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(71) Applicant: SUN PHARMACEUTICAL INDUSTRIES
LIMITED [IN/IN]; Sun House, Plot No. 201 B/1, Western
Express Highway, Goregaon (E), Mumbai, Maharashtra
400 063 (IN).

(72) Inventors: AGARWAL, Ravindra; House No. 3DH 29,
Sector - 5, Prabhat Nagar, Hiran Magri, Udaipur, Rajasthan
313002 (IN). KOCHHAR, Ravi; A-118, Ground Floor,
Greenwoods City, Sector - 45, Gurgaon, Haryana 122003
(IN). KUMAR, Amit; s/o Vinod KUMAR, Ganga Babu ki
Theki, Lal imli, P.O. Begampur, Patna, Bihar 800009 (IN).
GUPTA, Puneet, Kumar; House No. 445, Phase - II, Urban
Estate, Dugri, Ludhiana, Punjab 141013 (IN). DESH-
MUKH, Subodh; 54 Scotch Cap Road, Quaker Hill, Con-
necticut 06375 (US). SANTHAKUMAR, Rita; V-11/36,

FF-1, DLF Phase 3, Gurgaon, Haryana 122002 (IN). GAN-
GULY, Somenath; B79, Ground Floor, Southend Floor,
Sector 48-49, Sohna Road, Gurgaon, Haryana 122018
(IN). WADHWA, Deepika; House No. 697, Sector 46,
Gurgaon, Haryana 122002 (IN).

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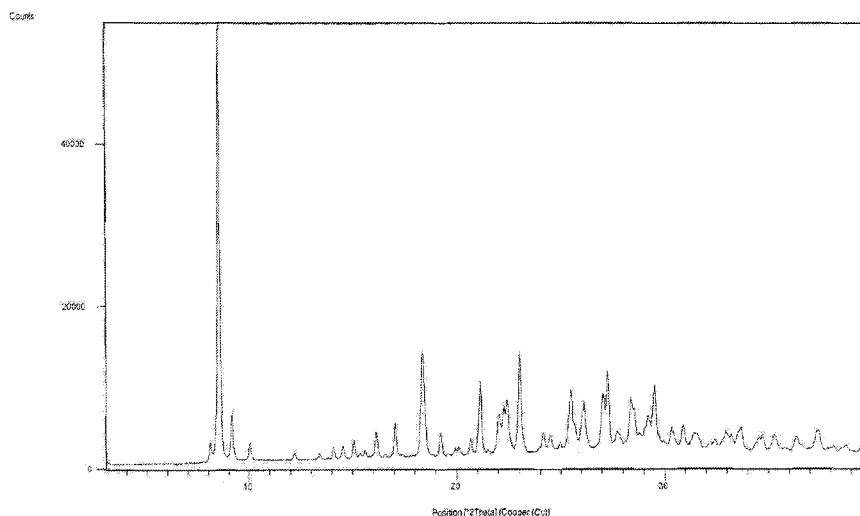
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(54) Title: CRYSTALLINE FORM X OF BOSUTINIB

FIGURE 1



(57) Abstract: The present invention provides a crystalline Form X of bosutinib, a process for its preparation, its pharmaceutical composition and a method of use thereof.

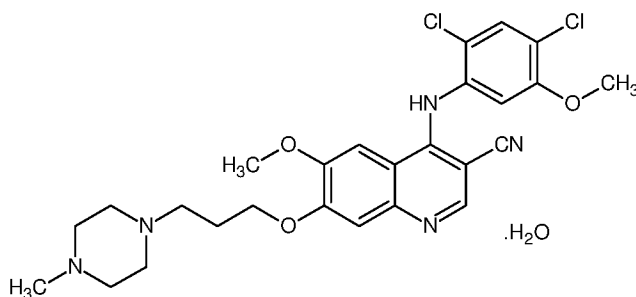
CRYSTALLINE FORM X OF BOSUTINIB

Field of the Invention

The present invention provides a crystalline Form X of bosutinib, a process for its preparation, its pharmaceutical compositions and a method of use thereof.

Background of the Invention

Bosutinib monohydrate is chemically designated as 3-quinolinecarbonitrile, 4-[(2,4-dichloro-5-methoxyphenyl)amino]-6-methoxy-7-[3-(4-methyl-1-piperazinyl)propoxy]-, hydrate (1:1), as depicted by Formula I.



Formula I

U.S. Patent Nos. 6,002,008 and RE42,376 disclose bosutinib generically.

U.S. Patent Nos. 7,767,678 and 8,445,496 allegedly disclose crystalline Forms I to VI and a non-crystalline form of bosutinib.

Chinese Publication No. 104447542 allegedly discloses crystalline bosutinib monohydrate with particular XRD peaks.

Organic Process Research & Development 2013, 17, 500-504 discloses a process for the preparation of bosutinib Form I and different solvates.

PCT Publication No. WO 2015/123758 allegedly discloses crystalline propylene glycol and acetonitrile solvates of bosutinib and amorphous form of bosutinib.

PCT Publication No. WO 2015/149727 allegedly discloses crystal modifications 1, 2, 3, 4, 5, 6, and amorphous form of bosutinib.

In the pharmaceutical industry, there is a constant need to identify critical physicochemical parameters of a drug substance such as novel salts, polymorphic forms,

and co-crystals that affect the drug's performance, solubility, and stability, and which may play a key role in determining the drug's market acceptance and success.

The discovery of new forms of a drug substance may improve desirable processing properties of the drug, such as ease of handling, storage stability, and ease of purification. The present invention provides a crystalline Form X of bosutinib and a simple, cost-effective, and commercially advantageous process for the preparation of the crystalline Form X of bosutinib. Crystalline Form X of bosutinib is also obtained when bosutinib is formulated with pharmaceutical excipients following certain parameters and steps.

Summary of the Invention

The present invention provides a crystalline Form X of bosutinib.

The present invention also provides a process for the preparation of a crystalline Form X of bosutinib comprising treating bosutinib with water.

The present invention also provides a pharmaceutical composition comprising a crystalline Form X of bosutinib and one or more pharmaceutically acceptable excipients.

The present invention also provides a process for the preparation of a pharmaceutical composition comprising Form X of bosutinib and one or more pharmaceutically acceptable excipients selected from one or more of a diluent, a disintegrant, a binder, a surfactant, lubricant and glidant wherein the process comprises the steps of:

- i) granulating bosutinib with an aqueous solution of a binder and/or a surfactant, and
- ii) optionally drying the granules.

The present invention also provides use of a crystalline Form X of bosutinib for treating cancer, for example, Chronic Myelogenous Leukemia.

Brief Description of the Drawings

Figure 1 is a X-ray powder diffraction (XRPD) pattern of a crystalline Form X of bosutinib prepared by Example 1.

Figure 2 is a Differential Scanning Calorimetry (DSC) thermogram of a crystalline Form X of bosutinib prepared by Example 1.

Figure 3 is a Differential Thermal Analysis (DTA TG) thermogram of a crystalline Form X of bosutinib prepared by Example 1.

Figure 4 is a Fourier Transform Infra-Red (FT-IR) spectra of a crystalline Form X of bosutinib prepared by Example 1.

Figure 5 is a Raman spectra of a crystalline Form X of bosutinib prepared by Example 1.

Figure 6 is a Scanning Electron Microscope (SEM) image of a crystalline Form X of bosutinib prepared by Example 1.

Figure 7 is a X-ray powder diffraction (XRPD) pattern of wet granules of bosutinib prepared by Example 4 and tested after storage for seven days.

Figure 8 is a X-ray powder diffraction (XRPD) pattern of dried granules of bosutinib prepared by Example 3 and tested after storage for 49 days.

Figure 9 is a X-ray powder diffraction (XRPD) pattern of dried granules of bosutinib prepared by Example 3 and tested after 11 months storage.

Figure 10 is a X-ray powder diffraction (XRPD) pattern of the tablet composition of bosutinib prepared by Example 5 and tested after 3 months storage.

Detailed Description of the Invention

Various embodiments and variants of the present invention are described hereinafter.

The term “about,” as used herein, refers to any value which lies within the range defined by a variation of up to $\pm 10\%$ of the value.

The term “treating,” as used herein, includes adding, dissolving, suspending, slurring, stirring, reacting, heating, cooling, condensing, or combinations thereof.

The term “stable,” as used herein, refers to a crystalline form as characterized by XRPD, wherein XRPD remains unchanged over a period of time.

A first aspect of the present invention provides a crystalline Form X of bosutinib.

The crystalline Form X of bosutinib, as prepared by Example 1, is characterized by an XRPD pattern having interplanar spacing (d) values at about 6.3, 6.1, 5.9, 5.5, and 4.8 Å.

The crystalline Form X of bosutinib is further characterized by an XRPD pattern having additional interplanar spacing (d) values at about 10.9, 10.3, 4.5, 4.4, 3.7, and 3.6 Å.

Table 1 provides XRPD peak values ($^{\circ}2\theta$), their corresponding d-spacing values (Å), and the relative intensities for the crystalline Form X of bosutinib.

Table 1

Position (°2 θ)	d-spacing (Å)	Relative Intensity (%)
8.1	10.9	5.4
8.5	10.3	100.0
9.2	9.6	12.2
10.1	8.8	4.8
12.2	7.3	2.6
13.4	6.6	2.5
14.1	6.3	3.8
14.5	6.1	4.1
15.1	5.9	5.0
15.4	5.8	2.5
15.6	5.7	3.2
16.2	5.5	7.2
16.6	5.3	2.2
17.1	5.2	9.4
18.4	4.8	24.5
19.3	4.6	7.0
20.0	4.5	3.4
20.1	4.4	3.7
20.7	4.3	5.6
21.1	4.2	18.8
22.0	4.0	10.3
22.3	4.0	13.2
22.4	4.0	14.4
23.0	3.9	25.4
24.2	3.7	7.1
24.5	3.6	6.7
25.0	3.6	4.9
25.5	3.5	16.9
26.1	3.4	14.4
27.0	3.3	15.9
27.3	3.3	20.9
27.7	3.2	7.1
28.4	3.1	14.8
28.6	3.1	12.3
29.2	3.1	10.9
29.5	3.0	18.1
30.3	2.9	7.9
30.9	2.9	8.7
31.4	2.8	6.8
31.6	2.8	6.4
32.2	2.8	4.7
32.4	2.8	5.3

33.0	2.7	7.4
33.2	2.7	6.5
33.7	2.7	8.3
34.7	2.6	6.4
35.3	2.5	6.4
36.4	2.5	6.0
37.5	2.4	7.2
38.2	2.4	3.9
38.8	2.3	4.1

The crystalline Form X of bosutinib is further characterized by a DSC thermogram having endothermic peaks at about 91°C, 121°C and 152°C under hermetically sealed crucible.

The crystalline Form X of bosutinib is further characterized by a DTA TG having endothermic peaks at about 48°C, 61°C and 81°C under open pan and shows a mass loss of about 13.2%.

The crystalline Form X of bosutinib is further characterized by plate shape particles having a crystal habit, wherein the ratio between the width and the length of the crystals is between 1:3 and 1:1. The crystalline Form X of bosutinib is further characterized by plate shape particles having an aspect ratio of about 0.68.

The crystalline Form X of bosutinib is further characterized as hydrated form, wherein the number of water molecules may be equal to or greater than 4.

The crystalline Form X of bosutinib prepared by Example 1, is further characterized by an XRPD pattern substantially as depicted in Figure 1. The crystalline Form X of bosutinib prepared by Example 1 is further characterized by a DSC thermogram substantially as depicted in Figure 2, a DTA TG substantially as depicted in Figure 3, a FT-IR spectra substantially as depicted in Figure 4, a Raman spectra substantially as depicted in Figure 5, and a SEM image substantially as depicted in Figure 6.

The crystalline Form X of bosutinib of the present invention as characterized by XRPD, wherein the XRPD pattern remains unchanged on exposure to a temperature of 40°C and relative humidity of 75% for duration of 7 days.

A second aspect of the present invention provides a process for the preparation of a crystalline Form X of bosutinib comprising treating bosutinib with water.

Bosutinib may be prepared by following the processes as disclosed in the art, for example, U.S. Patent No. 6,002,008 and RE42,376.

The treatment of bosutinib with water is carried out at a temperature of about 10°C to about 30°C, for example, at about 20°C to about 25°C.

The treatment of bosutinib with water is carried out for about 2 hours to about 30 hours, for example, for about 5 hours to about 25 hours.

Crystalline Form X of bosutinib may be isolated by filtration, decantation, extraction, distillation, evaporation, chromatography, precipitation, concentration, crystallization, centrifugation, or recrystallization.

Further, the crystalline Form X of bosutinib may be dried to provide the crystalline Form I of bosutinib.

A third aspect of the present invention provides a pharmaceutical composition comprising a crystalline Form X of bosutinib and one or more pharmaceutically acceptable excipients.

According to a first embodiment of the above aspect, the pharmaceutical composition is in the form of tablets, capsules, powder, solution, or suspension.

According to a second embodiment of the above aspect, the pharmaceutical composition may have water content of from about 4% to about 20%; from about 4% to about 15%; from about 4% to about 12% or from about 5% to about 10%.

According to a third embodiment of the above aspect, the pharmaceutical composition of bosutinib comprising Form X of bosutinib and one or more pharmaceutically acceptable excipients, wherein the pharmaceutical excipient is selected from one or more of a diluent, a disintegrant, a binder, a surfactant, lubricant and glidant.

According to a fourth embodiment of the above aspect, the pharmaceutical excipient is selected from a binder and a surfactant.

According to another embodiment, the binder is povidone and the surfactant is poloxamer.

According to another embodiment, the diluent is microcrystalline cellulose, the disintegrant is croscarmellose sodium, the binder is povidone and the surfactant is poloxamer.

A fourth aspect of the present invention provides a process for the preparation of a pharmaceutical composition comprising Form X of bosutinib and one or more pharmaceutically acceptable excipients selected from the group consisting of one or more of a diluent, a disintegrant, a binder, a surfactant, lubricant and glidant wherein the process comprises the steps of:

- i) granulating bosutinib with an aqueous solution of a binder and/or a surfactant, and
- ii) optionally drying the granules.

According to a first embodiment of the above aspect, the pharmaceutical composition has a water content of from about 4% to about 20%.

According to a second embodiment of the above aspect, the binder is povidone and the surfactant is poloxamer.

According to a third embodiment of the above aspect, the pharmaceutical composition is prepared by a process comprising the steps of:

- i) granulating a mixture of bosutinib, diluent and disintegrant with an aqueous solution of a binder and/or a surfactant, and
- ii) optionally drying the granules.

According to another embodiment, the diluent is microcrystalline cellulose, the disintegrant is croscarmellose sodium, the binder is povidone and the surfactant is poloxamer.

The granules may be further processed into other dosage forms such as tablets and capsules.

The X-ray powder diffraction (XRPD) pattern of wet granules of bosutinib prepared by Example 4 and tested at the 7th day of storage is shown in Figure 7. The crystalline Form X of bosutinib remains unchanged over this period of time.

The XRPD pattern of dried granules of bosutinib prepared by Example 3 and tested after 49 days of storage is shown in Figure 8. The crystalline Form X of bosutinib remains unchanged over this period of time.

The XRPD pattern of dried granules of bosutinib prepared by Example 3 and tested after 11 months of storage is shown in Figure 9. The crystalline Form X of bosutinib remains unchanged over this period of time.

The XRPD pattern of a tablet composition of bosutinib prepared by Example 5 and tested after 3 months is shown in Figure 10. The crystalline Form X of bosutinib remains unchanged over this period of time.

A fifth aspect of the present invention provides use of a crystalline Form X of bosutinib for treating cancer, for example, Chronic Myelogenous Leukemia.

The crystalline Form X of bosutinib may be used for of treating Chronic Myelogenous Leukemia (CML) in humans, which comprises administering to the infected individual an effective amount of the crystalline Form X of bosutinib of present invention, or a pharmaceutical composition of the invention. The dose provided to a patient will vary depending upon what is being administered, the purpose of the administration, the manner of administration, and the like. A “therapeutically effective amount” is an amount sufficient to cure or ameliorate symptoms of Chronic Myelogenous Leukemia (CML).

The crystalline Form X of bosutinib may be delivered alone or in combination with other compounds used to treat Chronic Myelogenous Leukemia (CML). Such compounds include but are not limited to GLEEVEC, hydroxyurea, IFN- α , cytotoxic agents, 17-(Allylamino)-17-demethoxygeldanamycin or derivatives thereof, or wortmannin.

The crystalline Form X of bosutinib is used as part of a pharmaceutical composition. It may be formulated in a conventional manner using one or more pharmaceutically acceptable excipients. Thus the crystalline form X of bosutinib may be formulated for oral, buccal, parenteral (e.g., intralesional, intraperitoneal, intramuscular or intravenous injection; infusion), urethral, transdermal, intrathecal, ocular, otic delivery or rectal administration. The crystalline form X of bosutinib may also be formulated for controlled drug release.

The crystalline Form X of bosutinib may be formulated with conventional pharmaceutically acceptable excipients, such as a filler, a disintegrating agent, a binder, a lubricant, a flavoring agent, or a carrier. The carrier may be, for example, a diluent, an aerosol, a topical carrier, an aqueous solution, a nonaqueous solution or a solid carrier. The carrier may be a polymer. A carrier encompasses any of the standard pharmaceutically accepted carriers, such as phosphate buffered saline solution, acetate buffered saline

solution, water, emulsions such as an oil/water emulsion or a triglyceride emulsion, various types of wetting agents, tablets, coated tablets and capsules.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets, or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binders, diluents, lubricants, disintegrants, or wetting agents. The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups, or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable excipients such as suspending agents, emulsifying agents, non-aqueous vehicles, and preservatives.

The pharmaceutical compositions for oral use can be obtained by combining the active ingredient with solid carriers, if desired granulating a mixture obtained, and processing the mixture or granules, if desired or necessary, after addition of suitable excipients to give tablets or tablet cores.

The crystalline Form X of bosutinib may be formulated for parenteral administration by injection, including using conventional catheterization techniques or infusion. Formulations for injection may be prepared in unit dosage form, e.g. in ampules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulating agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the crystalline Form X of bosutinib may be in powder form for reconstitution with suitable vehicle, e.g., sterile pyrogen free water before use. The crystalline Form X of bosutinib may also be formulated as a rectal composition such as suppositories or retention enemas.

The crystalline Form X of bosutinib may also be delivered orally via controlled release compositions such as capsule, tablet, particles, beads, pellets, powder, controlled release suspension, emulsions and the like. Other controlled release compositions include parenteral compositions such as lipophilic depots (for example, fatty acids, waxes, oils), controlled release injections in the form of an emulsion or suspension including injections based on liposomal, nanoparticle and microparticle technology.

The term “pharmaceutical composition,” as used herein, may include tablets, capsules, granules, powders and the like.

The term “pharmaceutically acceptable excipients,” as used herein includes any physiologically inert additives that are routinely used in pharmaceutical dosage forms. Pharmaceutically acceptable excipients are selected from the group comprising diluents, disintegrants, binders, surfactants, lubricants and glidants.

Suitable diluents are selected from the group comprising microcrystalline cellulose, *e.g.*, microcrystalline PH 101 and microcrystalline PH 102; lactose, *e.g.*, directly compressible lactose (Pharmatose[®] DCL 11), lactose monohydrate, lactose anhydrous, and spray dried lactose; sugar alcohols, *e.g.* sorbitol, erythritol, xylitol, mannitol; sugars, *e.g.*, sucrose, Di-Pac[®] (a directly compressible, co-crystallized sugar consisting of 97% sucrose and 3% maltodextrin), starch, *e.g.*, pregelatinized starch. Preferably, the diluents are microcrystalline cellulose, preferably microcrystalline PH 101, directly compressible lactose, sorbitol, pregelatinized starch and combinations thereof.

Suitable disintegrants are selected from the group comprising croscarmellose sodium, hydroxypropyl cellulose (L-HPC), crospovidone, carboxymethyl cellulose sodium, carboxymethyl cellulose calcium, sodium starch glycolate, gums, alginic acid or alginates, pregelatinized starch, corn starch, modified starch, carboxymethyl starch, polyacrylates and combinations thereof.

Suitable binders are selected from the group comprising povidone; copovidone; celluloses, *e.g.* hydroxypropyl methylcellulose, in particular, HPMC[®] E-5, hydroxy ethylcellulose, hydroxypropyl cellulose, methylcellulose and ethylcellulose; starch, *e.g.* pregelatinized starch and low density starch; microcrystalline cellulose; lactose; xanthan gum; gum acacia; sodium alginate; propylene glycol; polyvinyl alcohol; corn syrup; methacrylates; carboxyvinyl polymers *e.g.* carbomers and combinations thereof.

Suitable surfactants are selected from the group comprising a copolymer consisting of a central hydrophobic block of polypropylene glycol flanked by two hydrophilic blocks of polyethylene glycol (Poloxamer), polyoxyethylene sorbitan monooleate (Tween[®] 80), sodium lauryl sulphate, sorbitan monolaurate, sorbitan trioleate, polyoxyethylene sorbitol, sorbitan tristearate, polyoxyethylene sorbitol hexastearate, ethylene glycol fatty acid ester, propylene glycol fatty acid ester, propylene glycol monostearate, glycerol monostearate and sorbitan monooleate. Preferably, suitable surfactants are copolymers consisting of a central hydrophobic block of polypropylene glycol flanked by two hydrophilic blocks of polyethylene glycol (Poloxamer).

Suitable lubricants are selected from the group comprising magnesium stearate, talc and silica.

Suitable glidants are selected from the group comprising magnesium stearate, stearic acid, calcium stearate, colloidal silicon dioxide, starch, talc and combinations thereof.

While the present invention has been described in terms of its specific aspects and embodiments, certain modifications and equivalents will be apparent to those skilled in the art, and are intended to be included within the scope of the present invention.

Methods:

X-ray diffraction patterns were recorded using a PANalytical® X'pert PRO with X'celerator as the detector, 0.02 as step size, and 3-40° 2θ as range, using CuKα radiation.

DSC endotherm of the sample was recorded using a Mettler Toledo® 821e. Range 30-300°C, 10°/minute hermetically sealed crucible.

DTA TG was recorded using a Shimadzu™ DTG-60A instrument.

FT-IR was recorded using a Perkin Elmer® spectrum using KBr disc method.

Raman spectrum was recorded using a Ranishaw® Spectrometer.

SEM image was recorded on a JEOL microscope.

Aspect Ratio was determined using a Morphology® G3 instrument.

The Karl Fischer method may be used to determine the water content of the pharmaceutical compositions.

The following examples are for illustrative purpose only and should not be construed as limiting the scope of the invention in any way.

EXAMPLES

Example 1: Preparation of a crystalline Form X of bosutinib

Bosutinib (1 g) was suspended in water (10 mL) and the mixture was stirred for 5 hours at 25°C. The suspension was kept for 15 hours and then stirred again for 4 hours at 25°C. It was filtered through Whatman filter paper and the residue obtained was dried under nitrogen atmosphere to obtain the title compound, Form X of bosutinib.

Weight: 0.8 g

Example 2: Preparation of a pharmaceutical composition of Form X of bosutinib

Ingredients	Quantity (Mg)
Bosutinib	100.00
Microcrystalline cellulose	13.250
Croscarmellose sodium	3.000
Povidone	3.000
Poloxamer	4.500
Water	q.s.

Procedure:

- (i) Bosutinib, microcrystalline cellulose and croscarmellose sodium were sifted and mixed together.
- (ii) Povidone and poloxamer were dissolved in water.
- (iii) The mixture of step (i) was granulated with the solution of step (ii).
- (iv) The granules of step (iii) were analyzed by XRPD at 4 hours, 24 hours, and 48 hours.

The XRPD at the 4 hours, 24 hours, and 48 hours showed the characteristic peaks of Form X.

Example 3: Preparation of a pharmaceutical composition of Form X of bosutinib

Ingredients	Quantity (Mg)
Bosutinib	100.00
Povidone	3.000
Poloxamer	4.500
Water	q.s.

Procedure:

- (i) Bosutinib was sifted.
- (ii) Povidone and poloxamer were dissolved in water.
- (iii) The bosutinib of step (i) was granulated with the solution of step (ii).
- (iv) A part of the granules of step (iii) were dried at 50°C.
- (v) The wet and dry granules of steps (iii) and (iv) were analyzed by XRPD.

The XRPD showed the characteristic peaks of Form X in these granules. The dried granules of step (iv) were stored for 49 days at room temperature in a triple laminated polybag, and analyzed by XRPD. The resulting XRPD after 49 days storage at room temperature showed the characteristic peaks of Form X.

Example 4: Preparation of pharmaceutical composition of Form X of bosutinib

Ingredients	Quantity (Mg)
Bosutinib	100.00
Microcrystalline cellulose	13.250
Croscarmellose sodium	3.000
Povidone	3.000
Poloxamer	4.500
Water	q.s.

Procedure:

- (i) Bosutinib, microcrystalline cellulose and croscarmellose sodium were sifted and mixed together.
- (ii) Povidone and poloxamer were dissolved in water.
- (iii) The mixture of step (i) was granulated with the solution of step (ii).
- (iv) The wet granules of step (iii) were stored in a closed container.
- (v) The stored granules of step (iv) were analyzed by XRPD at 5.5 hour, 24 hour, 48 hours, 72 hours and 7 days.
- (vi) The stored granules of step (iv) were analyzed by XRPD after drying respectively at 5.5 hours, 24 hours, 48 hours, 72 hours and 7 days. The granules were dried at 50°C.

The XRPD of both wet and dry granules at 5.5 hours, 24 hours, 48 hours, 72 hours and 7th day of storage showed the characteristic peaks of Form X.

Example 5: Pharmaceutical composition of Form X of bosutinib (Tablet):

Ingredients	mg/cap (500 mg)
Bosutinib	500.000
Microcrystalline cellulose	66.250
Croscarmellose sodium	15.000
Povidone	15.000
Poloxamer 188	22.500
Microcrystalline cellulose	80.850
Croscarmellose sodium	15.000
Magnesium stearate	5.400
Opadry® Red 85F15642	25.000

Composition of Opadry® Red 85F15642:

Ingredients
Polyvinyl alcohol-part. hydrolyzed (USP,FCC,PhEur, JPE)
Titanium dioxide (USP,FCC, PhEur, JP)
Macrogol/PEG (NF, FCC, PhEur, JECFA, JP)
Talc (USP,FCC, PhEur, JP)
Iron Oxide Red (NF,JPE)

The pharmaceutical composition of bosutinib in the form of tablets showed the characteristic XRPD peaks of Form X, when tested after 3 months.

Claims:

1. A crystalline Form X of bosutinib, wherein the crystalline form is stable.
2. The crystalline Form X of bosutinib according to claim 1, characterized by an XRPD pattern having interplanar spacing (d) values at about 6.3, 6.1, 5.9, 5.5, and 4.8 Å.
3. The crystalline Form X of bosutinib according to claim 1, further characterized by an XRPD pattern having additional interplanar spacing (d) values at about 10.9, 10.3, 4.5, 4.4, 3.7, and 3.6 Å.
4. The crystalline Form X of bosutinib according to claim 1, characterized by a differential scanning calorimetry (DSC) thermogram having endothermic peaks at about 91°C, 121°C and 152°C.
5. The crystalline Form X of bosutinib according to claim 1, characterized by a DTA TG having endothermic peaks at about 48°C, 61°C and 81°C.
6. The crystalline Form X of bosutinib according to claim 1, characterized by plate shape particles having a crystal habit, wherein the ratio between the width and the length of the crystals is between 1:3 and 1:1.
7. The crystalline Form X of bosutinib according to claim 1, characterized by plate shape particles having an aspect ratio of about 0.68.
8. The crystalline Form X of bosutinib according to claim 1, characterized by an XRPD pattern substantially as depicted in Figure 1.
9. The crystalline Form X of bosutinib according to claim 1, characterized by a DSC thermogram substantially as depicted in Figure 2.
10. The crystalline Form X of bosutinib according to claim 1, characterized by a DTA TG substantially as depicted in Figure 3.
11. The crystalline Form X of bosutinib according to claim 1, characterized by a FT-IR spectra substantially as depicted in Figure 4.
12. The crystalline Form X of bosutinib according to claim 1, characterized by a Raman spectra substantially as depicted in Figure 5.
13. The crystalline Form X of bosutinib according to claim 1, characterized by a SEM image substantially as depicted in Figure 6.
14. A process for the preparation of a crystalline Form X of bosutinib comprising treating bosutinib with water.

15. A pharmaceutical composition comprising a crystalline Form X of bosutinib and one or more pharmaceutically acceptable excipients.
16. The pharmaceutical composition according to claim 15, wherein the excipient is selected from the group consisting of one or more of a diluent, a disintegrant, a binder, a surfactant, a lubricant and a glidant.
17. A process for the preparation of a pharmaceutical composition comprising Form X of bosutinib and one or more pharmaceutically acceptable excipients selected from one or more of a diluent, a disintegrant, a binder, a surfactant, a lubricant and a glidant wherein the process comprises the steps of:
 - i) granulating bosutinib with an aqueous solution of a binder and/or a surfactant, and
 - ii) optionally drying the granules.
18. The pharmaceutical composition according to claim 17, wherein the granules are further processed into dosage forms such as tablets and capsules.
19. Use of a crystalline Form X of bosutinib for treating cancer.

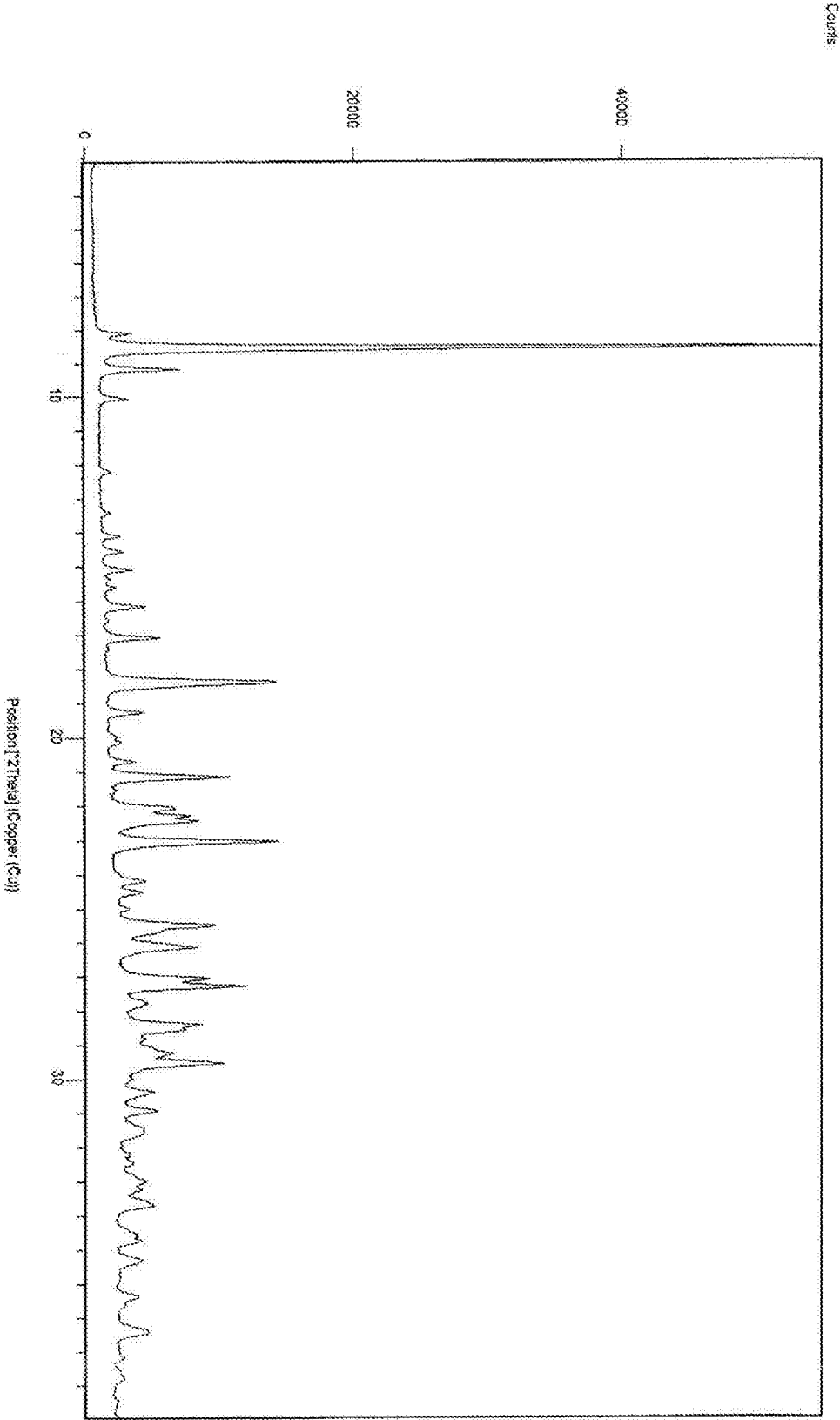


FIGURE 1

FIGURE 2

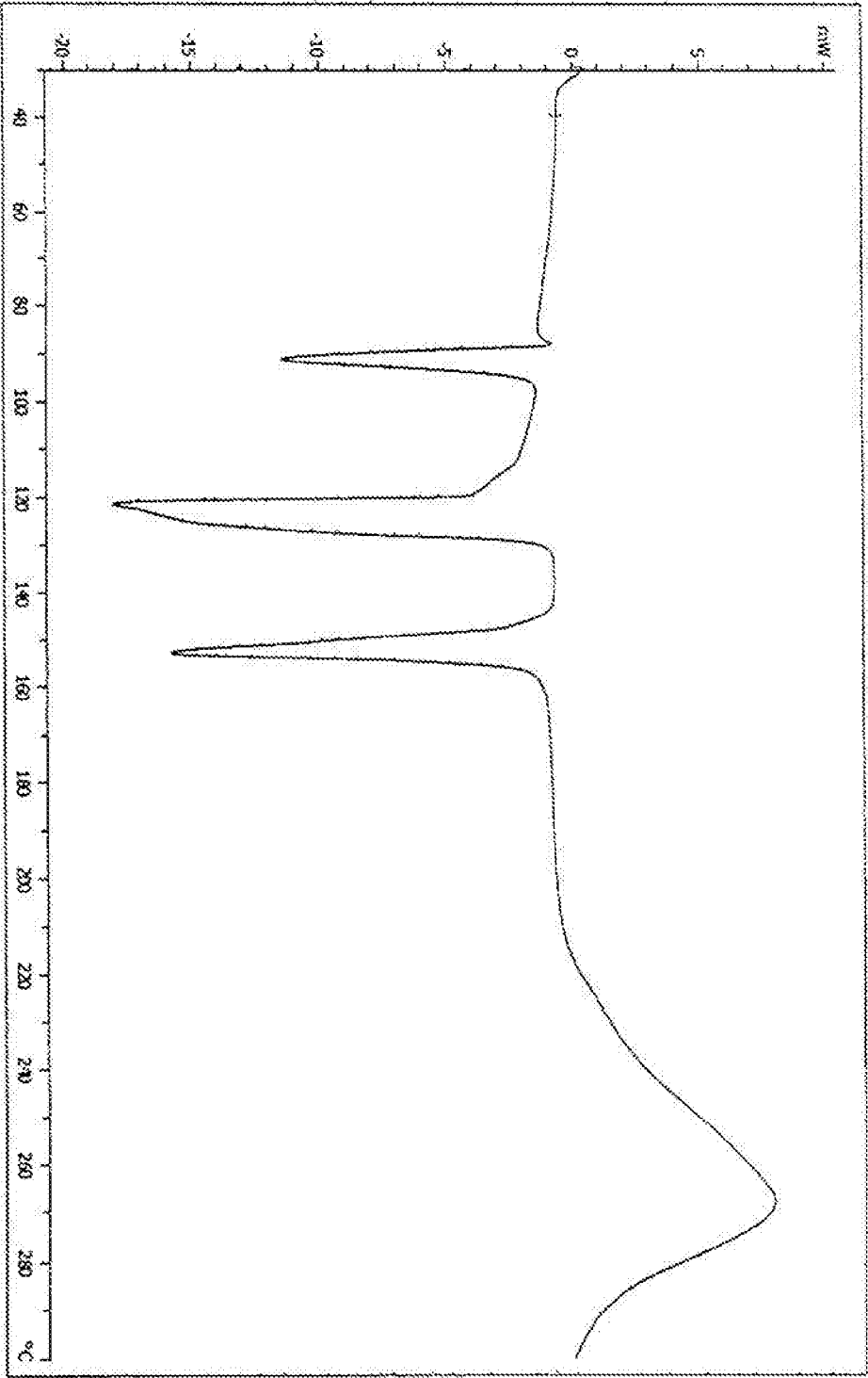
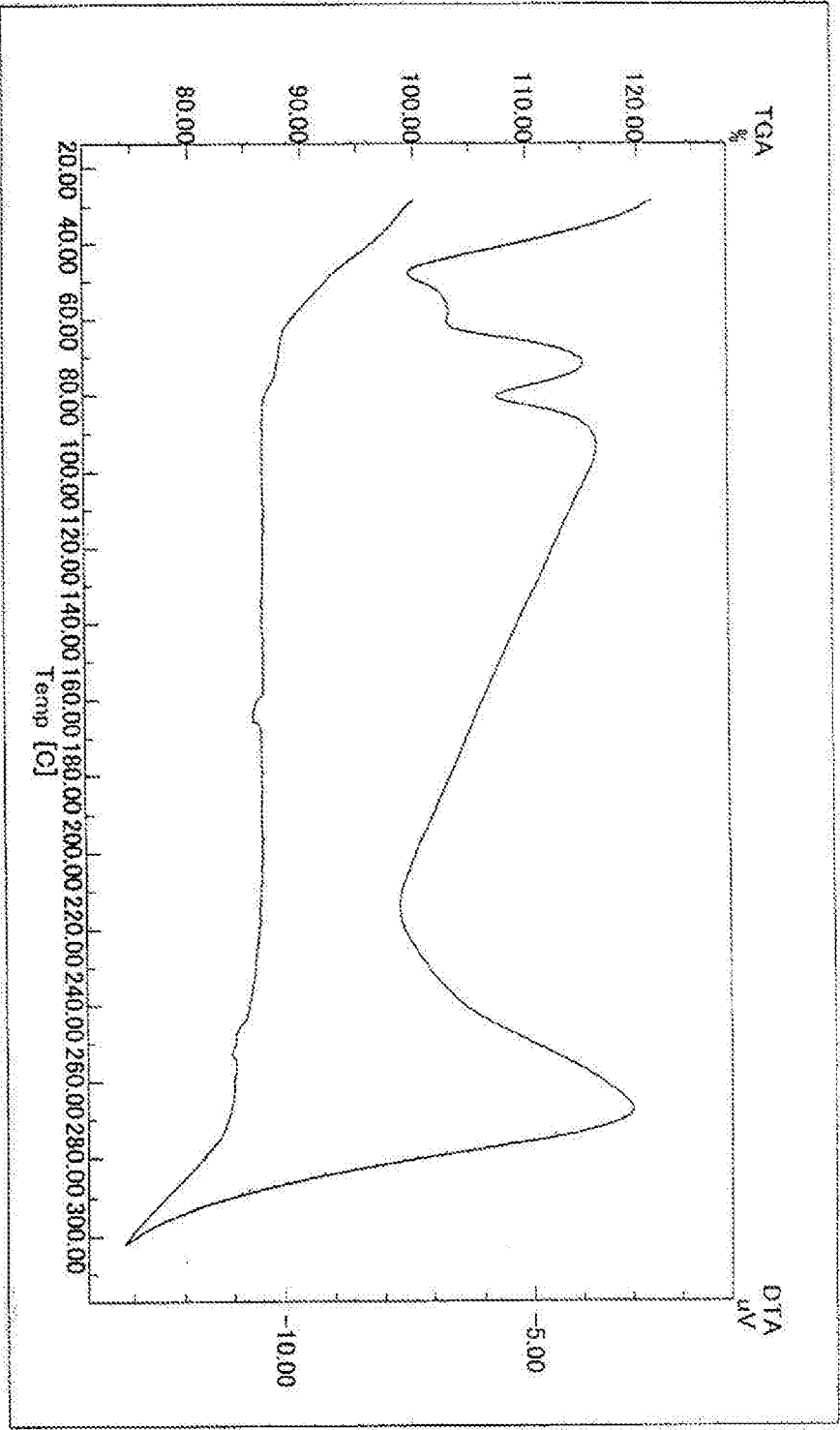


FIGURE 3



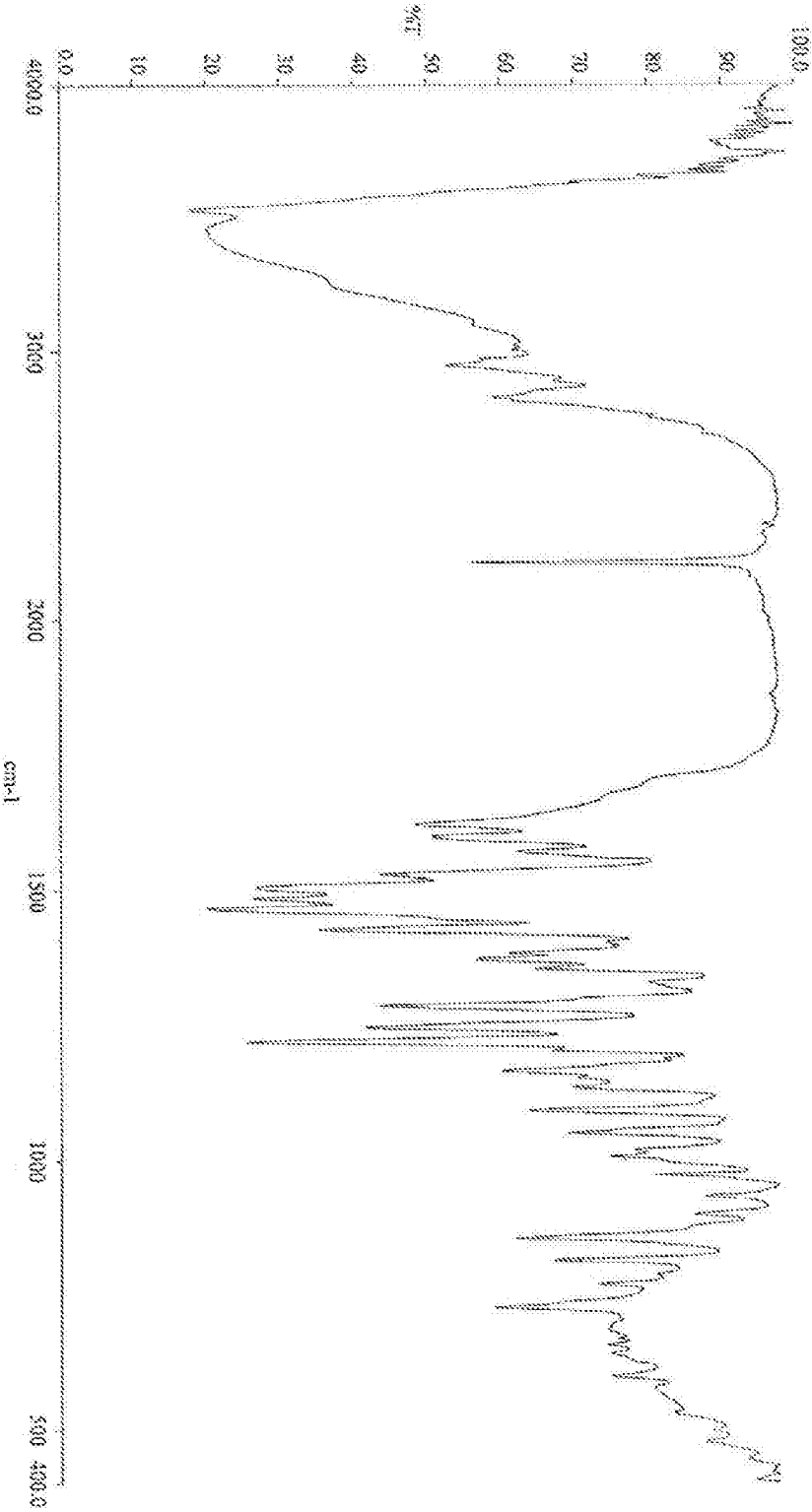


FIGURE 4

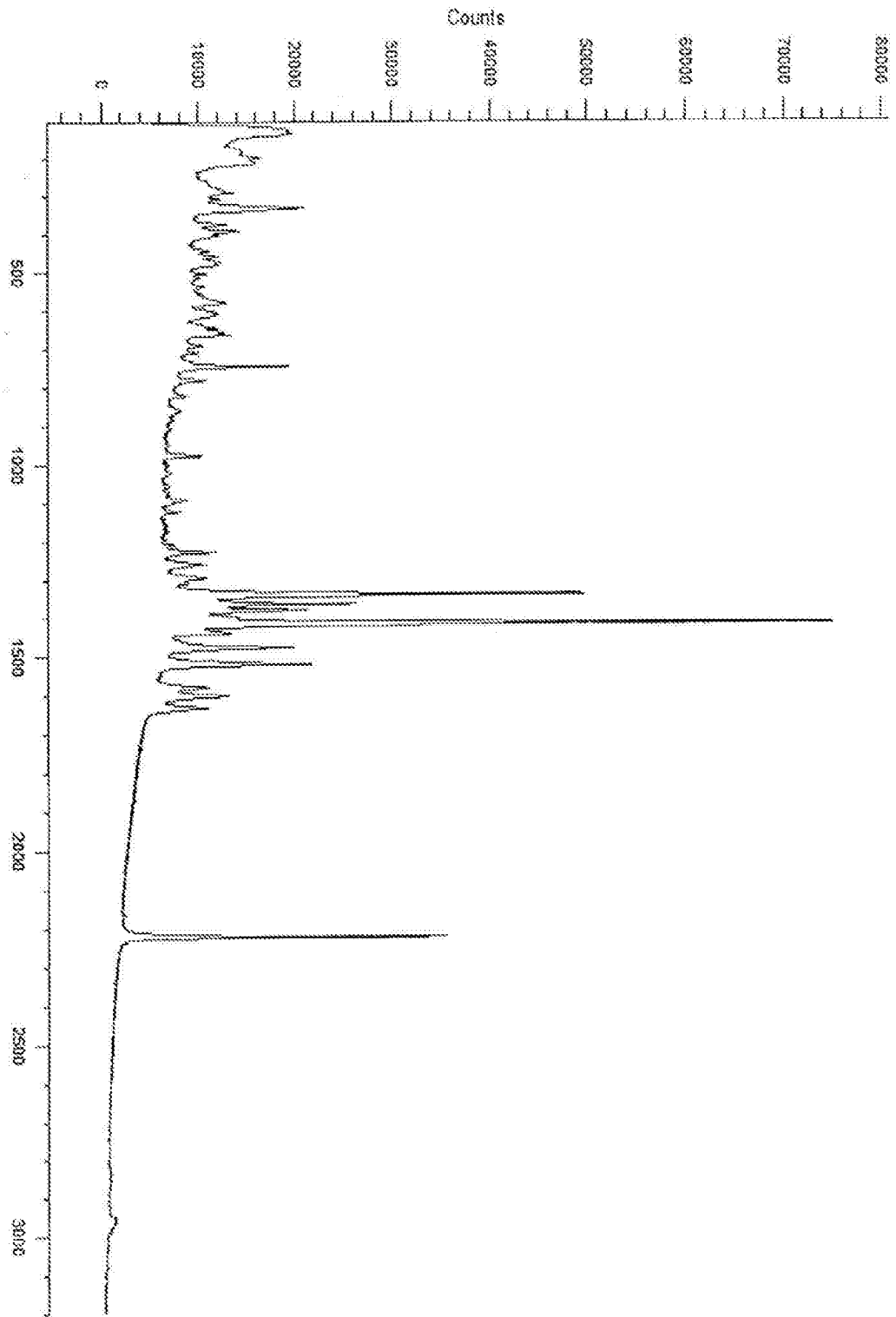
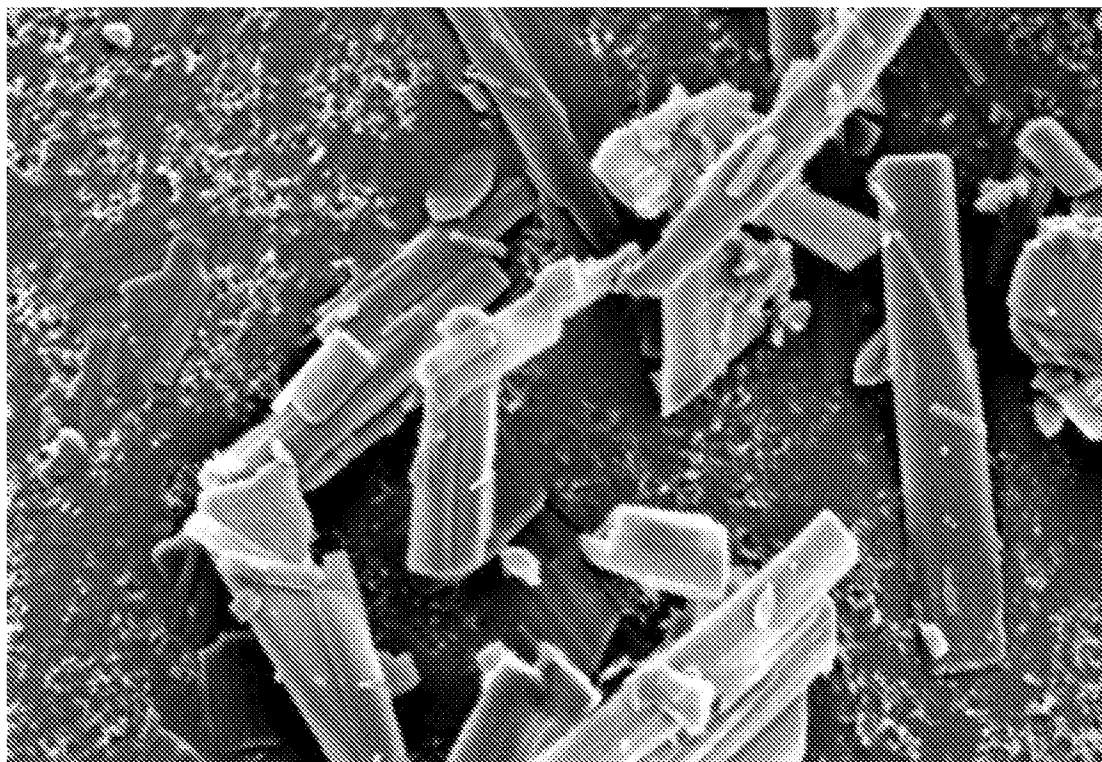


FIGURE 5



Counts

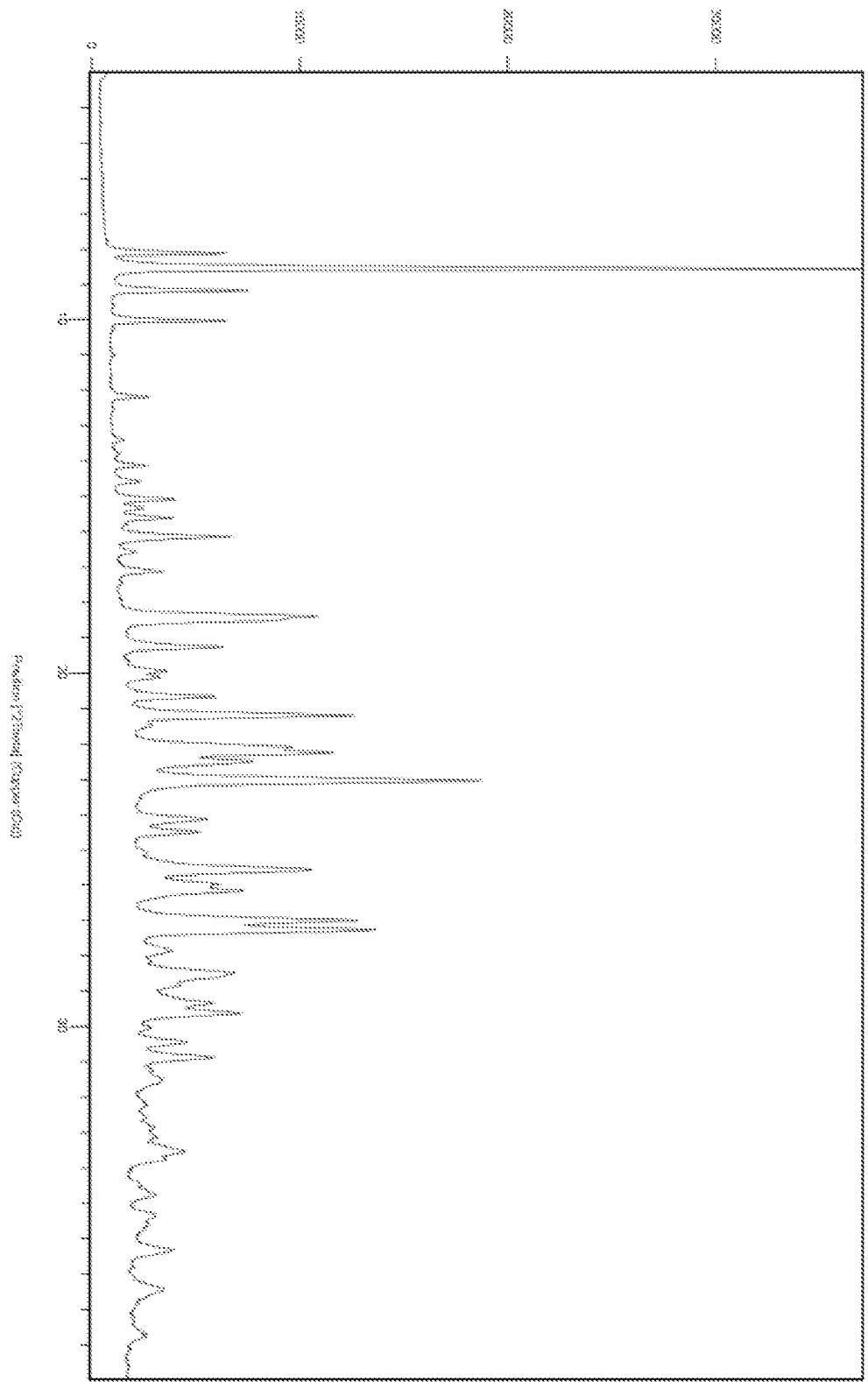


FIGURE 7

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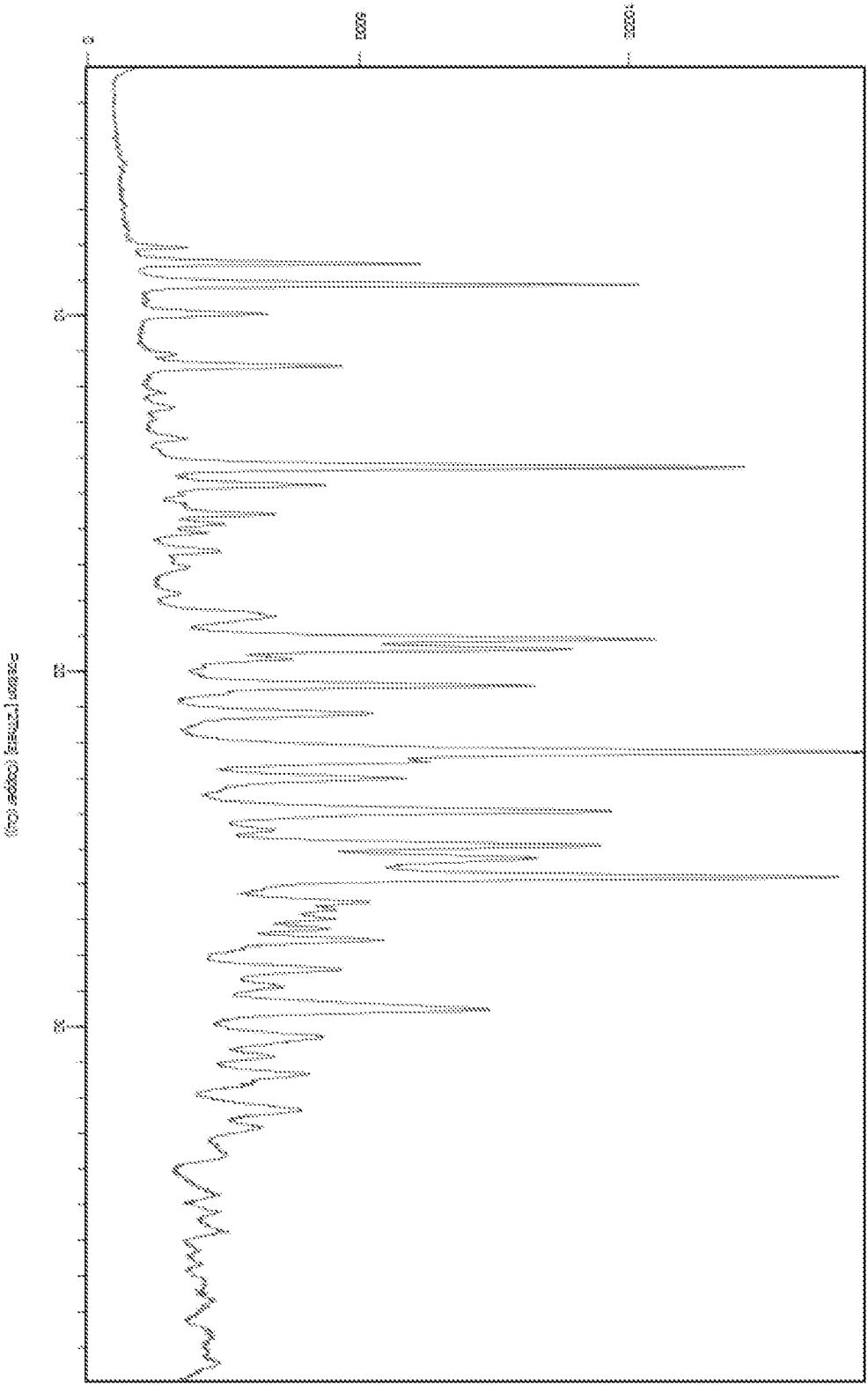


FIGURE 8

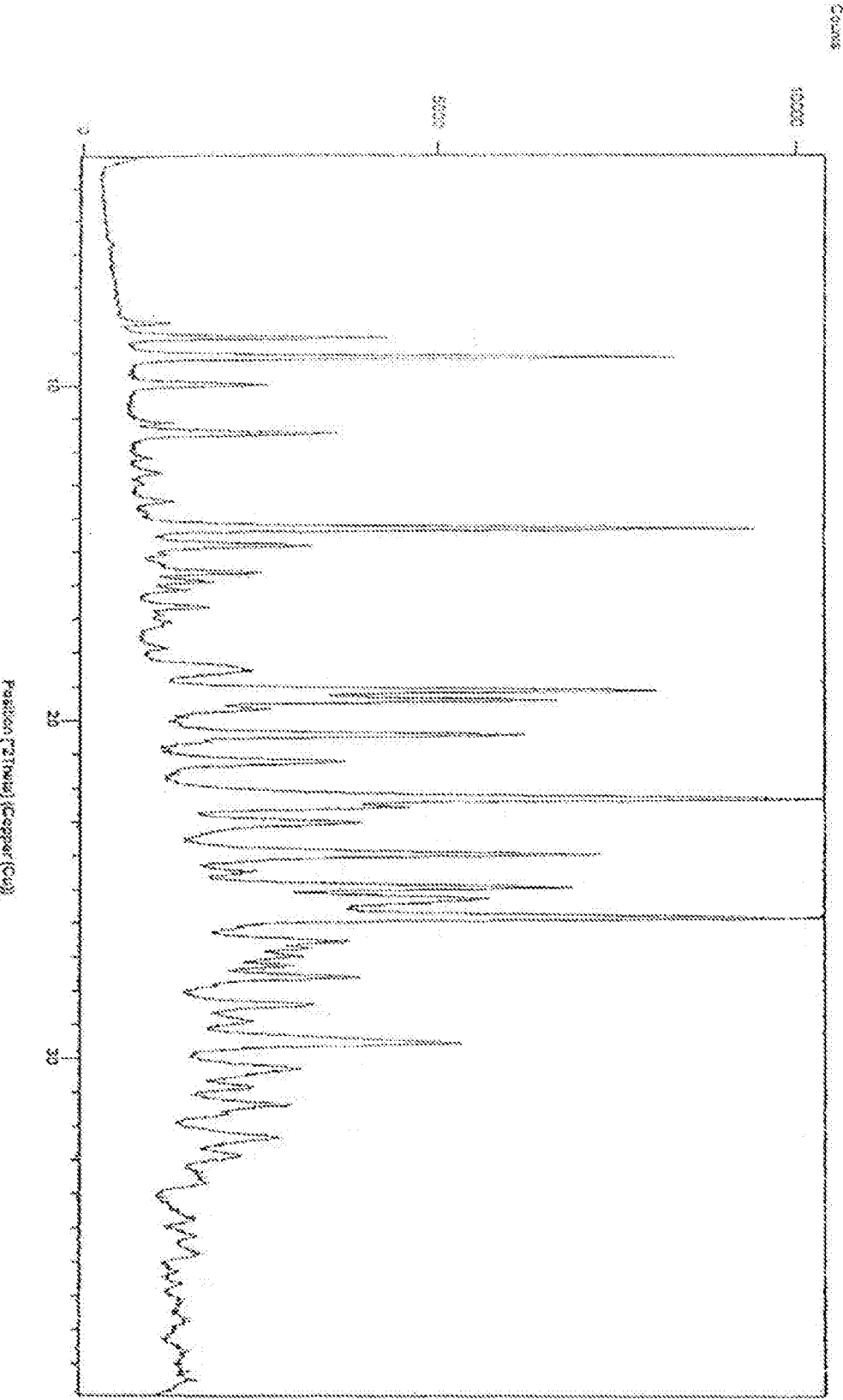


FIGURE 9

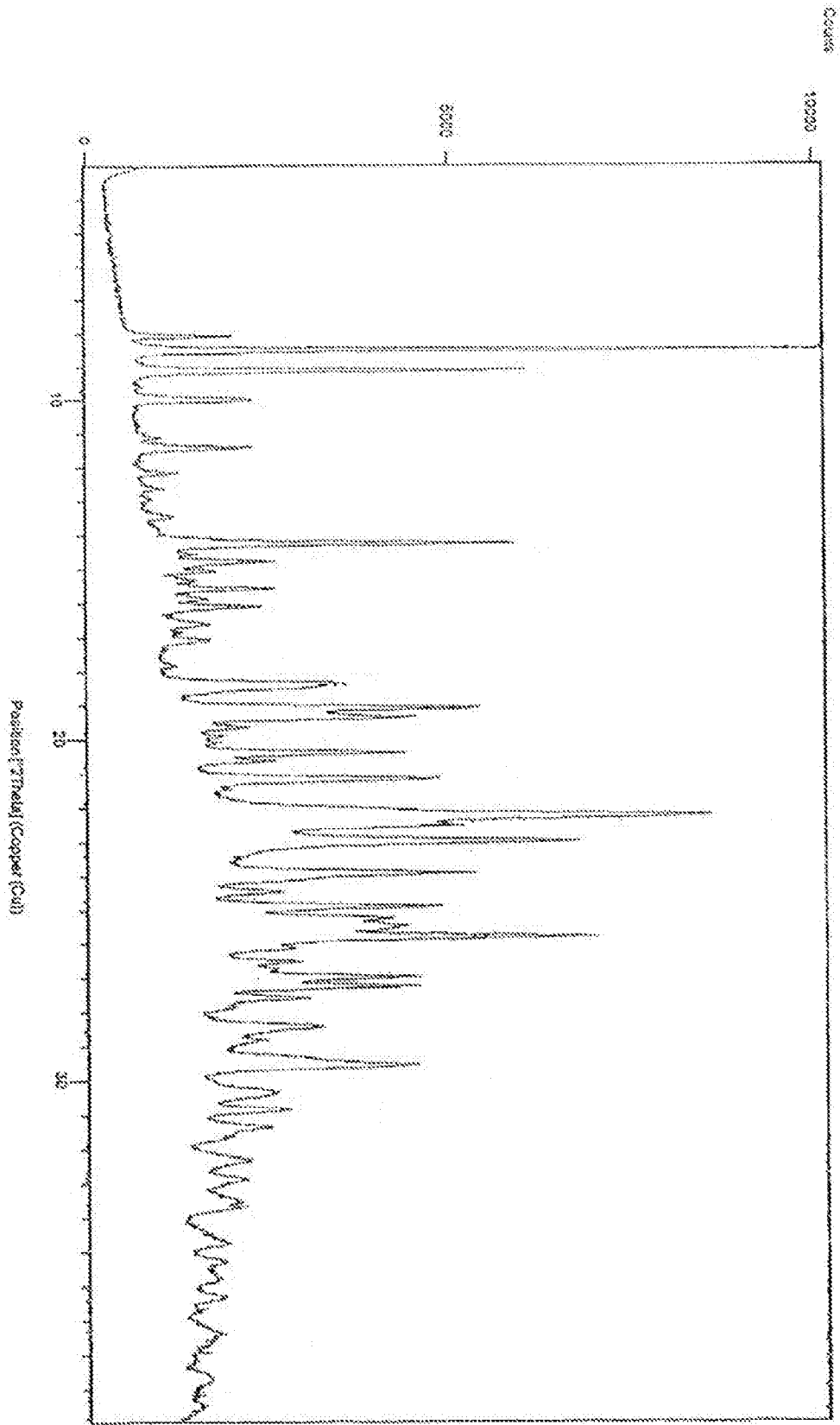


FIGURE 10

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB17/51042

A. CLASSIFICATION OF SUBJECT MATTER
 IPC - A61K 31/4706, 31/4709, 31/496 (2017.01)
 CPC - A61K 31/4706, 31/4709, 31/496

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)

See Search History document

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

See Search History document

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

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2010/0324066 A1 (TESCONI, MS et al) 23 December 2010; abstract; figure 4; paragraphs [0003], [0014], [0024], [0026]-[0027], [0032]-[0033], [0041]-[0042], [0047]-[0050]; claim 12	1-3, 8, 14-16, 19
Y		6-7, 17-18
Y	THEIVASANTHI, et al. X-Ray Diffraction Studies of Copper Nanopowder. 31 Mar 2010, pp. 1-6 [online], [retrieved on 2017-05-18]. Retrieved from the Internet <URL: https://arxiv.org/abs/1003.6068 > < https://arxiv.org/ftp/arxiv/papers/1003/1003.6068.pdf >; page 4, lines 15-25	1
Y	WO 2015/123758 A1 (APOTEX INC) 27 August 2015; abstract; page 4, lines 25-30; page 23, lines 28-31; page 24, lines 9-10; figure 13	17-18
Y	US 2010/0234469 A1 (ESCUDE, AG et al) 16 September 2010; abstract; figure 2; paragraphs [0002], [0021]-[0022], [0082]	6-7
Y	GRIVENNIKOV, SI et al. Immunity, Inflammation, and Cancer. Cell, Vol. 140, 19 March 2010, pp. 883-899; abstract	6
Y	US 9,051,250 B2 (SYNTA PHARMACEUTICALS CORP) 9 June 2015; abstract; column 8, lines 47-53	7
A	WO 2015/149727 A1 (ZENTIVA, K.S) 8 October 2015; page 2, paragraph 1	4-5, 9-12
A	US 2012/0270108 A1 (SHIN, CS et al) 25 October 2012; figure 3A; paragraphs [0053], [0109]	13

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

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Date of the actual completion of the international search

18 May 2017 (18.05.2017)

Date of mailing of the international search report

15 JUN 2017

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