) = 2.122°, laboratory temperature 22-25 °C. Zero background sample holders. Prior to analysis, the samples were gently ground with a mortar and pestle in order to obtain a fine powder.

A silicon internal standard can be used to calibrate peak positions and to eliminate effects related to sample preparation. The internal standard possesses a diffraction with defined position at 28.44 degrees 2-theta. The internal standard can be mixed with a sample, X-ray powder diffraction is then acquired and the current position of the aforementioned internal standard diffraction peak is determined. The difference between the current position of the diffraction and its nominal value of 28.44 degrees 2-theta is calculated. The current positions of all relevant sample peaks are then re-calculated by means of the above difference to obtain the true positions of the sample diffractions.

Measurement parameters:
- Scan range: at least 3 - 40° 2-theta;
- Scan mode: continuous;
- Step size: 0.0167°;
- Time per step: 42 s;
- Sample spin: 16 rpm;
- Sample holder: quartz plate.

2. $^{13}$C NMR

All $^{13}$C CP/MAS NMR spectra were measured at 125 MHz using a Bruker Avance 500 WB/US NMR spectrometer (Karlsruhe, Germany, 2003) at magic angle spinning (MAS) frequency $\omega_{12}\pi = 11$ kHz. In all cases finely powdered samples were placed into the 4mm Zr02 rotors and standard CPMAS pulse program was used. During acquisition of the data a high-power dipolar decoupling TPPM (two-pulse phase-modulated) was applied. The phase modulation angle was 15°, and the flip-pulse length was 4.8 $\mu$s. Applied nutation frequency of Bi$^8$H) field was $\omega_{12}\pi = 89.3$ kHz. Nutation frequency of Bi($^{13}$C) and Bi$^8$H) fields during cross-polarization was
$\omega_0 T = 62.5 \text{ kHz}$ and repetition delay was 5 s. The number of scans was 7200. Consequently the total experimental time was about 6 hours. Taking into account frictional heating of the samples during fast rotation all NMR experiments were performed at 305 K (precise temperature calibration was performed). As used herein, the term "$^{13}$C NMR chemical shifts" refers to the shifts measured under above specified conditions; however, these shifts can slightly differ instrument to instrument and can be shifted either upfield or downfield due to the different instrumental setup and calibration used. Nevertheless the sequence of individual peaks remains identical.

EXAMPLES

Example 1: preparation of sunitinib D, L-malate form A1
[00063] Sunitinib base (10.0 g) was suspended in a mixture of water (22 mL) and ethanol (45 mL). The mixture was heated to 40°C and solid D, L-malic acid (3.6 g) and ethanol (45 mL) were added. The mixture was heated to 60°C to complete dissolution of malic acid. The obtained solution was cooled to 35°C over 1 hour, and kept at 35°C for half an hour. No crystals formed at this point. The solution was further cooled to 25°C for 1 hour. A copious precipitation occurred. The suspension was cooled to 0°C for 1 hour and the product was separated by filtration (bed filtration), washed with ethanol (20 ml) and dried under vacuum at 60°C for 6 h.

Example 2: preparation of sunitinib D, L-malate form A2
[00064] Sunitinib base (300 mg) was dissolved in THF (6 ml) by heating for about 5 min and D,L-malic acid (101 mg) dissolved in methanol (1 ml) was added. The resulting suspension was allowed to stand for 20h at 20°C. The solid precipitate was then separated by filtration, washed with t-butyl methyl ether (10 ml) and air dried 3 h at 20°C.

Example 3: Preparation of a composition comprising Sunitinib base, L-malic acid and fumaric acid form Gamma 1
[00065] Sunitinib base (300 mg) was dissolved in boiling dioxane (10 ml). L-Malic acid (101 mg) and fumaric acid (87 mg, molar ratio of components is 1:1:1) were added in water (2 ml). The resulting mixture was heated to reflux for 3 min, and
then allowed to cool down to room temperature. Crystals formed overnight, and were separated by filtration, washed with TBME (5 ml) and air dried.

Example 4: Preparation of composition of sunitinib, L-malic acid and succinic acid
(form Gamma 2)

Sunitinib base (300 mg) was dissolved in boiling dioxane (10 ml). L-Malic acid (101 mg) and succinic acid (89 mg, molar ratio of components is 1:1:1) were added in water (2 ml). The resulting mixture was heated to reflux for 3 min, and then allowed to cool. The mixture was further cooled to -30°C, and the resulting frozen mixture was lyophilized at 1 mBar.

Example 5: Preparation of composition of sunitinib, L-malic acid and L-tartric acid
(form Gamma 3)

Sunitinib base (300 mg) was dissolved in boiling dioxane (10 ml). L-Malic acid (101 mg) and L-tartric acid (113 mg, molar ratio of components is 1:1:1) were added in water (2 ml). The resulting mixture was heated to reflux for 3 min, and then allowed to cool. The mixture was further cooled to -30°C, and the resulting frozen mixture was lyophilized at 1 mBar.

Example 6: Preparation of composition of sunitinib, L-malic acid and D-tartric acid
(form Gamma 4)

Sunitinib base (300 mg) was dissolved in boiling dioxane (10 ml). L-Malic acid (101 mg) and D-tartric acid (113 mg, molar ratio of components is 1:1:1) were added in water (2 ml). The resulting mixture was heated to reflux for 3 min, and then allowed to cool. The mixture was further cooled to -30°C, and the resulting frozen mixture was lyophilized at 1 mBar.

Example 7: Preparation of composition of sunitinib, L-malic acid and malonic acid
(form Gamma 5)

Sunitinib base (300 mg) was dissolved in boiling dioxane (10 ml). L-Malic acid (101 mg) and malonic acid (78 mg, molar ratio of components is 1:1:1) were added in water (2 ml). The resulting mixture was heated to reflux for 3 min, and
then allowed to cool. The mixture was further cooled to -30°C, and the resulting frozen mixture was lyophilized at 1 mBar.

Example 8: Preparation of composition of sunitinib, L-malic acid and adipic acid (form Gamma 6)

[00070] Sunitinib malate (150 mg, Form I) was dissolved in boiling dioxane/water (10 ml, 1:1). Adipic acid (55 mg, molar ratio of components is 1:1:1) was added. The resulting mixture was heated to reflux for 3 min, and then allowed to cool. The mixture was further cooled to -30°C, and the resulting frozen mixture was lyophilized at 1 mBar.

Example 9: Preparation of composition of sunitinib, L-malic acid and fumaric acid (form Gamma 7)

[00071] Sunitinib malate (150 mg, Form I) was dissolved in boiling dioxane/water (10 ml, 1:1). Fumaric acid (45 mg, molar ratio of components is 1:1:1) was added. The resulting mixture was heated to reflux for 3 min, and then allowed to cool. The mixture was further cooled to -30°C, and the resulting frozen mixture was lyophilized at 1 mBar.

Example 10: Preparation of composition of sunitinib, L-malic acid and fumaric acid (form Gamma 8)

[00072] Sunitinib malate (150 mg, Form I) was dissolved in boiling water (10 ml). Fumaric acid (45 mg, molar ratio of components is 1:1:1) was added. The resulting mixture was heated to reflux for 3 min, and then allowed to cool. The mixture was further cooled to -30°C, and the resulting frozen mixture was lyophilized at 1 mBar.

Example 11: Preparation of crystalline Sunitinib fumarate form Delta

[00073] Sunitinib base (300 mg) was dissolved in dioxane (10 ml) by heating to 100°C for 10 min. A solution of fumaric acid (88 mg) in hot ethanol (2 ml) was added. The resulting mixture was heated for an additional 10 min to reflux temperature. The solution was then allowed to cool to 20°C. The volume of the solution was reduced to 1/2 on a vacuum evaporator and the reduced volume mixture
was allowed to stand for 3 hrs at 20°C. Crystals formed and were collected by filtration, washed with t-BME (5 ml) and air dried for 3 hrs at 20°C.

Example 12: Preparation of Sunitinib DX-malate form B

[00074] Sunitinib base (9 g) was dissolved in ethanol (120 ml) and acetic acid (6 ml) by heating to 78°C for 10 min forming the solution of sunitinib acetate. Crystalline D,L-malic acid (3.3 g) was added to form a suspension. The suspension was heated for an additional 10 min to the reflux temperature facilitating complete dissolution. The solution was allowed to cool to 20°C and stand for 12 h at 20°C. Crystals formed and were collected by filtration, washed with t-BME (50 ml) and air dried for 3 h at 20°C.

Example 13: Preparation of Sunitinib D.L-malate form B

[00075] Sunitinib base (9 g) was dissolved in 1-butanol (80 ml) by heating to 117°C for 10 min. A solution of D,L-malic acid (3.3 g) in water (6 ml) was added. The resulting solution was heated for additional 10 min and then allowed to cool to 20°C and stand for 3 h at 20°C. The crystals formed thereby were collected by filtration, washed with t-BME (50 ml) and air dried for 3 h at 20°C.

Example 14: Preparation of Sunitinib DX-malate form B

[00076] Sunitinib acetate form Beta (900 mg) was dissolved in 1-butanol (6 ml) by heating to 117°C for 10 min. A solution of D,L-malic acid (300 mg) in water (0.8 ml) was added. The resulting solution was heated for an additional 10 min and allowed to cool to 20°C and stand 3 hrs at 20°C. Crystals formed and were collected by filtration, washed with t-BME (20 ml) and air dried for 3 hrs at 20°C.

Example 15: Preparation of Sunitinib DX-malate form B

[00077] Sunitinib acetate Form a (900 mg) was dissolved in 1-butanol (5 ml) by heating to 117°C for 10 min. A solution of D,L-malic acid (300 mg) in water (0.8 ml) was added. The resulting solution was heated for an additional 10 min and allowed to cool to 20°C and stand 3 hrs at 20°C. Crystals formed and were collected by filtration, washed with t-BME (20 ml) and air dried for 3 hrs at 20°C.
**Example 16: Preparation of Sunitinib hydrochloride form Epsilon**

[00078] Sunitinib base (5g, form VIII) was suspended in n-butanol (25 ml) with stirring at 20°C. Then 1.05eq (1.1ml) of HCl 37% was added together with 15ml of water. Dissolution and then re-precipitation was observed. The mixture was heated to 40°C and 75ml of MTBE were added over about 60 minutes. The resulting mixture was cooled to 0°C over 2 hours. After 30 minutes at 0°C, the solid precipitate that had formed was filtered, washed with 2x20ml of MTBE and dried on the filter for 1h at 40°C under vacuum for 2 hours.

**Example 17: Preparation of Sunitinib acetate form Beta**

[00079] Sunitinib base (6 g) was dissolved in 1-butanol (40 ml) by heating to 60-70°C, and acetic acid (2.0 ml) was added with stirring. Then t-BME (150 ml) was added over 15 min with stirring of a hot solution (which became a suspension). The suspension was allowed to cool to 20 °C and then to 0 °C, and then maintained at 0°C for 12 h. The solid precipitate that formed was recovered by filtration, washed with t-BME (20 ml) and air dried for 10 hrs at 20 °C.

**Example 18: Preparation of Sunitinib acetate, form Beta**

[00080] Sunitinib base (6 g) was dissolved in n-butanol (30 ml) and acetic acid (10 ml) by stirring 2 hrs at 20 °C. The solution was then allowed to cool to 0°C over 12 hrs. The solid precipitate that formed was recovered by filtration, washed with t-BME (50 ml) and air dried for 10 hrs at 20 °C.

**Example 19: Preparation of Sunitinib base form VIII**

[00081] Sunitinib base, obtained by reaction of Sunitinib activated carboxylic acid derivative with excess of N, N'-diethylaminoethylamine in 2-methyltetrahydrofuran, was dissolved in 15 volumes of water (150ml for 10g of sunitinib base) at pH 2 (obtained by addition of HCl 1M) at 70°C. The mixture was then cooled to 25°C and precipitated by adding ammonia (30%) sufficient to raise the pH to 8.5 at 25°C. The resulting mixture was stirred for one hour and filtered at 25°C. The collected solid was washed with water and dried in an oven under vacuum for 16 hours at 60°C.
Example 20- Preparation of Sunitinib base form D

[00082] In a 500 ml reactor, 15.0 g of 5-(5-fluoro-2-oxo-1, 2-dihydro-indol-(3Z)-ylidenemethyl)-2, 4-dimethyl-lH-pyrrole-3-carboxylic acid were suspended into 300ml of toluene (ratio 20/1.0 v/w. starting material) under vigorous stirring at room temperature. 0.755 g. of dimethylformamide (ratio 0.2/1.0 w/w) was added to the mixture.

[00083] The temperature was set at 70°C and at this temperature, 5.1 g. of thionyl chloride (ratio 1.4/1.0 w/w) were dropped in a range of sixty minutes. The reaction was kept at 70°C for 7 hours under stirring.

[00084] Then 140 ml of solvent were distilled to remove excess of thionyl chloride from the suspension and the reaction filtered on gooch P3 washing with 3v/w of toluene. The wet solid (sunitinib acyl chloride derivative) was re-loaded into the reactor and 300ml Methyl-tetrahydrofuran loaded and stirred. Then the reaction mixture was heated to 70°C and 6.35g of 2-diethylamino-ethylamine (ratio 1.1/1.0 w/w starting material) were dropped in five minutes at 70°C. After one hour the reaction was completed and 150 ml of water and HCl 2N until pH 2 were added to the suspension.

[00085] The mixture was filtered using a decalite pad to obtain a clarified phase. The two phases were separated at 50°C and the organic phase discarded. The aqueous phase was washed once more with 300ml of Methyl-tetrahydrofuran at 50°C under stirring. The two phases separated again and the organic phase discarded. The aqueous phase was then basified to pH 8.5 with 5% ammonia solution at 50 °C. After one hour stirring, the suspension was filtered on gooch P3 and the wet solid dried at 60°C under vacuum overnight. 15.9 g. of sunitinib base were obtained with a purity of not less than (NLT) 99.5% by HPLC.
What is claimed is:

1. A Sunitinib salt selected from sunitinib hydrochloride and sunitinib fumarate.
2. Crystalline form Epsilon of Sunitinib hydrochloride.
3. The crystalline Form Epsilon of Sunitinib hydrochloride according to claim 2, characterized by data selected from: an X-ray powder diffraction pattern having peaks at 6.5, 11.1, 15.2, 18.4 and 26.2 ± 0.2 degrees 2-theta; and an X-ray powder diffraction pattern substantially as depicted in Figure 18; and combinations thereof.
4. Crystalline form Delta of Sunitinib fumarate.
5. The crystalline Form Delta of Sunitinib fumarate according to claim 4, characterized by data selected from: an X-ray powder diffraction pattern having peaks at 6.7, 6.9, 17.8, 18.4 and 20.6 ± 0.2 degrees 2-theta; an X-ray powder diffraction pattern substantially as depicted in Figure 11; a solid-state \(^{13}\)C NMR spectrum with signals at 173.1, 139.8, 135.5 and 113.0 ± 0.2 ppm; a solid-state \(^{13}\)C NMR spectrum having chemical shift differences between the signal exhibiting the lowest chemical shift and another in the chemical shift range of 100 to 180 ppm of 66.4, 33.1, 28.8 and 6.3 ± 0.1 ppm; a \(^{13}\)C NMR spectrum substantially as depicted in Figure 12; a solid-state \(^{13}\)C NMR spectrum substantially as depicted in Figure 13; and combinations thereof.
7. The crystalline form A1 of racemic sunitinib malate according to claim 6, characterized by data selected from: an X-ray powder diffraction pattern having peaks at 3.8, 6.4, 7.4, 11.7 and 16.3 ± 0.2 degrees 2-theta; an X-ray powder diffraction pattern substantially as depicted in Figure 1; and combinations thereof.
8. The crystalline form A1 of claim 7, further characterized by additional X-ray powder diffraction peaks at 12.8, 13.5, 24.5 and 25.4 ± 0.2 degrees 2-theta.
10. The crystalline form A2 of racemic sunitinib malate according to claim 9, characterized by data selected from: an X-ray powder diffraction pattern having peaks at 3.2, 6.8, 21.2, 25.1 and 25.6 ± 0.2 degrees 2-theta; an X-ray powder diffraction pattern substantially as depicted in Figure 2; and combinations thereof.
11. The crystalline form A2 of claim 10, further characterized by additional X-ray powder diffraction peaks at 8.2, 13.2, 16.3 and 24.2 ± 0.2 degrees 2-theta.

12. A crystalline form of a composition comprising Sunitinib base, L-malic acid and another carboxylic acid selected from a group consisting of forms Gamma 1, Gamma 2, Gamma 3, Gamma 4, Gamma 5, Gamma 6, Gamma 7 and Gamma 8; wherein the ratio between the Sunitinib base, L-malic acid and the other carboxylic acid is about 1:1:1 (mole: mole: mole).

13. The use of at least one crystalline form according to any one of claims 2, 4, 6, 9 and 12 in the manufacture of a pharmaceutical composition.

14. The use of a crystalline form according to any one of claims 2, 4, 6, 9 and 12 in the manufacture of sunitinib malate.

15. A pharmaceutical composition comprising at least one crystalline form according to any one of claims 2, 4, 6, 9 and 12, and at least one pharmaceutically acceptable excipient.

16. A method for treating gastrointestinal stromal tumor after disease progression or intolerance to imatinib mesylate, or for treating advanced renal cell carcinoma, comprising administering a pharmaceutically effective amount of at least one crystalline form according to any one of claims 2, 4, 6, 9 and 12, to a subject in need of such treatment.
Note: The peak marked with "Si" belongs to the silicon internal standard.

Figure 11