(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
16 April 2020 (16.04.2020)

WIPO | PCT

(10) International Publication Number
WO 2020/075199 A1

(51) International Patent Classification:
C07D 213/81 (2006.01) *C07D 213/82* (2006.01)
C07D 207/16 (2006.01) *C07D 473/12* (2006.01)

(21) International Application Number:
PCT/IN2019/050759

(22) International Filing Date:
11 October 2019 (11.10.2019)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
201841038858 12 October 2018 (12.10.2018) IN
201941008154 01 March 2019 (01.03.2019) IN

(71) Applicant: **MYLAN LABORATORIES LIMITED** [IN/IN]; Plot No 564/A/22, Road No 92, Jubilee Hills, Hyderabad 500033 (IN).

(72) Inventors: **JETTI, Ramakoteswara Rao**; Mylan Laboratories Ltd, Plot No 564/A/22, Road No 92, Jubilee Hills, Hyderabad 500033 (IN). **PILLI, Narasimha Murty**; Mylan Laboratories Limited, Plot No 564/A/22, Road No 92, Jubilee Hills, Hyderabad 500033 (IN). **PATHURI, Srinivasarao**; Mylan Laboratories Ltd, Plot No 564/A/22, Road No 92, Jubilee Hills, Hyderabad 500033 (IN). **GOLIVI, Ramamohana Rao**; Mylan Laboratories Ltd, Plot No 564/A/22, Road No 92, Jubilee Hills, Hyderabad 500033 (IN). **JAYACHANDRA, Sureshbabu**; Mylan Laboratories Ltd, Plot No 564/A/22, Road No 92, Jubilee Hills, Hyderabad 500033 (IN).

(74) Agent: **HASAN, Afzal** et al.; Hasan and Singh, Flat No. 04, Sree Nilayam Apartment, Plot No. 12, Camelot Layout (Near Chirec Public School), Kondapur, Hyderabad 500084 (IN).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
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— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*
— *of inventorship (Rule 4.17(iv))*

Published:
— *with international search report (Art. 21(3))*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*
— *in black and white; the international application as filed contained color or greyscale and is available for download from PATENTSCOPE*

(54) Title: POLYMORPHIC FORMS OF VADADUSTAT

(57) Abstract: Described is a process for the preparation of crystalline Form C of Vadadustat. Also described are Vadadustat co-crystals and processes for the preparation thereof.

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POLYMORPHIC FORMS OF VADADUSTAT

CROSS-REFERENCE TO RELATED APPLICATIONS

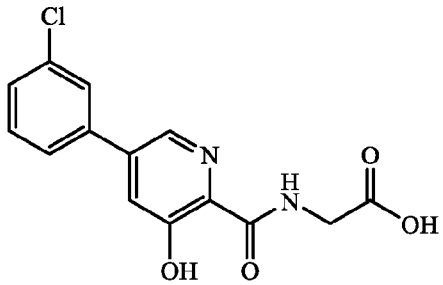
This application claims the benefit of earlier Indian provisional patent application No. IN201941008154 filed on March 1, 2019; and Indian provisional patent application No. IN201841038858 filed on October 12, 2018, the entire contents of each of which are incorporated by reference herein.

FIELD OF THE INVENTION

The present invention relates to processes for the preparation of crystalline Form C of Vadadustat. This invention also relates to Vadadustat co-crystals and processes for the preparation thereof.

BACKGROUND OF THE INVENTION

Vadadustat was first disclosed in U.S Patent No. 7,811,595. Vadadustat is chemically known as N-[[5-(3-chlorophenyl)-3-hydroxy-2-pyridinyl]carbonyl]glycine, having the following structure:



Vadadustat

PCT Publication No. WO2015073779 discloses Vadadustat crystalline Form A, Form B and Form C.

The inventors of the present disclosure have developed a process for the preparation of crystalline Form C of Vadadustat. This invention also relates to Vadadustat co-crystals and processes for their preparation.

SUMMARY OF THE INVENTION

A first aspect of the present invention is to provide an improved process for the preparation of crystalline Form C of Vadadustat, comprising the steps of:

a) dissolving Vadadustat in an ether solvent at elevated temperature;
b) cooling the solution to room temperature;

c) adding the step (b) solution to an anti-solvent optionally containing a seed of crystalline form C of Vadadustat; and
d) isolating the crystalline Form C of Vadadustat.

Another aspect of the present invention is to provide a Vadadustat proline co-crystal.

Another aspect of the present invention is to provide a Vadadustat L-Proline co-crystal (1:2) characterized by a powder X-ray diffraction pattern having peaks at 8.12, 16.27, 18.72 and 25.14 ± 0.2 degrees 2θ.

In a specific aspect, Vadadustat L-Proline co-crystal (1:2) may be characterized by the powder X-ray diffraction pattern shown in Figure 7.

Another aspect of the present invention is to provide a Vadadustat L-Proline co-crystal (1:1) characterized by a powder X-ray diffraction pattern having peaks at 10.23, 15.72, 16.15 and 19.22 ± 0.2 degrees 2θ.

In a specific aspect, Vadadustat L-Proline co-crystal (1:1) may be characterized by the powder X-ray diffraction pattern shown in Figure 8.

Another aspect of the present invention is to provide a Vadadustat D-Proline co-crystal (1:2) characterized by a powder X-ray diffraction pattern having peaks at 8.11, 16.28, 18.73 and 25.13 ± 0.2 degrees 2θ.

In a specific aspect, Vadadustat D-Proline co-crystal (1:2) may be characterized by the powder X-ray diffraction pattern shown in Figure 9.

Another aspect of the present invention is to provide a Vadadustat D-Proline co-crystal (1:1) characterized by a powder X-ray diffraction pattern having peaks at 10.33, 15.83, 16.27 and 19.33 ± 0.2 degrees 2θ.

In a specific aspect, Vadadustat D-Proline co-crystal (1:1) may be characterized by the powder X-ray diffraction pattern shown in Figure 10.

Another aspect of the present invention is to provide a process for the preparation of Vadadustat Proline co-crystal, comprising the steps of:

a) mixing Vadadustat with proline in a solvent to form a suspension;
b) heating the suspension to 55-70°C;
c) slowly cooling the suspension to room temperature; and
d) isolating Vadadustat proline co-crystal from the suspension.

Another aspect of the present invention is to provide a Vadadustat caffeine co-crystal (1:1) characterized by a powder X-ray diffraction pattern having peaks at 12.62, 25.11, 25.92 and 26.19 ± 0.2 degrees 2θ.

In a specific aspect, Vadadustat caffeine co-crystal (1:1) may be characterized by the powder X-ray diffraction pattern shown in Figure 11.

Another aspect of the present invention is to provide a process for the preparation of Vadadustat caffeine co-crystal (1:1) comprising suspending Vadadustat and caffeine in a solvent at room temperature and isolating Vadadustat caffeine co-crystal (1:1).

Another aspect of the present invention is to provide a Vadadustat nicotinamide co-crystal (1:1) characterized by a powder X-ray diffraction pattern having peaks at 14.75, 16.78, 17.61 and 18.44 ± 0.2 degrees 2θ.

In a specific aspect, Vadadustat nicotinamide co-crystal (1:1) may be characterized by the powder X-ray diffraction pattern shown in Figure 12.

Another aspect of the present invention is to provide a process for the preparation of Vadadustat nicotinamide co-crystal (1:1) comprising the steps of:

a) dissolving nicotinamide in alcohol solvent at a temperature of 60±5°C;
b) adding the Vadadustat and a ketone solvent to the step (a) solution at 60±5°C temperature;
c) cooling the reaction mass to a temperature of 25±5°C; and
d) isolating the Vadadustat nicotinamide co-crystal.

Another aspect of the present invention is to provide a Vadadustat isonicotinamide co-crystal (2:1) characterized by a powder X-ray diffraction pattern having peaks at 14.26, 15.29, 18.20 and 20.15 ± 0.2 degrees 2θ.

In a specific aspect, Vadadustat isonicotinamide co-crystal (2:1) may be characterized by the powder X-ray diffraction pattern shown in Figure 13.

Another aspect of the present invention is to provide a process for the preparation of Vadadustat isonicotinamide co-crystal (2:1) comprising the steps of:

a) suspending isonicotinamide in alcohol solvent at a temperature of 60±5°C;
b) adding the Vadadustat and ketone solvent to step (a) suspension at 60±5°C temperature;
c) cooling the reaction mass to a temperature of 25±5°C; and
d) isolating the Vadadustat isonicotinamide co-crystal.

BRIEF DESCRIPTION OF THE FIGURES

Further aspects of the present invention together with additional features contributing thereto and advantages accruing therefrom will be apparent from the following description of embodiments of the disclosure, which are shown in the accompanying drawing figures wherein:

Figure. 1 is an X-ray powder diffractogram of amorphous Vadadustat.
Figure. 2 is an X-ray powder diffractogram of crystalline form B of Vadadustat.
Figure. 3 is an X-ray powder diffractogram of crystalline form C of Vadadustat.
Figure. 4 is a differential scanning calorimetry (DSC) analysis of crystalline form C of Vadadustat.
Figure. 5 is a thermal gravimetric analysis (TGA) of crystalline form C of Vadadustat.
Figure. 6 is an X-ray powder diffractogram of crystalline form of Vadadustat prepared as per reference example.
Figure. 7 is an X-ray powder diffractogram of Vadadustat L-Proline co-crystal in the molar ratio of 1:2.
Figure. 8 is an X-ray powder diffractogram of Vadadustat L-Proline co-crystal in the molar ratio of 1:1.
Figure. 9 is an X-ray powder diffractogram of Vadadustat D-Proline co-crystal in the molar ratio of 1:2.
Figure. 10 is an X-ray powder diffractogram of Vadadustat D-Proline co-crystal in the molar ratio of 1:1.
Figure. 11 is an X-ray powder diffractogram of Vadadustat Caffeine co-crystal in the molar ratio of 1:1.
Figure. 12 is an X-ray powder diffractogram of Vadadustat Nicotinamide co-crystal in the molar ratio of 1:1.
Figure. 13 is an X-ray powder diffractogram of Vadadustat Isonicotinamide co-crystal in the molar ratio of 2:1.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a process for the preparation of crystalline Form C of Vadadustat. This invention also relates to Vadadustat proline co-crystals and processes for their preparation thereof.

Within the context of the present disclosure, the term "about" when modifying a temperature measurement means the recited temperature plus or minus five degrees. Within the context of the present disclosure, the term "about" when modifying an absolute measurement, such as time, mass, or volume, means the recited value plus or minus 10% of the value.

Within the context of the present disclosure, the term "elevated temperature" means a temperature above 25°C and it is depending on the organic solvent ratio, water/organic solvent ratio and the concentration of Vadadustat.

As used herein, parenthetical ratios such as "(1:2)" and "(1:1)" following a reference to a co-crystal designate the molar ratio of Vadadustat to the other component of the co-crystal.

The PXRD measurements were carried out using PAN analytical X'Pert PRO powder diffractometer equipped with goniometer of θ/θ configuration and X'Celerator detector. The Cu-anode X-ray tube was operated at 40kV and 30mA. The experiments were conducted over the 2θ range of 2.0°-50.0°, 0.030° step size and 50 seconds step time.

The present invention relates to a process for the preparation of crystalline Form C of Vadadustat. This invention also relates to Vadadustat proline co-crystals and processes for their preparation thereof.

In an embodiment, the present invention provides a process for the preparation of amorphous Vadadustat comprising the steps of:

a) dissolving Vadadustat in a mixture of organic solvent and water at elevated temperature;
b) cooling the solution to room temperature; and
c) isolating the amorphous Vadadustat.

Within the context of this embodiment of the present invention, Vadadustat is dissolved in a mixture of organic solvent and water. The solvent employed may include acetonitrile, acetone, 1,4-dioxane and tetrahydrofuran. In particular, useful embodiments of the present invention, Vadadustat may be dissolved in a mixture of acetonitrile and water or mixture of 1,4-dioxane and water.

Within the context of this embodiment of the present invention, the organic solvent/water ratio employed is 5:1 to 1:5. In particular, useful embodiments, the organic solvent/water ratio is 3:1 or 1:1.

Within the context of this embodiment, Vadadustat may be dissolved at an elevated temperature about 50°C to about 65°C. In particular, useful embodiments, of the present invention, Vadadustat may be dissolved at about 55°C.

Within the context of this embodiment of the present invention, isolation of the amorphous Vadadustat can be done using any techniques in the art such as, lyophilization, decantation, filtration by gravity or suction, centrifugation, slow evaporation, distillation, ATFD and spray-drying. In particular, useful embodiments of the present invention, the amorphous Vadadustat is isolated by lyophilization.

Another embodiment of the present invention is to provide a process for the preparation of crystalline Form B of Vadadustat comprising the steps of:

a) dissolving Vadadustat in an organic solvent at elevated temperature;
b) cooling the solution to room temperature; and
c) isolating the crystalline Form B of Vadadustat.

Within the context of this embodiment of the present invention, Vadadustat is dissolved in an organic solvent. The solvent employed may include methanol, ethanol, isopropanol, n-butanol, 2-butanol, n-propanol, 2-propanol, 2-methyl-1-propanol, methyl isobutyl ketone (MIBK), methyl ethyl ketone (MEK),

and acetone. In particular, useful embodiments of the present invention, Vadadustat may be dissolved in ethanol or methyl isobutyl ketone.

Within the context of this embodiment, Vadadustat may be dissolved at an elevated temperature of about 55°C to about 70°C. In particular, in some useful embodiments of the present invention, Vadadustat may be dissolved at about 60°C.

Within the context of this embodiment of the present invention, the solution is then cooled to room temperature. In particular, in some useful embodiments of the present invention, it is cooled to about 20°C-35°C.

Within the context of this embodiment of the present invention, isolation of crystalline Form B of Vadadustat can be done using any techniques in the art such as decantation, filtration by gravity or suction, centrifugation and distillation. In particular, useful embodiments of the present invention, the crystalline Form B of Vadadustat is isolated by filtration.

Another embodiment of the present invention is to provide a process for the preparation of crystalline Form C of Vadadustat, comprising the steps of:

a) dissolving Vadadustat in an ether solvent at elevated temperature;
b) cooling the solution to room temperature;
c) adding the step (b) solution to an anti-solvent optionally containing a seed of crystalline form-C of Vadadustat; and
d) isolating the crystalline Form C of Vadadustat.

Within the context of this embodiment of the present invention, Vadadustat is dissolved in an ether solvent. The ether solvent employed may include 1,4-dioxane, tetrahydrofuran, cyclopentyl methyl ether, diisopropyl ether and methyl tert-butyl ether. In particular, useful embodiments of the present invention, Vadadustat may be dissolved in 2-methyltetrahydrofuran or methyl tert-butyl ether.

Within the context of this embodiment, Vadadustat may be dissolved at an elevated temperature of about 45°C to about 60°C. In particular, in some useful embodiments of the present invention, Vadadustat may be dissolved at about 50°C.

Within the context of this embodiment, Vadadustat clear solution is added to an anti-solvent optionally containing a seed of crystalline form C. The anti-solvent employed for this embodiment may include heptane and hexane.

Within the context of this embodiment of the present invention, isolation of Vadadustat crystalline Form C can be done using any techniques in the art such as decantation, filtration by gravity or suction,

centrifugation and distillation. In particular, useful embodiments of the present invention, the crystalline Vadadustat Form C is isolated by filtration.

Another embodiment of the present invention relates to Vadadustat proline co-crystals.

Another embodiment of the present invention, is a Vadadustat L-Proline co-crystal (1:2) that may be characterized by a powder X-ray diffraction pattern having peaks at 8.12, 16.27, 18.72 and 25.14 ± 0.2 degrees 2θ.

Within the context of this embodiment of the present invention, the Vadadustat L-Proline co-crystal (1:2) may be characterized by a powder X-ray diffraction pattern having peaks at 8.12, 11.10, 11.85, 16.27, 17.78, 18.72, 19.26, 19.50, 20.99, 21.58, 22.40, 22.98, 23.29, 23.92, 24.66, 25.14, 25.47, 25.98, 26.47, 26.84, 27.82, 28.77, 29.32, 29.73, 30.16, 30.56, 31.77, 32.44, 33.07, 33.61, 33.88, 34.64, 35.55, 36.08, 37.05, 37.54, 38.05, 39.25, 40.26, 41.98, 42.89, 44.03, 46.09, 46.72, 47.41 ± 0.2 degrees 2θ.

In another embodiment, the Vadadustat L-Proline co-crystal (1:2) may be characterized by the powder X-ray diffraction pattern shown in Figure 7.

Another embodiment of the present invention, is a Vadadustat L-Proline co-crystal (1:1) that may be characterized by a powder X-ray diffraction pattern having peaks at 10.23, 15.72, 16.15 and 19.22 ± 0.2 degrees 2θ.

Within the context of this embodiment of the present invention, the Vadadustat L-Proline co-crystal (1:1) may be characterized by a powder X-ray diffraction pattern having peaks at 5.22, 6.43, 6.77, 8.38, 8.86, 10.23, 10.46, 10.75, 11.39, 11.91, 12.88, 15.72, 16.15, 16.80, 17.23, 17.80, 18.03, 18.69, 19.22, 20.16, 20.46, 20.97, 21.80, 22.35, 22.64, 23.24, 23.97, 24.27, 24.65, 25.11, 25.96, 26.39, 27.09, 27.83, 28.13, 29.38, 30.25, 31.26, 32.53, 33.50, 33.67, 34.91, 36.36, 37.49, 38.43, 38.98, 39.94, 40.69, 41.32, 41.86, 43.20, 44.40, 45.08, 46.26, 46.75, 46.75, 48.27 49.17 ± 0.2 degrees 2θ.

In another embodiment, the Vadadustat L-Proline co-crystal (1:1) may be characterized by the powder X-ray diffraction pattern shown in Figure 8.

Another embodiment of the present invention is a Vadadustat D-Proline co-crystal (1:2) that may be characterized by a powder X-ray diffraction pattern having peaks at 8.11, 16.28, 18.73 and 25.13 ± 0.2 degrees 2θ.

Within the context of this embodiment of the present invention, the Vadadustat D-Proline co-crystal (1:2) may be characterized by a powder X-ray diffraction pattern having peaks at 8.11, 11.11, 11.85, 16.28, 17.78, 18.73, 19.50, 20.96, 21.57, 22.40, 23.27, 23.89, 24.62, 25.13, 25.42, 25.97, 26.44, 26.80,

27.81, 28.73, 29.31, 30.14, 30.54, 31.73, 32.40, 33.06, 33.55, 34.64, 36.03, 36.97, 38.03, 39.20, 40.25, 42.00, 42.60, 42.92, 44.02 ± 0.2 degrees 2θ.

In another embodiment, the Vadadustat D-Proline co-crystal (1:2) may be characterized by the powder X-ray diffraction pattern shown in Figure 9.

Another embodiment of the present invention is a Vadadustat D-Proline co-crystal (1:1) that may be characterized by a powder X-ray diffraction pattern having peaks at 10.33, 15.83, 16.27 and 19.33 ± 0.2 degrees 2θ.

Within the context of this embodiment of the present invention, the Vadadustat D-Proline co-crystal (1:1) may be characterized by a powder X-ray diffraction pattern having peaks at 5.34, 6.53, 6.88, 8.49, 8.99, 10.33, 10.88, 11.51, 12.02, 12.99, 15.83, 16.27, 16.93, 17.33, 17.80, 18.17, 19.33, 20.27, 20.57, 21.05, 21.91, 22.45, 22.76, 23.37, 24.05, 25.05, 25.20, 26.12, 27.22, 28.19, 29.49, 30.27, 31.38, 32.61, 33.60, 34.99, 36.60, 37.59, 39.95, 41.35 ± 0.2 degrees 2θ.

In another embodiment, the Vadadustat D-Proline co-crystal (1:1) may be characterized by the powder X-ray diffraction pattern shown in Figure 10.

Another embodiment of the present invention is t a process for the preparation of Vadadustat Proline co-crystal comprising the steps of:

a) mixing Vadadustat with proline in a solvent to form a suspension;
b) heating the suspension to 55-70°C;
c) slowly cooling the suspension to room temperature; and
d) isolating Vadadustat proline co-crystal.

Within the context of the present disclosure, the process may include contacting Vadadustat and proline in an organic solvent at room temperature to form a suspension, heating the suspension to 55°C-70°C, slowly cooling the reaction mixture to room temperature and filtering the reaction mass to get Vadadustat proline co-crystal. In particularly useful embodiments, the reaction mixture may be heated to about 60°C-65°C. The solvents may be selected from ketones and alcohols. The ketonic solvents include, but are not limited to acetone, methyl isobutyl ketone or methyl ethyl ketone and mixtures thereof. Preferably the suitable ketonic solvent is acetone. Alcohols include, but are not limited to methanol, ethanol, isopropanol, n-propanol or t-butanol. Preferably the suitable alcohol solvent is methanol.

Within the context of the present disclosure, proline is selected from L-Proline, D-Proline or DL-Proline.

Within the context of this embodiment of the present invention, isolation of Vadadustat co-crystal can be done using any techniques in the art such as decantation, filtration by gravity or suction,

centrifugation, slow evaporation, or distillation. In particularly useful embodiments of the present invention, the Vadadustat co-crystal is isolated by filtration.

Another embodiment of the present invention, the molar ratio of Vadadustat to proline is about 1 to 2.

Another embodiment of the present invention is a Vadadustat caffeine co-crystal (1:1) that may be characterized by a powder X-ray diffraction pattern having peaks at 12.62, 25.11, 25.92 and 26.19 ± 0.2 degrees 2θ.

Within the context of this embodiment of the present invention, the Vadadustat caffeine co-crystal (1:1) may be characterized by a powder X-ray diffraction pattern having peaks at 8.27, 12.62, 12.89, 14.42, 15.13, 17.18, 19.85, 20.40, 22.16, 22.49, 22.99, 23.83, 24.78, 25.11, 25.92, 26.19, 26.75, 27.63, 27.97, 28.58, 29.10, 30.13, 30.65 ± 0.2 degrees 2θ.

In another embodiment, the Vadadustat caffeine co-crystal (1:1) may be characterized by the powder X-ray diffraction pattern shown in Figure 11.

Another embodiment of the present invention is a process for the preparation of Vadadustat caffeine co-crystal (1:1) comprising: suspending Vadadustat and caffeine in a solvent at room temperature and isolating Vadadustat caffeine co-crystals (1:1).

Within the context of this embodiment of the present invention, Vadadustat and caffeine may be suspended in a solvent at room temperature. The solvents may be selected from acetonitrile, tetrahydrofuran and acetone. Preferably the solvent is acetonitrile.

Within the context of this embodiment of the present invention, isolation of Vadadustat caffeine co-crystal can be done using any techniques in the art such as decantation, filtration by gravity or suction, centrifugation, slow evaporation, distillation. In particular, useful embodiments of the present invention, the Vadadustat caffeine co-crystal is isolated by filtration.

Another embodiment of the present invention is a Vadadustat nicotinamide co-crystal (1:1) that may be characterized by a powder X-ray diffraction pattern having peaks at 14.75, 16.78, 17.61 and 18.44 ± 0.2 degrees 2θ.

Within the context of this embodiment of the present invention, the Vadadustat nicotinamide co-crystal (1:1) may be characterized by a powder X-ray diffraction pattern having peaks at 7.39, 14.75, 16.78, 17.61, 18.44, 23.16, 23.91, 26.51, 27.06, 28.40 ± 0.2 degrees 2θ.

In another embodiment, the Vadadustat nicotinamide co-crystal (1:1) may be characterized by the powder X-ray diffraction pattern shown in Figure 12.

Another embodiment of the present invention is a process for the preparation of Vadadustat nicotinamide co-crystal (1:1) comprising the steps of:

a) dissolving nicotinamide in alcohol solvent at a temperature of 60±5°C;
b) adding the Vadadustat and a ketone solvent to step (a) solution at 60±5°C temperature;
c) cooling the reaction mass to a temperature of 25±5°C; and
d) isolating the Vadadustat nicotinamide co-crystal.

Suitable alcohol solvents include methanol, ethanol and isopropanol. Preferably the alcohol solvent is ethanol.

Suitable ketone solvents include acetone, methyl ethyl ketone and Methyl iso butyl ketone. Preferably the ketone solvent is methyl ethyl ketone.

Isolation of Vadadustat nicotinamide co-crystal can be done using any techniques in the art such as decantation, filtration by gravity or suction, centrifugation, slow evaporation, distillation. In particular useful embodiments of the present invention the Vadadustat nicotinamide co-crystal is isolated by filtration.

Another embodiment of the present invention is a Vadadustat isonicotinamide co-crystal (2:1) that may be characterized by a powder X-ray diffraction pattern having peaks at 14.26, 15.29, 18.20 and 20.15 ± 0.2 degrees 2θ.

Within the context of this embodiment of the present invention, the Vadadustat Isonicotinamide co-crystal (2:1) may be characterized by a powder X-ray diffraction pattern having peaks at 7.71, 14.26, 15.29, 15.79, 18.20, 20.15, 25.86, 29.21, 29.54, 30.45± 0.2 degrees 2θ.

In another embodiment, the Vadadustat Isonicotinamide co-crystal (2:1) may be characterized by the powder X-ray diffraction pattern shown in Figure 13.

Another embodiment of the present invention is t a process for the preparation of Vadadustat isonicotinamide co-crystal (2:1) comprising the steps of:

a) suspending isonicotinamide in alcohol solvent at a temperature of 60±5°C;
b) adding the Vadadustat and a ketone solvent to step (a) suspension at 60±5°C temperature;
c) cooling the reaction mass to a temperature of 25±5°C; and
d) isolating the Vadadustat isonicotinamide co-crystal.

Suitable alcohol solvents include methanol, ethanol and isopropanol. Preferably the alcohol solvent is ethanol.

Suitable ketone solvents include acetone, methyl ethyl ketone and methyl iso butyl ketone. Preferably the ketone solvent is methyl ethyl ketone.

Isolation of Vadadustat isonicotinamide co-crystal can be done using any techniques in the art such as decantation, filtration by gravity or suction, centrifugation, slow evaporation, distillation. In particular, in some useful embodiments of the present invention, the Vadadustat nicotinamide co-crystal is isolated by filtration.

Indicative stability:

In one embodiment, the physical and chemical stability of Vadadustat form C was determined by storing the samples at 40°C/75% relative humidity (RH) and at 25°C/60% relative humidity (RH) conditions for three months as mentioned below in Table 1. The samples were then analyzed by PXRD and HPLC. The Vadadustat form C was found to be physically and chemically stable at 40°C/75% relative humidity (RH) and at 25°C/60% relative humidity (RH) up to three months.

In yet another embodiment, the physical stability of 1:1 co-crystal of Vadadustat L-Proline was determined by storing the samples at 40°C/75% relative humidity (RH) and at 25°C/60% relative humidity (RH) conditions for three months as mentioned below in Table 1. The samples were then analyzed by PXRD. The 1:1 co-crystal of Vadadustat L-Proline was found to be physically stable at 40°C/75% relative humidity (RH) and at 25°C/60% relative humidity (RH) up to three months.

In yet another embodiment, the physical stability of 1:1 co-crystal of Vadadustat D-Proline was determined by storing the samples at 40°C/75% relative humidity (RH) and at 25°C/60% relative humidity (RH) conditions for three months as mentioned below in Table 1. The samples were then analyzed by PXRD. The 1:1 co-crystal of Vadadustat D-Proline was found to be physically stable at 40°C/75% relative humidity (RH) and at 25°C/60% relative humidity (RH) up to three months.

In yet another embodiment, the physical stability of 1:2 co-crystal of Vadadustat L-Proline was determined by storing at 25°C/60% relative humidity (RH) conditions for two months as mentioned below in Table 2. The samples were then analyzed by PXRD. The 1:2 co-crystal of Vadadustat L-Proline was found to be physically stable at 25°C/60% relative humidity (RH) up to two months.

In yet another embodiment, the physical stability of 1:2 co-crystal of Vadadustat D-Proline was determined by storing at 25°C/60% relative humidity (RH) conditions for two months as mentioned below in Table 2. The samples then were analyzed by PXRD. The 1:2 co-crystal of Vadadustat D-Proline was found to be physically stable at 25°C/60% relative humidity (RH) up to two months.

Table 1

Conditions/ Polymorph	Vadadustat Form C		1:1 Co-crystal of Vadadustat L-Proline	1:1 Co-crystal of Vadadustat D-Proline
	PXRD	HPLC purity (%)	PXRD	PXRD
at 40°C/75% RH				
Initial	Crystalline	99.79	Co-crystal	Co-crystal
1 month	Stable	--	Stable	Stable
2 months	Stable	99.83	Stable	Stable
3 months	Stable	99.84	Stable	Stable
at 25°C/60% RH				
Initial	Crystalline	99.73	Co-crystal	Co-crystal
1 month	Stable	--	Stable	Stable
2 months	Stable	99.82	Stable	Stable
3 months	Stable	99.84	Stable	Stable

Table 2

Conditions/ Polymorph	1:2 Co-crystal of Vadadustat L-Proline	1:2 Co-crystal of Vadadustat D-Proline
	PXRD	PXRD
at 25°C/60% RH		
Initial	Co-crystal	Co-crystal
1 month	Stable	Stable
2 months	Stable	Stable

Certain specific aspects and embodiments of the present application will be explained in greater detail with reference to the following examples, which are provided only for purposes of illustration and should not be construed as limiting the scope of the disclosure in any manner. Reasonable variations of the described procedures are intended to be within the scope of the present application. While particular aspects of the present application have been illustrated and described, it would be apparent to those skilled in the art that various changes and modifications can be made without departing from the spirit and scope of the disclosure. It is therefore intended to encompass all such changes and modifications that are within the scope of this disclosure.

EXAMPLES

U.S. Patent No. 9,145,366 B2, Example 4 discloses a process for preparation of Vadadustat. The US '366 patent process involves hydrolysis of Vadadustat methyl ester (obtained as per Example 3 and 4 of US'366) with sodium hydroxide, followed by acidifying the reaction mass with hydrochloric acid

resulting in crude Vadadustat, which, upon slurrying in hot water, resulted in pure Vadadustat as an off-white solid. The US '366 patent does not disclose any polymorphic information on the resulting Vadadustat.

Comparative Example 1: Repetition of process according to Example 4 of US 9145366

Vadadustat crude (13g) obtained as per example 4 of U.S. Patent No. 9,145,366 B2 was suspended in deionized water (105mL) at 25±2°C. The suspension was heated to 70±2°C and maintained for 16 hours at 70±2°C. The reaction mass was then cooled to 25±2°C and stirred for 2 hours at 25±2°C. The reaction mass was then filtered, washed with deionized water (13mL) and dried under vacuum at 50°C for 15 hours. The powder X-ray diffractogram of pure Vadadustat obtained according to US 9145366B2 is shown in Figure 4.

Working Examples

Example 1: Preparation of Amorphous form of Vadadustat

Vadadustat (200mg) was dissolved in a mixture of acetonitrile (6mL) and water (2mL) at 55±5°C. The resulting clear solution was filtered to remove any undissolved particulate and subjected to lyophilization using Labocon lyophilizer (Model: LFD-BT-104) to yield amorphous form of Vadadustat.

Example 2: Preparation of Amorphous form of Vadadustat

Vadadustat (200mg) was dissolved in a mixture of 1,4-dioxane (2mL) and water (2mL) at 55±5°C. The resulting clear solution was filtered to remove any undissolved particulate and subjected to lyophilization using Labocon lyophilizer (Model: LFD-BT-104) to yield amorphous form of Vadadustat.

Example 3: Preparation of crystalline Form B of Vadadustat

Vadadustat (200mg) was dissolved in ethanol (2mL) at 60±2°C and maintained for 1h at 60±2°C. The clear solution was cooled to 25±2°C and maintained under stirring for 16 hours at 25±2°C. The reaction mass was filtered, and the solid obtained was identified as crystalline Vadadustat Form B.

Example 4: Preparation of crystalline Form B of Vadadustat

Vadadustat (50mg) was dissolved in methyl isobutyl ketone (MIBK) (1mL) at 60±2°C and maintained for 1 hour at 60±2°C. The reaction mass was cooled to 25±2°C and maintained under stirring for 16 hours at 25±2°C. The reaction mass was filtered, and the solid obtained was identified as crystalline Vadadustat Form B.

Example 5: Preparation of crystalline Form C of Vadadustat

Vadadustat (0.5g) and methyl tert-butyl ether (MTBE) (20 mL) were charged in a round-bottom flask (RBF) at 25±5°C and heated to 50±5°C, The reaction mass was stirred for 30 minutes, and the obtained clear solution was filtered through hyflo to remove any undissolved particles. The clear solution was

then added to heptane (10mL) at 25±5°C and stirred for 15 hours. The solid was filtered and suck dried under vacuum at 25±5°C for 30 min. The product obtained was confirmed as Vadadustat Form C. Yield= 0.3g

Example 6: Preparation of crystalline Form C of Vadadustat

Vadadustat (10g) and methyl tert-butyl ether (MTBE) (350 mL) were charged in a RBF at 25±5°C and heated to 50±5°C, The reaction mass was stirred for 30 minutes and the obtained clear solution was filtered through hyflo to remove any undissolved particles. The clear solution was then added to heptane (200mL) containing Vadadustat Form C seed (20mg) at 25±5°C and stirred for 15 hours. The solid was filtered and suck dried under vacuum at 25±5°C for 30 minutes. The product obtained was conformed as Vadadustat Form C. Yield= 7.9g

Example 7: Process for the preparation of Vadadustat L-Proline co-crystal (1:2)

Vadadustat (1.0g), L-Proline (0.38g) and acetone (20mL) were charged in a RBF at 25±5°C and the contents were heated to 60-65°C and stirred for 15-30 minutes at 60-65°C. The reaction mass was slowly cooled to 25±5°C and maintained under stirring at 25±5°C for 16 hours. The product obtained was filtered and dried under vacuum for 4 hours at 35°C. The solid obtained was identified as 1:2 co-crystal of Vadadustat L-Proline. Yield: 0.78g

Example 8: Process for the preparation of Vadadustat L-Proline co-crystal (1:2)

Vadadustat (4.0g), L-Proline (2.85g) and acetone (60mL) were charged in a RBF at 25±5°C and the contents were heated to 60-65°C and stirred for 60 minutes at 60-65°C. The reaction mass was slowly cooled to 25±5°C and maintained under stirring at 25±5°C for 16 hours. The product obtained was filtered, washed with acetone (8 mL) and dried under vacuum for 16 hours at 40°C. The solid obtained was identified as 1:2 co-crystal of Vadadustat L-Proline. Yield: 6.1g

Example 9: Process for the preparation of Vadadustat D-Proline co-crystal (1:2)

Vadadustat (0.5g), D-Proline (0.36g) and acetone (8mL) were charged in a RBF at 25±5°C and the contents were heated to 60-65°C and stirred for 30-40 minutes at 60-65°C. The reaction mass was slowly cooled to 25±5°C and maintained under stirring at 25±5°C for 16 hours. The product obtained was filtered, washed with acetone (2 mL) and dried under vacuum for 16 hours at 40°C. The solid obtained was identified as 1:2 co-crystal of Vadadustat D-Proline. Yield: 0.76g

Example 10: Process for the preparation of Vadadustat L-Proline co-crystal (1:1)

Vadadustat (0.5g), L-Proline (0.36g) and methanol (8mL) were charged in a RBF at 25±5°C and the contents were heated to 60-65°C and stirred for 30-40 minutes at 60-65°C. The reaction mass was slowly cooled to 25±5°C and maintained under stirring at 25±5°C for 16 hours. The product obtained was filtered and dried under vacuum for 16 hours at 40°C. The solid obtained was identified as 1:1 co-crystal of Vadadustat L-Proline. Yield: 0.47g

Example 11: Process for the preparation of Vadadustat D-Proline co-crystal (1:1)

Vadadustat (1.0g), D-Proline (0.71g) and methanol (16mL) were charged in a RBF at 25±5°C and the contents were heated to 60-65°C and stirred for 30-40 minutes at 60-65°C. The reaction mass was slowly cooled to 25±5°C and maintained under stirring at 25±5°C for 16 hours. The product obtained was filtered, washed with prechilled methanol (1mL) and dried under vacuum for 16 hours at 40°C. The solid obtained was identified as 1:1 co-crystal of Vadadustat D-Proline. Yield: 0.86g.

Example 12: Process for the preparation of Vadadustat caffeine co-crystal (1:1)

Vadadustat (0.5g), caffeine (0.35g) and acetonitrile (5mL) were charged in a RBF at 25±5°C. The reaction mass was maintained under stirring at 25±5°C for 16 hours. The product obtained was filtered and dried under vacuum for 3 hours at 40°C. The solid obtained was identified as 1:1 co-crystal of Vadadustat Caffeine. Yield: 0.55g.

Example 13: Process for the preparation of Vadadustat nicotinamide co-crystal (1:1)

Ethanol (1.5mL) and nicotinamide (0.2g) were charged in a RBF at 25±5°C and the contents were heated to 60-65°C and stirred for 30 min at 60-65°C. Methyl ethyl ketone (15mL) and Vadadustat (0.5g) were charged into the reaction mass at 60-65°C. The reaction mass was stirred for 30 minutes at 60-65°C. The mass was then slowly cooled to 25±5°C and maintained under stirring at 25±5°C for 16 hours. The reaction mass was cooled to 0-5°C and stirred for 2-3 hours. The product obtained was filtered, washed with methyl ethyl ketone (2 mL) and dried under vacuum for 3 hours at 40°C. The solid obtained was identified as 1:1 co-crystal of Vadadustat Nicotinamide. Yield: 0.45 g.

Example 14: Process for the preparation of Vadadustat isonicotinamide co-crystal (2:1)

Ethanol (3mL) and isonicotinamide (0.2g) were charged in a RBF at 25±5°C and the contents were heated to 60-65°C and stirred for 30 minutes at 60-65°C. Methyl ethyl ketone (30mL) and Vadadustat (0.5g) were charged into the reaction mass at 60-65°C. The reaction mass was stirred for 30 minutes at 60-65°C. The mass was then slowly cooled to 25±5°C and maintained under stirring at 25±5°C for 16 hours. The product obtained was filtered, washed with methyl ethyl ketone (1 mL) and dried under vacuum for 2 hours at 40°C. The solid obtained was identified as 2:1 co-crystal of Vadadustat Isonicotinamide. Yield: 0.6 g.

We claim:

1. A process for the preparation of crystalline Form C of Vadadustat, comprising the steps of:
    a) dissolving Vadadustat in an ether solvent at elevated temperature to form a solution;
    b) cooling the solution to room temperature;
    c) adding the step (b) solution to an anti-solvent optionally containing a seed of crystalline form C of Vadadustat; and
    d) isolating the crystalline Form C of Vadadustat.
2. The process according to claim 1, wherein the ether solvent is selected from the group consisting of tetrahydrofuran and methyl tert-butyl ether and the anti-solvent is heptane.
3. The process according to claim 1, wherein the elevated temperature is about 45°C to about 60°C.
4. The process according to claim 1, wherein the crystalline Form C is isolated by filtration and distillation.
5. A Vadadustat L-Proline co-crystal (1:2) characterized by a powder X-ray diffraction pattern having peaks at 8.12, 16.27, 18.72 and 25.14 ± 0.2 degrees 2θ.
6. The Vadadustat L-Proline co-crystal (1:2) of claim 5, further characterized by a powder X-ray diffraction pattern having peaks at 8.12, 11.85, 16.27, 17.78, 18.72, 24.66 and 25.14 ± 0.2 degrees 2θ.
7. The Vadadustat L-Proline co-crystal (1:2) of claim 5, further characterized by a PXRD pattern as shown in Figure 7.
8. A Vadadustat L-Proline co-crystal (1:1) characterized by a powder X-ray diffraction pattern having peaks at 10.23, 15.72, 16.15 and 19.22 ± 0.2 degrees 2θ.
9. The Vadadustat L-Proline co-crystal (1:1) of claim 8, further characterized by a powder X-ray diffraction pattern having peaks at 7.79, 10.23, 10.46, 15.72, 16.15 and 19.22 ± 0.2 degrees 2θ.
10. The Vadadustat L-Proline co-crystal (1:1) of claim 8, further characterized by a PXRD pattern as shown in Figure 8.
11. A Vadadustat D-Proline co-crystal (1:2) characterized by a powder X-ray diffraction pattern having peaks at 8.11, 16.28, 18.73 and 25.13 ± 0.2 degrees 2θ.
12. The Vadadustat D-Proline co-crystal (1:2) of claim 11, further characterized by a powder X-ray diffraction pattern having peaks at 8.11, 11.85, 16.28, 17.78, 18.73, 24.62 and 25.13 ± 0.2 degrees 2θ.
13. The Vadadustat D-Proline co-crystal (1:2) of claim 11, further characterized by a PXRD pattern as shown in Figure 9.
14. A Vadadustat D-Proline co-crystal (1:1) characterized by a powder X-ray diffraction pattern having peaks at 10.33, 15.83, 16.27 and 19.33 ± 0.2 degrees 2θ.
15. The Vadadustat D-Proline co-crystal (1:1) of claim 14, further characterized by a powder X-ray diffraction pattern having peaks at 5.34, 12.99, 10.33, 15.83, 16.27, 19.33, 29.49 and 31.38 ± 0.2 degrees 2θ.

16. The Vadadustat D-Proline co-crystal (1:1) of claim 14, further characterized by a PXRD pattern as shown in Figure 10.
17. A process for the preparation of Vadadustat Proline co-crystal comprising the steps of:
    a) mixing Vadadustat with proline in a solvent to form a suspension;
    b) heating the suspension to 55-70°C;
    c) slowly cooling the suspension to room temperature; and
    d) isolating Vadadustat Proline co-crystal from the suspension.
18. The process according to claim 17, wherein the proline is selected from the group consisting of L-Proline, D-Proline and DL-Proline.
19. The process according to claim 17, wherein the solvent is selected from the group consisting of acetone, methyl isobutyl ketone, methyl ethyl ketone, methanol, ethanol, isopropanol, n-propanol and t-butanol.
20. The process according to claim 17, wherein the Vadadustat Proline co-crystal is isolated by filtration and distillation.
21. A Vadadustat caffeine co-crystal (1:1) characterized by a powder X-ray diffraction pattern having peaks at 12.62, 25.11, 25.92 and 26.19± 0.2 degrees 2θ.
22. The Vadadustat caffeine co-crystal (1:1) of claim 21, further characterized by a powder X-ray diffraction pattern having peaks at 8.27, 12.62, 12.89, 14.42, 24.78, 25.11, 25.92, 26.19 and 26.75 ± 0.2 degrees 2θ.
23. The Vadadustat caffeine co-crystal (1:1) of claim 21, further characterized by a PXRD pattern as shown in Figure 11.
24. A process for the preparation of Vadadustat caffeine co-crystal (1:1) comprising: suspending Vadadustat and caffeine in a solvent at room temperature to form a suspension and isolating Vadadustat caffeine co-crystal (1:1) from the suspension.
25. The process according to claim 24, wherein the solvent is selected from the group consisting of acetonitrile, tetrahydrofuran and acetone.
26. A Vadadustat nicotinamide co-crystal (1:1) characterized by a powder X-ray diffraction pattern having peaks at 14.75, 16.78, 17.61 and 18.44± 0.2 degrees 2θ.
27. The Vadadustat nicotinamide co-crystal (1:1) of claim 26, further characterized by a powder X-ray diffraction pattern having peaks at 7.39, 14.75, 16.78, 17.61, 18.44, 23.16, 23.91, 26.51, 27.06, 28.40 ± 0.2° degrees 2θ.
28. The Vadadustat nicotinamide co-crystal (1:1) of claim 26, further characterized by a PXRD pattern as shown in Figure 12.
29. A Vadadustat isonicotinamide co-crystal (2:1) characterized by a powder X-ray diffraction pattern having peaks at 14.26, 15.29, 18.20 and 20.15 ± 0.2 degrees 2θ.
30. The Vadadustat Isonicotinamide co-crystal (2:1) of claim 29, further characterized by a powder X-ray diffraction pattern having peaks at 7.71, 14.26, 15.29, 15.79, 18.20, 20.15, 25.86, 29.21, 29.54, 30.45± 0.2 degrees 2θ.
31. The Vadadustat Isonicotinamide co-crystal (2:1) of claim 29, further characterized by a PXRD pattern as shown in Figure 13.

32. A process for the preparation of Vadadustat nicotinamide co-crystal (1:1) comprising the steps of:
    a) dissolving nicotinamide in an alcohol solvent at a temperature of 60±5°C to form a solution;
    b) adding Vadadustat and a ketone solvent to the step (a) solution at 60±5°C temperature to produce a reaction mass;
    c) cooling the reaction mass to a temperature of 25±5°C; and
    d) isolating the Vadadustat nicotinamide co-crystal from the reaction mass.
33. A process for the preparation of Vadadustat isonicotinamide co-crystal (2:1) comprising the steps of:
    a) suspending isonicotinamide in an alcohol solvent at a temperature of 60±5°C to form a suspension;
    b) adding Vadadustat and a ketone solvent to the step (a) suspension at 60±5°C temperature to produce a reaction mass;
    c) cooling the reaction mass to a temperature of 25±5°C; and
    d) isolating the Vadadustat isonicotinamide co-crystal from the reaction mass.
34. The process according to claim 32 or 33, wherein the alcohol solvent is selected from the group consisting of methanol, ethanol, and isopropanol and the ketone solvent is selected from the group consisting of acetone, methyl ethyl ketone and methyl iso butyl ketone.
35. The process according to any one of claims 24, 32 and 33, wherein the Vadadustat caffeine co-crystal (1:1) or the Vadadustat nicotinamide co-crystal (1:1) or the Vadadustat isonicotinamide co-crystal (2:1) is isolated by filtration and distillation.

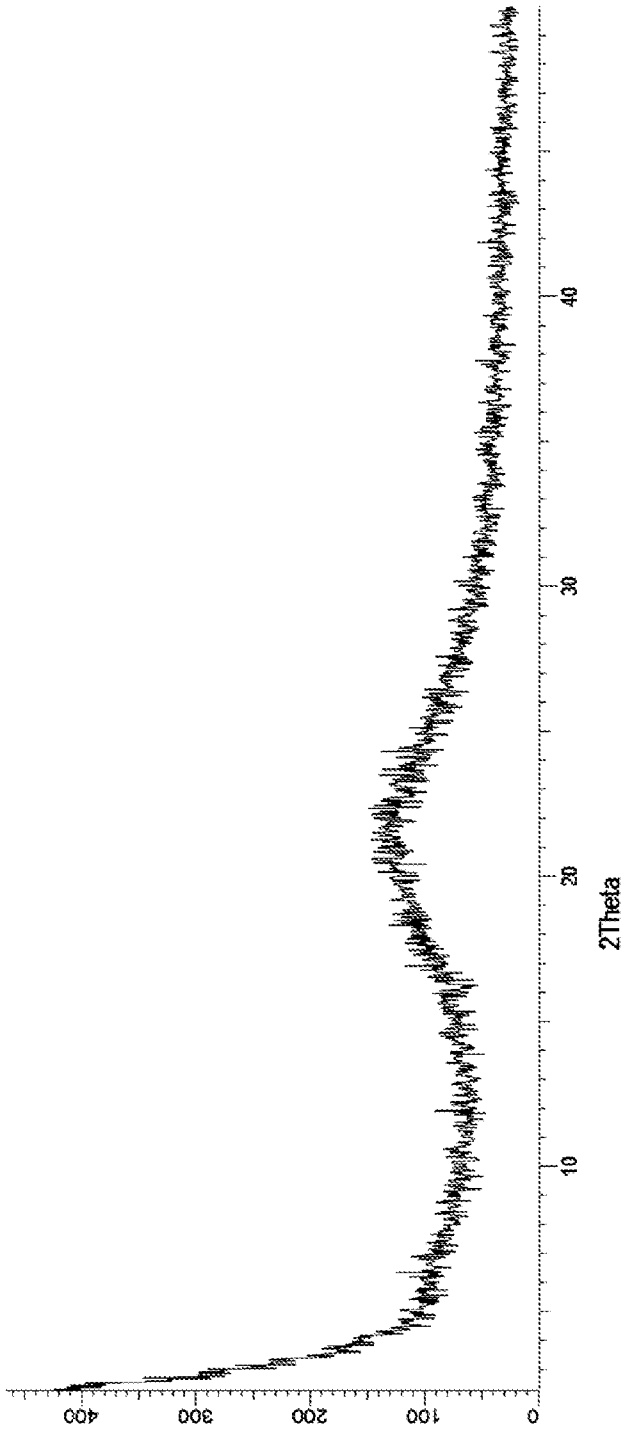


Figure 1

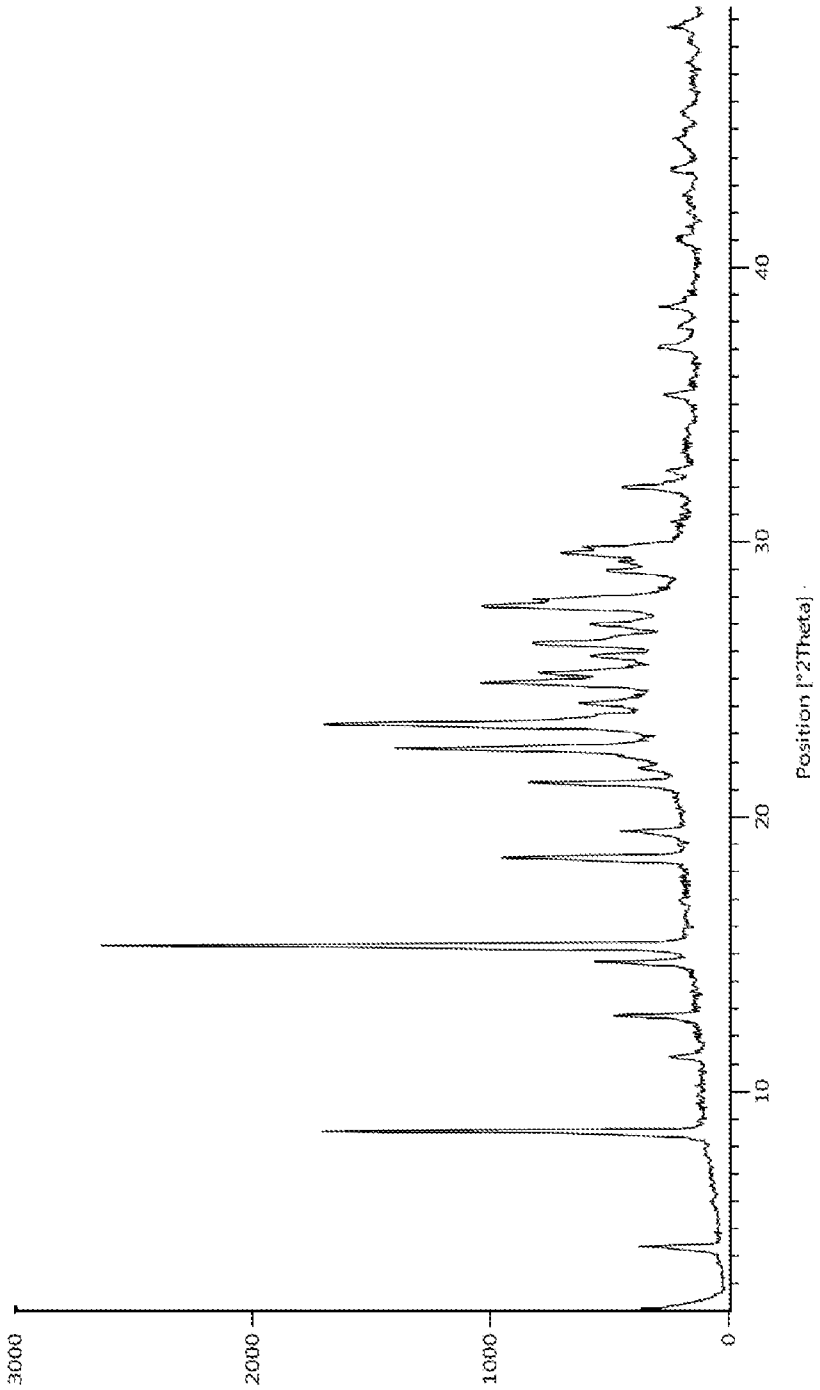


Figure 2

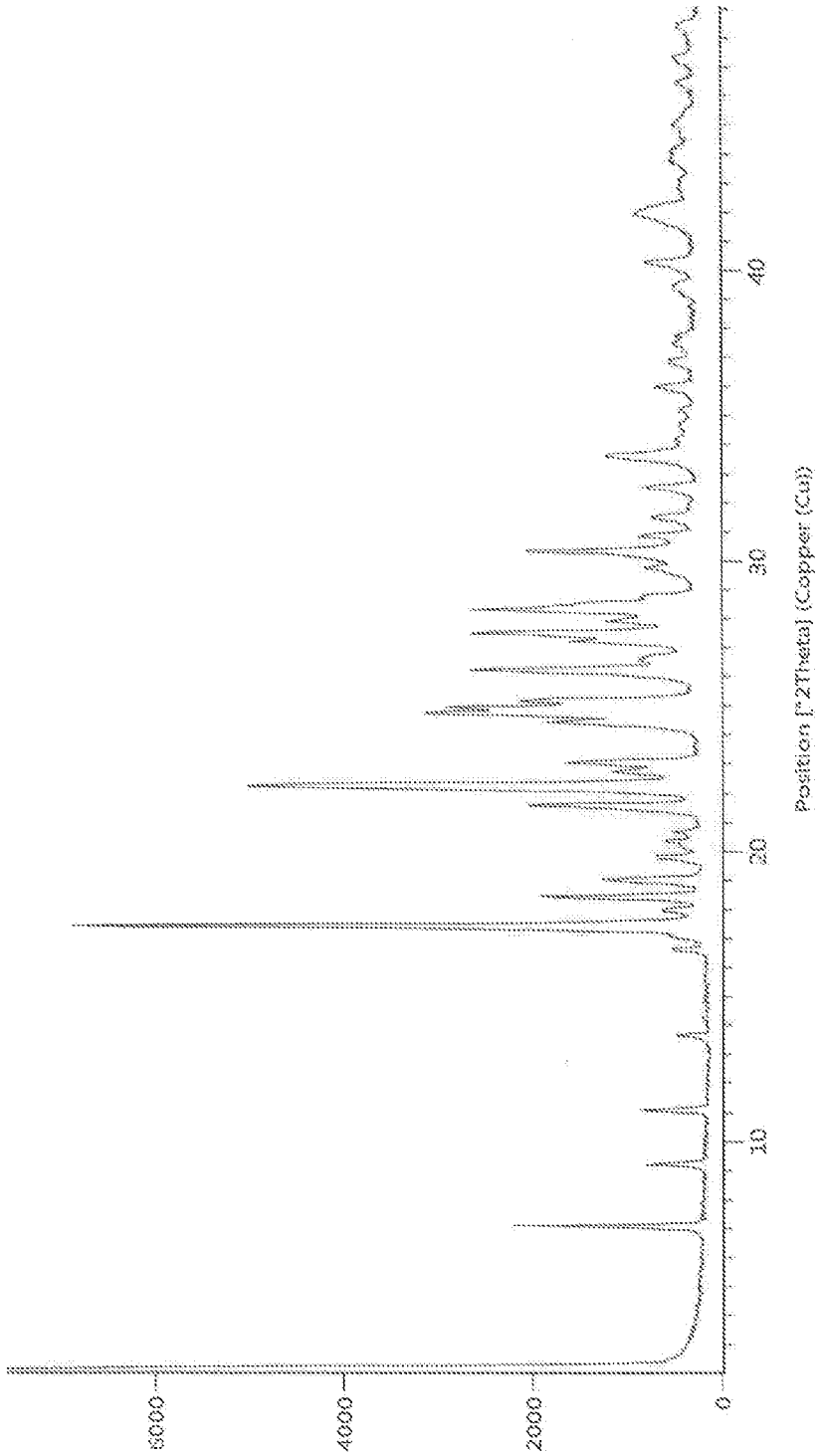
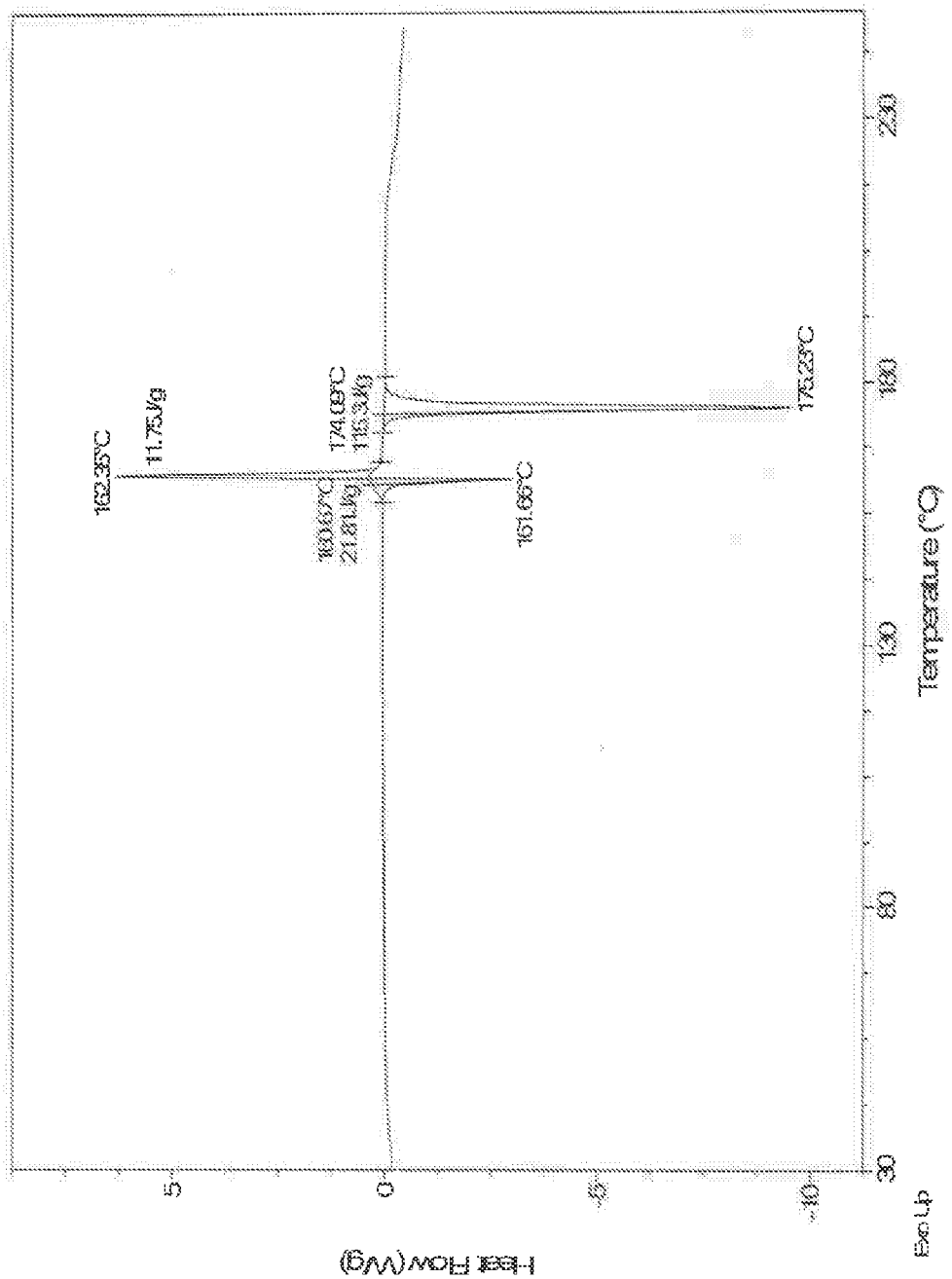


Figure 3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-5
-10
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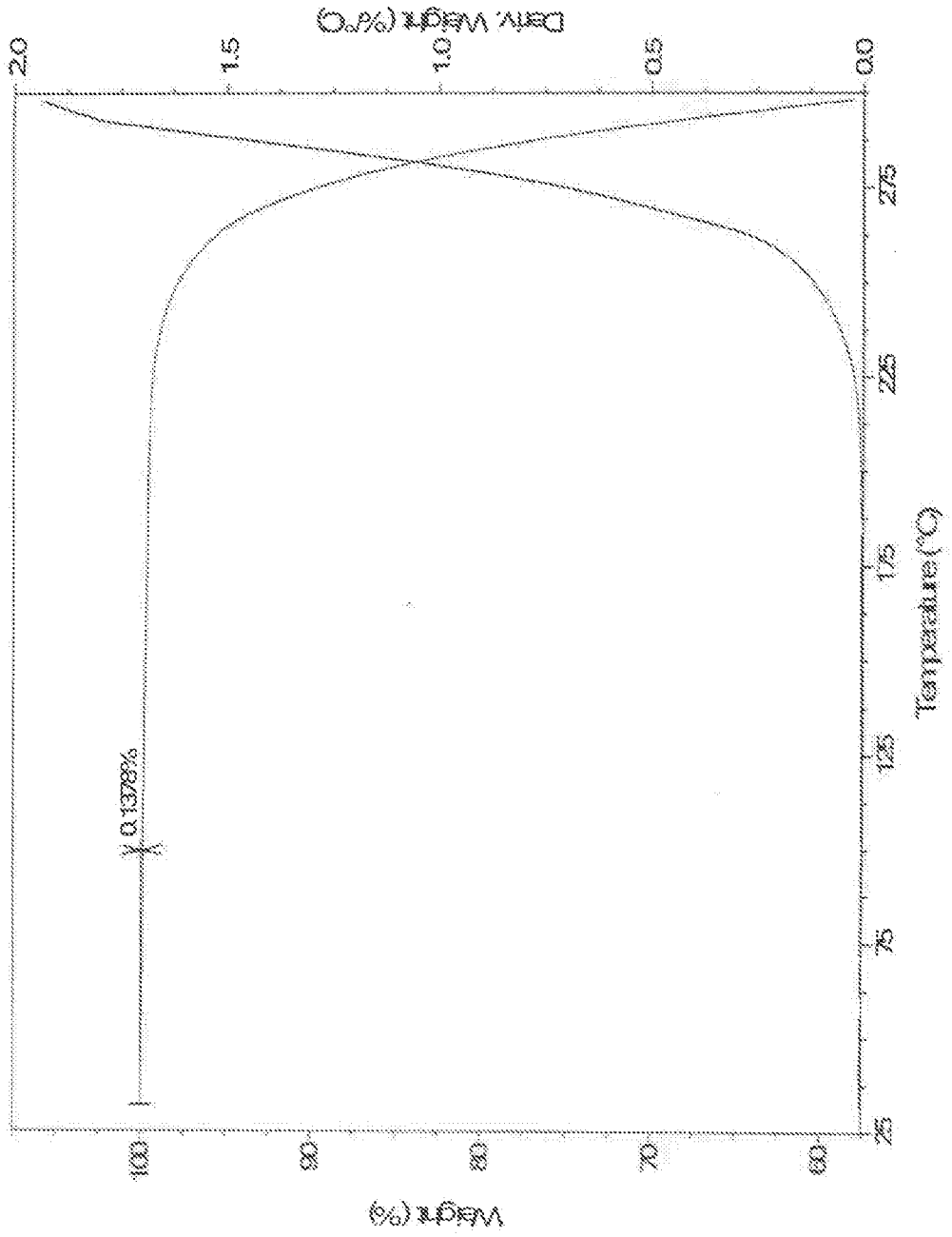
161.66°C
175.28°C

Figure 4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Temperature (°C)
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80
70
60
Weight (%)

Figure 5

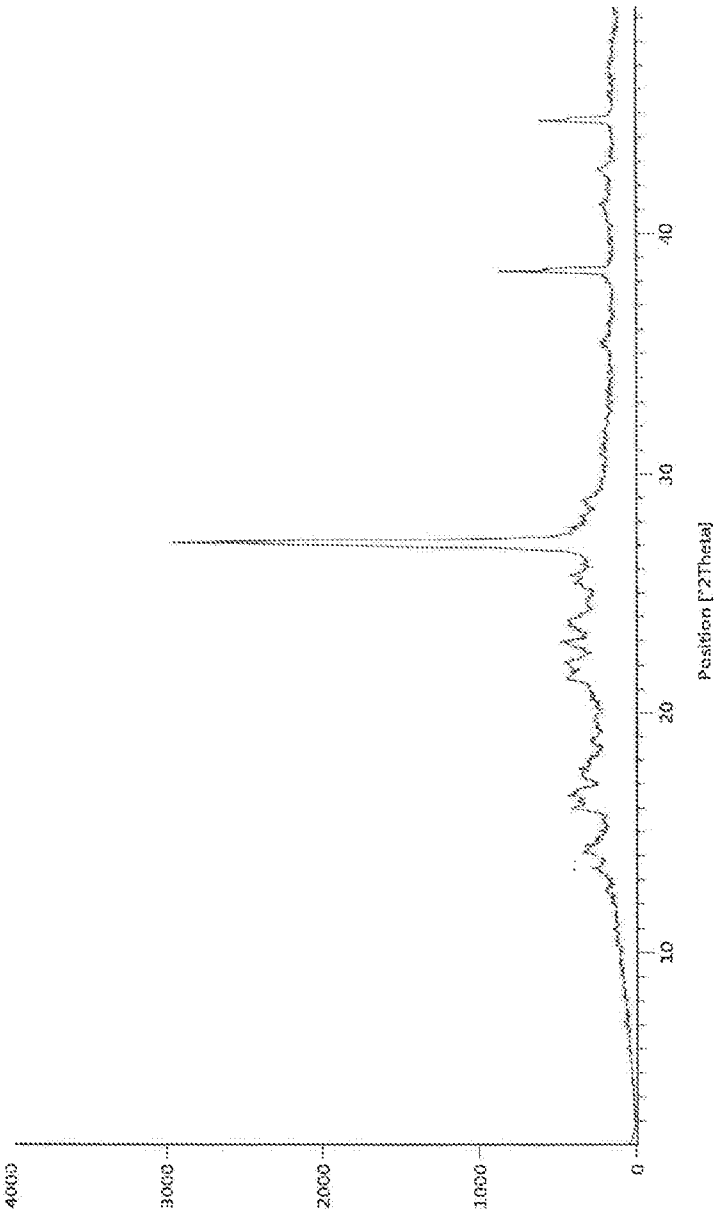

Figure 6

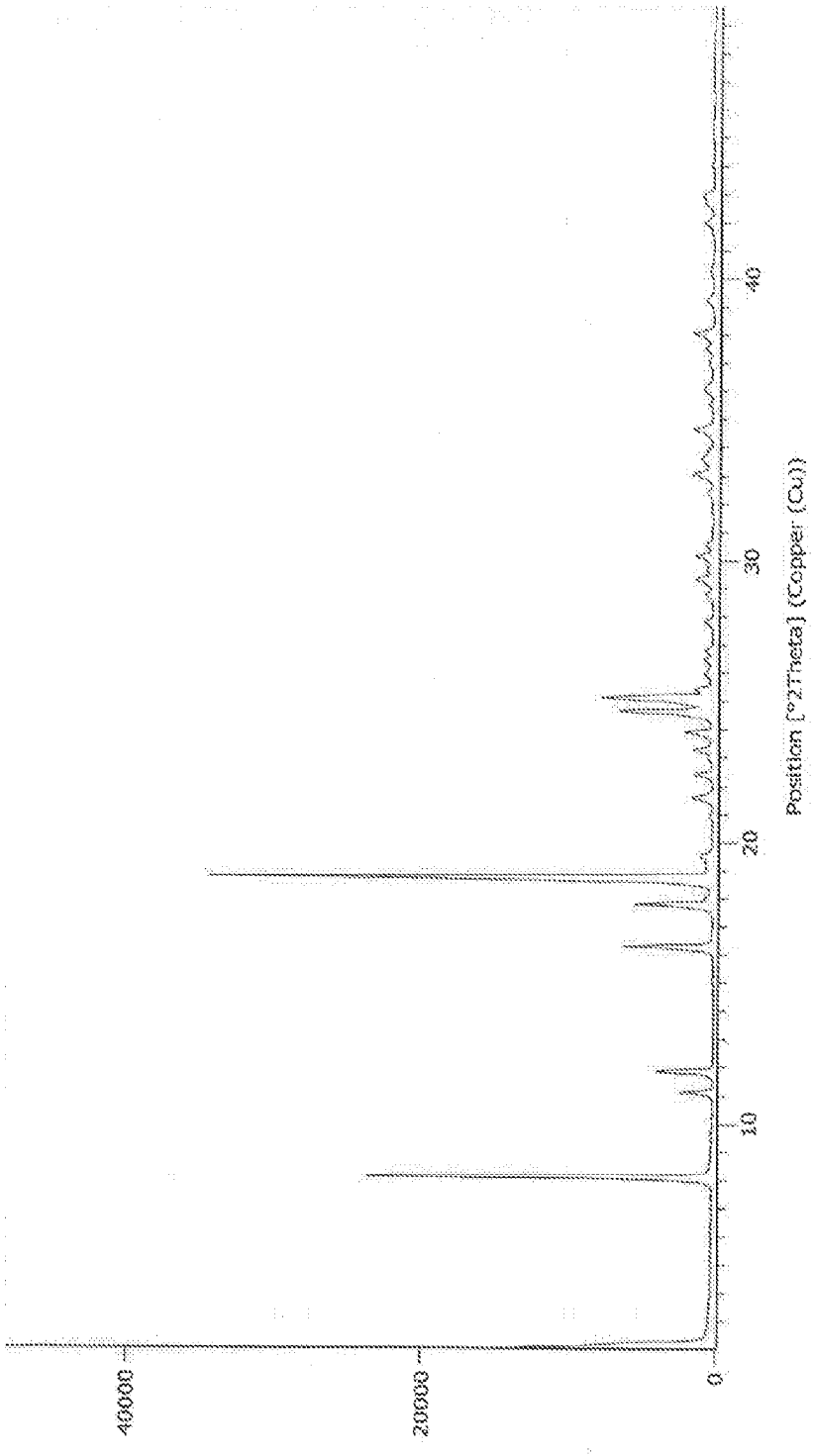

Figure 7

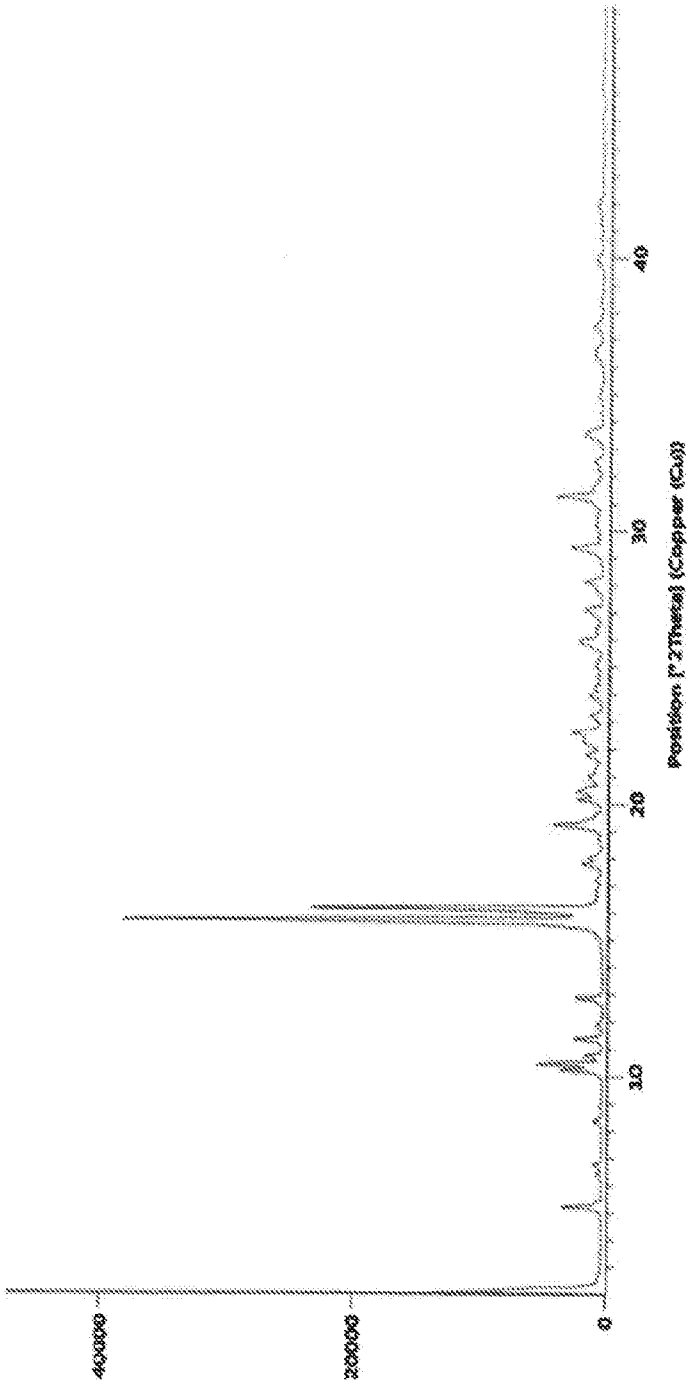

Figure 8

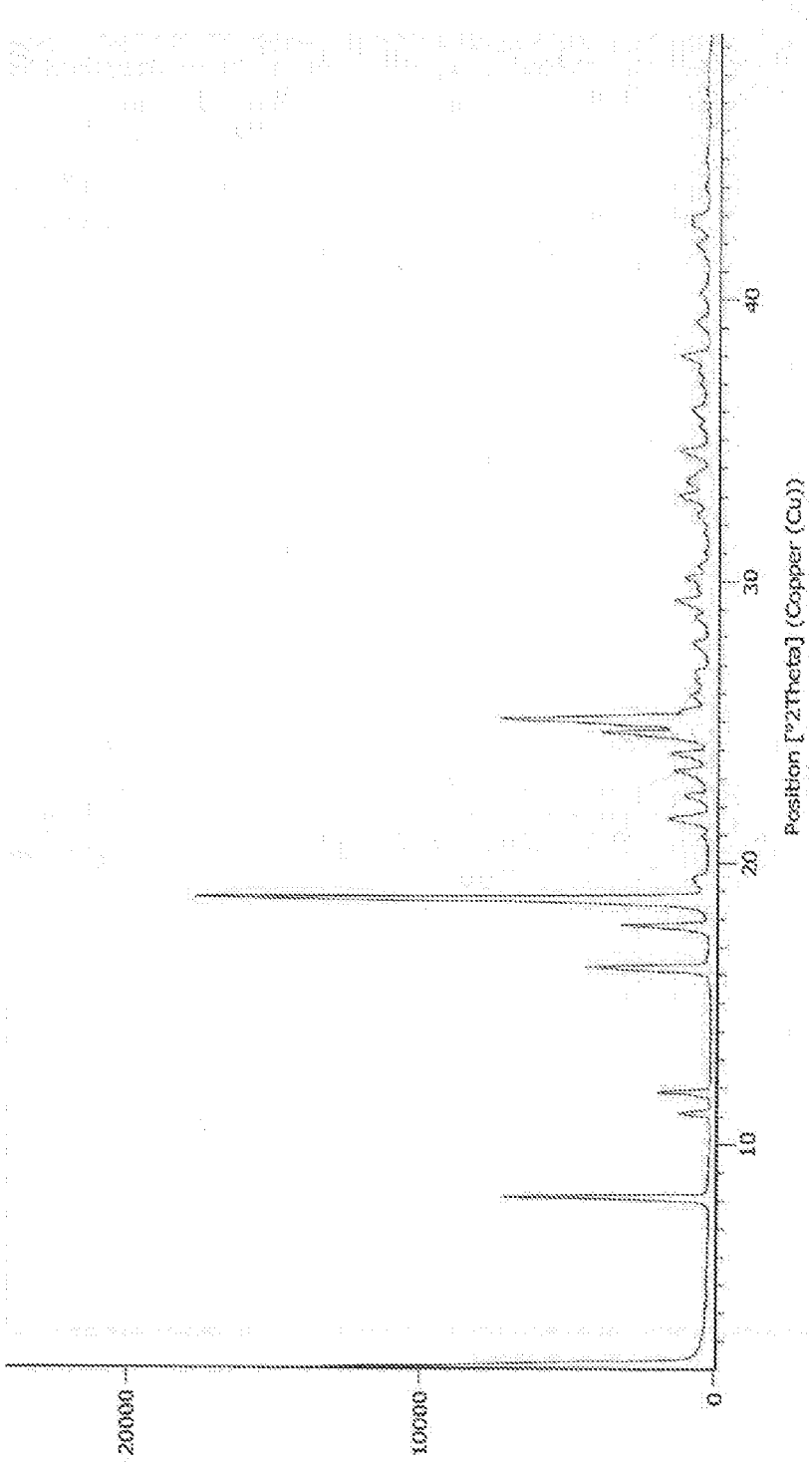

Figure 9

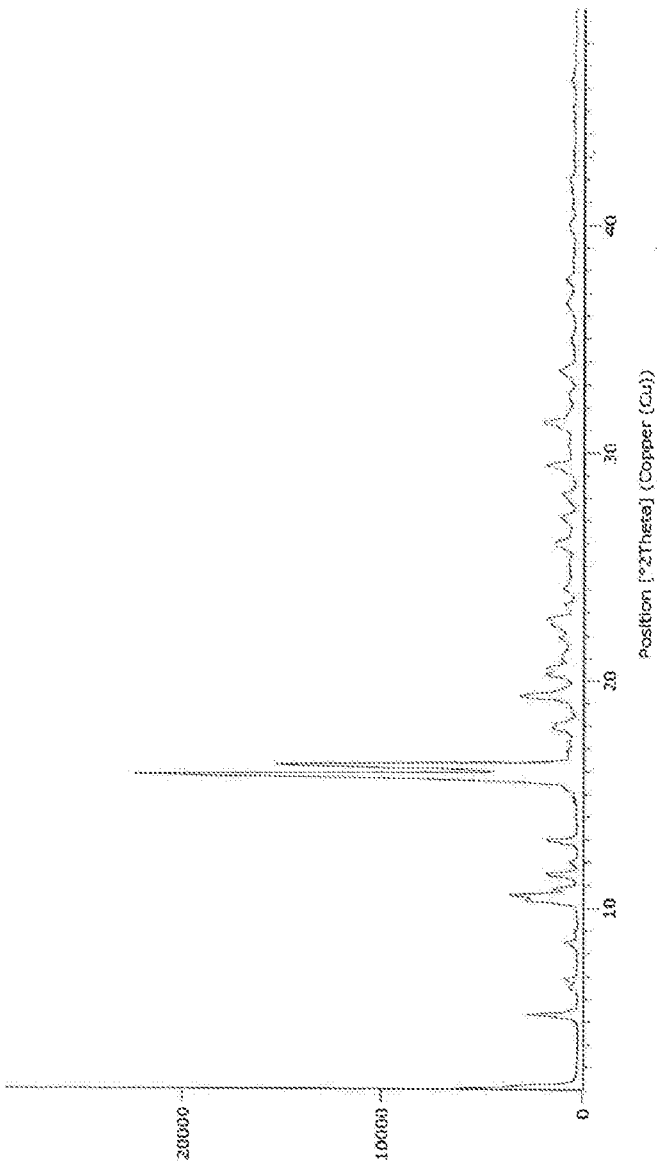

Figure 10

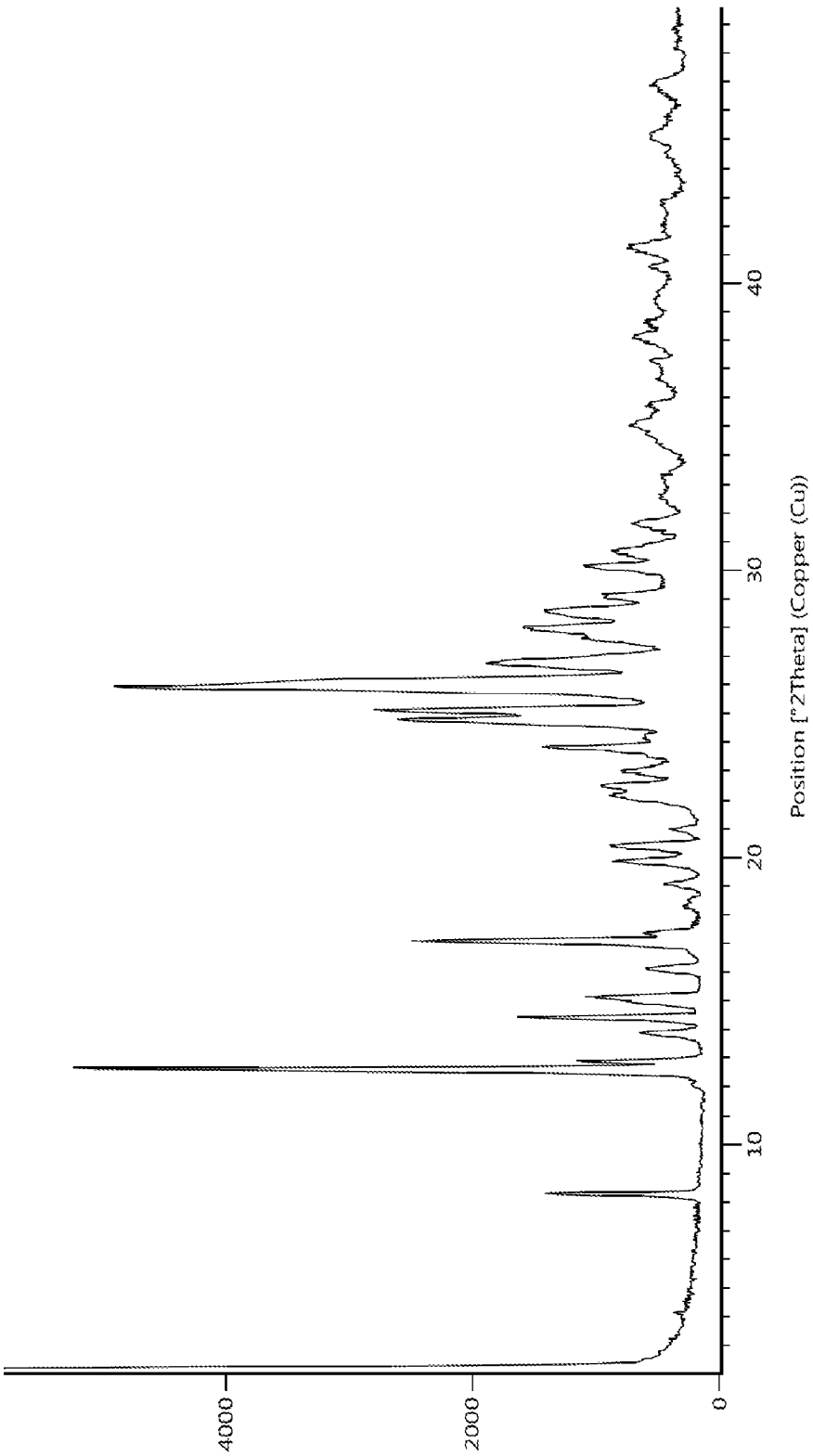

Figure 11

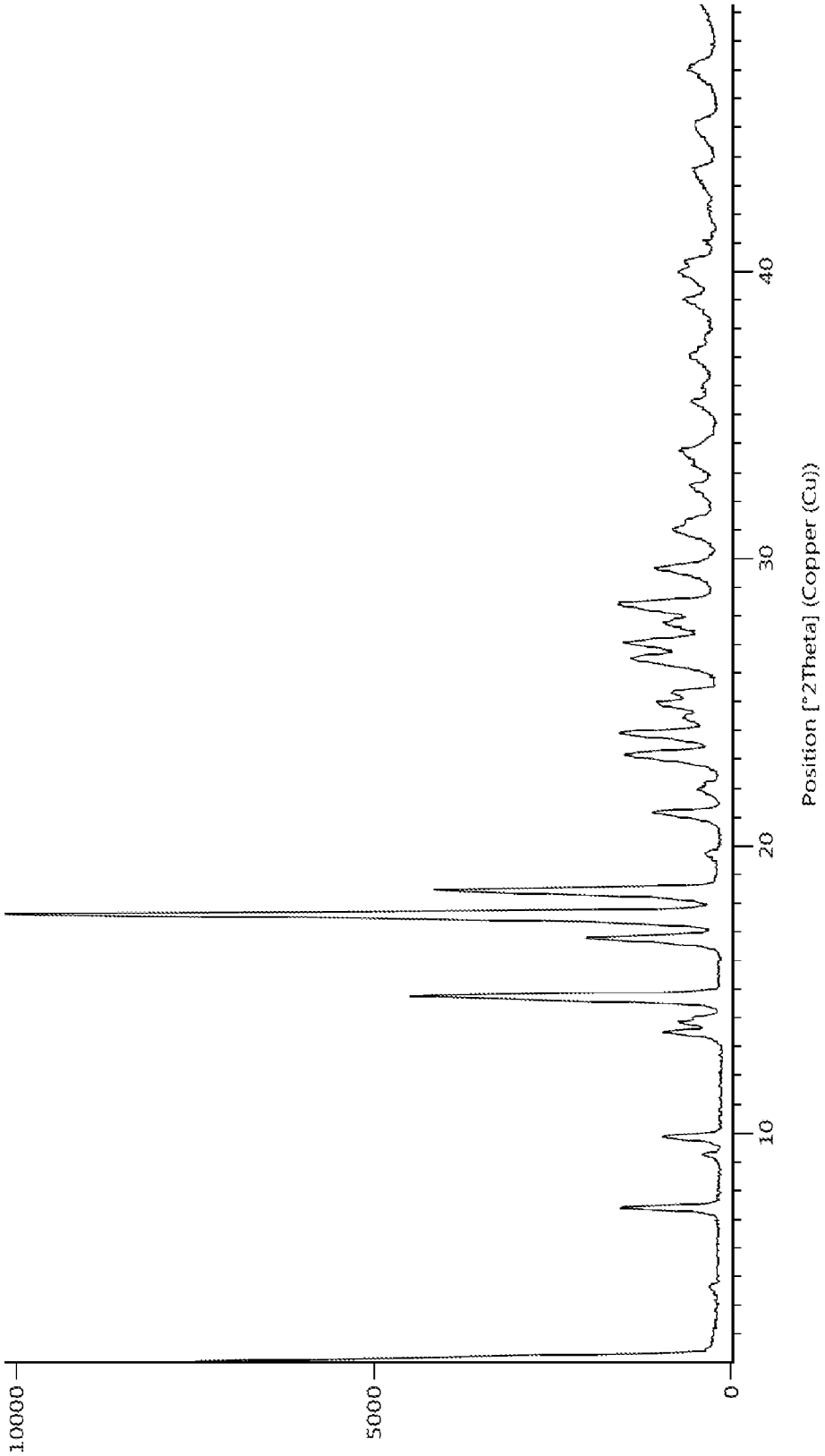

Figure 12

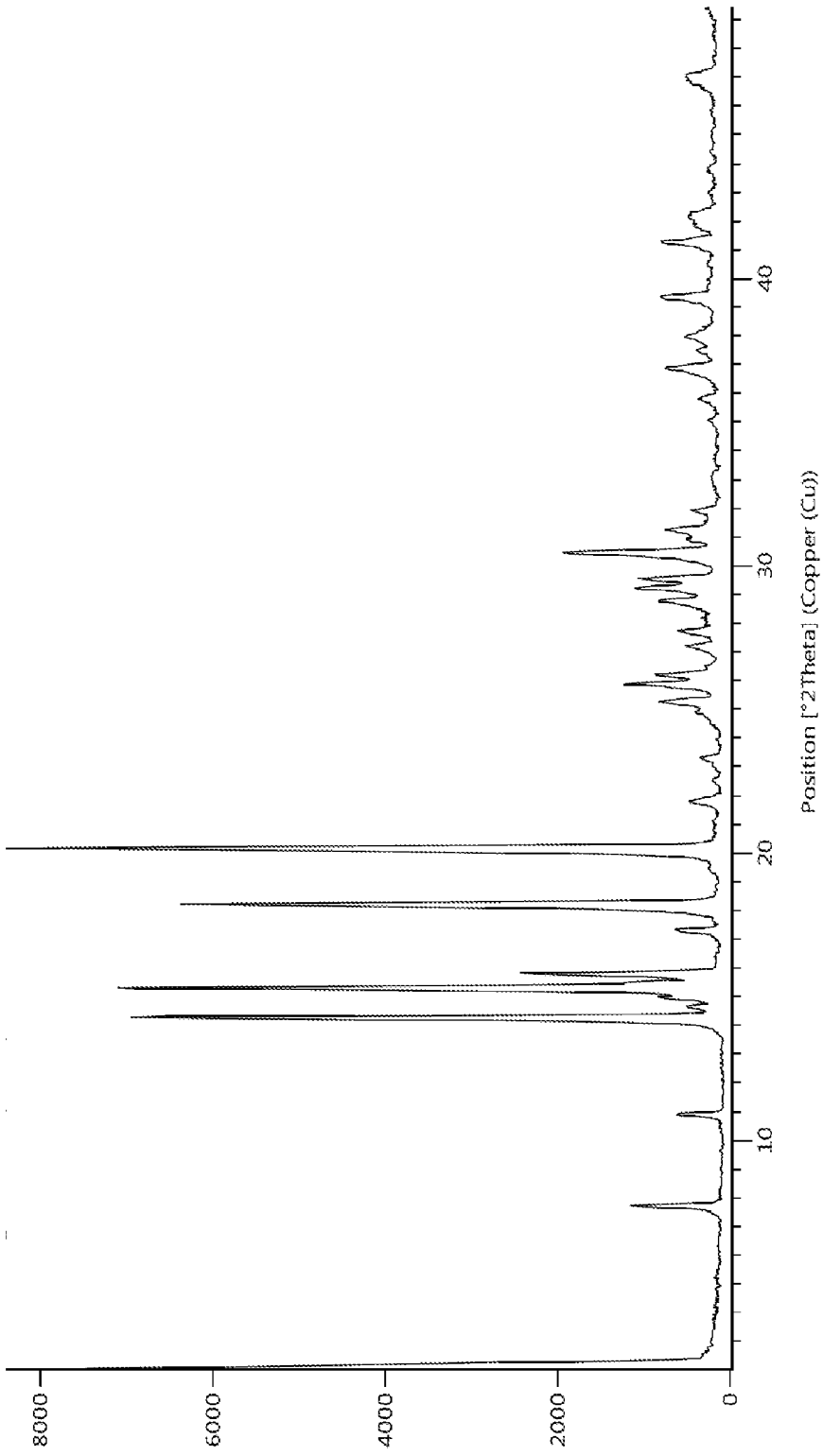

Figure 13

INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2019/050759

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D213/81 C07D207/16 C07D213/82 C07D473/12
ADD.

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

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 practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 2019/217550 A1 (AKEBIA THERAPEUTICS INC [US]) 14 November 2019 (2019-11-14) Example 5 in p. 26-27	1-4
X	WO 2015/073779 A1 (AKEBIA THERAPEUTICS INC [US]) 21 May 2015 (2015-05-21) cited in the application point 6.4 in p. 50 and fig. 12	1-4
A	WO 2018/108101 A1 (CRYSTAL PHARMACEUTICAL SUZHOU CO LTD [CN]) 21 June 2018 (2018-06-21) abstract and Figures 1, 4 and 8	1-4

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

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 January 2020	26/03/2020

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Sahagún Krause, H

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2019/050759

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-4

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-4

   Process for the preparation of crystalline Form C of Vadadustat

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2. claims: 5-35

   Vadadustat co-crystals and processes for the preparation of Vadadustat co-crystals.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IN2019/050759

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2019217550 A1	14-11-2019	TW 201946903 A	16-12-2019
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