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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
27 July 2023 (27.07.2023)

WIPO | PCT

(10) International Publication Number
WO 2023/140809 A1

(51) International Patent Classification:
A61P 35/00 (2006.01) *C07D 213/40* (2006.01)

(21) International Application Number:
PCT/TR2022/050047

(22) International Filing Date:
20 January 2022 (20.01.2022)

(25) Filing Language: English

(26) Publication Language: English

(71) Applicant: DEVA HOLDING [TR/TR]; Halkali Merkez Mah. Basin Ekspres Cad. No:1, 34303 Kucukcekmece/Istanbul (TR).

(72) Inventors: HAAS, Philipp Daniel; Halkali Merkez Mah. Basin Ekspres Cad. No:1, 34303 Kucukcekmece/Istanbul (TR). **STECKEL, Hartwig Andreas**; Halkali Merkez Mah. Basin Ekspres Cad. No:1, 34303 Kucukcekmece/Istanbul (TR). **BELLUR ATİCİ, Esen**; Halkali Merkez Mah. Basin Ekspres Cad. No:1, 34303 Kucukcekmece/Istanbul (TR). **BAŞLAR, Yıldıray**; Halkali Merkez Mah. Basin Ekspres Cad. No:1, 34303 Kucukcekmece/Istanbul (TR). **KESKİN, Elif**; Halkali Merkez Mah. Basin Ekspres Cad. No:1, 34303 Kucukcekmece/Istanbul (TR).

(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, IT, 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, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, 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).

Published:
— *with international search report (Art. 21(3))*

(54) Title: NOVEL POLYMORPH OF VISMODEGIB AND METHOD OF PREPARATION

(57) Abstract: The present invention relates to a new crystalline form of vismodegib, a methanol-solvate of vismodegib, namely Form S, and methods for its preparation. The vismodegib Form S is characterized by an XRPD pattern having characteristic peaks (2theta ± 0.2°) at 7.1, 14.0, 16.7, 19.1, 22.3, 24.6 and 28.0. The present invention also provides interconversion process of vismodegib Form S to crystalline vismodegib Form B, pharmaceutical compositions comprising vismodegib Form S, and medical use of vismodegib Form S.

WO 2023/140809 A1

NOVEL POLYMORPH OF VISMODEGIB AND METHOD OF PREPARATION

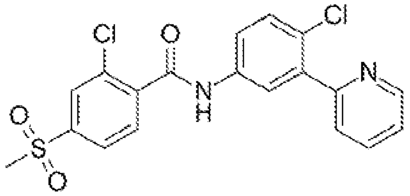
Technical Field

The present invention relates to a novel crystalline polymorphic form of vismodegib designated as Form S and a process for its preparation.

The invention further relates to pharmaceutical compositions comprising vismodegib Form S and use of vismodegib Form S in the treatment of cancer.

Background Art

Vismodegib is an oral Hedgehog signaling pathway inhibitor, which is approved for treatment of adults with metastatic basal cell carcinoma, or with locally advanced basal cell carcinoma that has recurred following surgery or who are not candidates for surgery and who are not candidates for radiation. Vismodegib is marketed by Genentech under the brand name ERIVEDGE®. Vismodegib is chemically designated as 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonyl)benzamide and represented by the following chemical structure;



The preparation and therapeutic use of vismodegib have been described for the first time in European patent EP 1789390, according to which vismodegib is prepared by coupling 4-chloro-3-(pyridin-2-yl)aniline and 2-chloro-4-methylsulfonylbenzoic acid or by coupling 4-chloro-3-(pyridin-2-yl)aniline and 2-chloro-4-(methylsulfonyl)benzoyl chloride.

Vismodegib may exist in different polymorphic forms.

European patent EP 1789390 discloses a crystalline free base of vismodegib, but polymorphic form of crystalline form is not defined or characterized. On the other hand, process for the preparation of said crystalline free base of vismodegib in European patent EP 1789390 was repeated in WO 2014195977. According to the teachings of European patent EP 1789390, prior art form of vismodegib was obtained by crystallizing vismodegib with acetone and ethyl acetate, then by recrystallizing from hot slurry of isopropyl acetate. The crystalline polymorphic form of vismodegib obtained by said process designated as Form I. The X-ray powder diffractogram (XRPD) of Form I was shown in Figure 1 of WO 2014195977.

WO2014195977 further discloses two polymorphic forms of vismodegib labeled as Form II, Form III and preparation thereof.

One another crystalline vismodegib polymorph Form SV has been disclosed in WO 2014147504.

The discovery of a new polymorph of an active ingredient provides an opportunity to improve its characteristics, increasing the possibilities available to a formulation specialist when developing a new pharmaceutical form, a drug with a particular release profile or a specific dissolution degree.

Based on these considerations, there still appears a need for new polymorphs of vismodegib having further improved physical and/or chemical properties. Hence it was thought worthwhile by the inventors of the present application to explore pharmaceutically novel polymorphs of vismodegib with good chemical purity and improved stability characteristics, which may further improve the characteristics of vismodegib in finished medicinal product.

Summary of the invention

The object of the present invention is to provide a new crystal form of vismodegib and process for the preparation of this novel crystal form of vismodegib.

Another object of the present invention is to provide pharmaceutical compositions comprising new crystal form of vismodegib.

Technical Problem

Active pharmaceutical ingredients (APIs) are individual components or mixture of components that are used as a part of a finished pharmaceutical drug or medicinal product, where they provide the pharmacological activity.

Research and development projects in the pharmaceutical industry mainly aim to investigate different possible synthetic routes, key intermediates, reaction steps, impurity profile, particle size, particle shape and polymorphism to produce these APIs with higher efficiency. Polymorphism, the occurrence of different crystal forms, is a property of some molecules and molecular complexes. A single molecule, may give rise to a variety of crystalline forms having distinct crystal structures and physical properties. The difference in the physical properties of different crystalline forms results from the orientation and intermolecular interactions of adjacent molecules or complexes in the bulk solid.

The relationship between crystal forms of pharmaceutically active substance and pharmaceutical product is well known in the pharmaceutical industry. Pharmaceutical formulation is affected by crystal form of the pharmaceutically active substance.

It is a well known fact that different crystal forms of the same drug may have substantial differences in certain pharmaceutically important properties such as dissolution characteristics, bioavailability patterns, handling properties, solubility, flow characteristics and stability. These different physical forms may also have different particle size, hardness and glass transition temperatures.

The discovery of new polymorphic forms and solvates of an active pharmaceutical ingredient provides a new opportunity to improve the performance characteristics of pharmaceutical finished product, therefore, the development of new crystal forms is always encouraged.

In this context, there is a need to develop novel crystal forms of vismodegib having advantageous properties which are useful and well suitable for the preparation of various pharmaceutical compositions.

Solution to Problem

In an embodiment invention relates to a novel solid form of vismodegib.

In another embodiment, this new form of vismodegib, besides being stable, meets the pharmaceutical requirements such as storage, shelf life, solubility and high purity.

Brief description of the drawings:

Fig. 1 shows the X-ray powder diffraction (XRPD) pattern of crystalline vismodegib Form S

Fig. 2 shows the X-ray powder diffraction (XRPD) pattern of crystalline vismodegib Form B

Fig. 3 shows the attenuated total reflectance Fourier transform infrared (ATR-FTIR) spectra of crystalline vismodegib Form S

Fig. 4 shows the attenuated total reflectance Fourier transform infrared (ATR-FTIR) spectra of crystalline vismodegib Form B

Fig. 5 shows the differential scanning calorimetry (DSC) thermogram of crystalline vismodegib Form S

Fig. 6 shows the differential scanning calorimetry (DSC) thermogram of crystalline vismodegib Form B

Fig. 7 shows the thermogravimetric analysis (TGA) of crystalline vismodegib Form S

Description of embodiments

A first aspect of the present invention relates to a novel crystal form of vismodegib. This new methanol solvate form hereinafter is referred as crystalline Form S of vismodegib. Form S is characterized by an XRPD pattern having characteristic peaks at 7.1 ± 0.2, 14.0 ± 0.2, 16.7 ± 0.2, 19.1± 0.2, 22.3 ± 0.2, 24.6 ± 0.2 and 28.0 ± 0.2 degree 2-theta. Furthermore, vismodegib Form S can be characterized by an XRPD pattern with characteristic peaks at 14.7 ± 0.2, 16.0 ± 0.2, 17.0 ± 0.2, 17.6 ± 0.2, 21.7 ± 0.2, 22.9 ± 0.2, 23.6 ± 0.2, 25.6 ± 0.2, 26.1 ± 0.2, 27.5 ± 0.2, and 29.0 ± 0.2 degree 2-theta.

Form S is characterized by a powder X-ray diffraction pattern, as shown in Figure 1.

Form S is also characterized by an IR spectrum as shown in Figure 3, by a DSC thermogram as shown in Figure 5 and by a TGA thermogram as shown in Figure 7.

A second aspect of the present invention relates to a process for preparing novel crystalline polymorphic Form S of vismodegib.

The Form S according to the present invention may be obtained by:

a) providing a solution and/or mixture of vismodegib in a suitable solvent and/or solvent mixture in presence of methanol,

b) stirring the mixture at a suitable temperature,

c) cooling the solution to a suitable temperature,

d) filtering and isolating the solid,

e) washing the obtained solid as pure crystalline vismodegib designated as Form S with a suitable solvent and/or solvent mixture.

Wherein suitable solvent in step (a) and step (e) is selected from, water, methanol, ethanol, 2-propanol, 1-propanol, 1-butanol, 2-butanol, tert-butyl alcohol, 1-pentanol, 2-pentanol, amyl alcohol, ethylene glycol, glycerol, acetone, butanone, 2-pentanone, 3-pentanone, methyl butyl ketone, methyl isobutyl ketone, ethyl formate, methyl acetate, ethyl acetate, propyl acetate, isopropyl acetate, butyl acetate, isobutyl acetate, *tert*-butyl acetate, toluene, xylene, chloroform, dichloromethane, carbon tetrachloride, ethylene dichloride, chlorobenzene, acetonitrile, diethyl ether, diisopropyl ether, tert-butyl methyl ether, dibutyl ether, tetrahydrofuran (THF), 1,4-dioxane, 2-methoxyethanol, *N*,*N*-dimethylformamide (DMF), *N*,*N*-dimethylacetamide (DMAc), *N*-methylpyrrolidone (NMP), pyridine, dimethyl sulfoxide (DMSO), sulfolane, formamide, acetamide, propanamide, pyridine, formic acid, acetic acid, propionic acid, hexane, heptane, cyclohexane, cycloheptane and cyclooctane or mixtures thereof.

The suitable temperature used in step (b) is selected from room temperature to reflux temperature of the solvent used.

A third aspect of the present invention relates to crystalline anhydrous form of vismodegib designated as Form B.

Form B is characterized by an XRPD pattern, as shown in Figure 2.

Form B is also characterized by an IR spectrum, as shown in Figure 4 and characterized by a DSC thermogram, as shown in Figure 6.

A fourth aspect of the present invention relates to a process for preparing Form S of vismodegib involving Form B of vismodegib.

A fifth aspect of the present invention relates to a process for preparing Form B of vismodegib involving Form S of vismodegib.

Form S is stable without polymorphic conversion under normal conditions and under heating up to 90 °C. Crystalline Form S of vismodegib (methanol solvate) starts to lose methanol above 95 °C and converts to crystalline anhydrous Form B of vismodegib.

The degree of purity of the active ingredient and the resulting possible changes of the efficacy, further important properties for the pharmaceutical processing can be affected in an adverse manner.

The process of the present invention affords Form S of vismodegib in high purity and high yield. The Form S of vismodegib is obtained having purity greater than 99.5% by area percentage in high performance liquid chromatography (HPLC).

Stability plays an important role in the drug development process. Stability of a pharmaceutical product may be defined as the capability of that particular formulation, in a specific container or closure system, to remain within its chemical, physical, microbiological, therapeutic and toxicological specifications to assure its attributed quality, e.g., identity, purity, strength etc. until drug expiry.

Stability of a pharmaceutical product is strongly influenced by changes in solid-state form of the API. The changes in solid state form of the API may be resulted from the conditions of product manufacturing process. For example, processes such as grinding, milling, heating, and applying compression, may cause polymorphic form interconversions. Manufacturing conditions that include a solvent (e.g., wet granulation, polymorphs in solution, and polymorphs in suspension) may facilitate changes in the solid-state form of API. These variations comprising polymorphic transformations, hydrate/solvate formations and dehydration/desolvation reactions in the solid-state form of API, may cause stability problems in finished pharmaceutical products. Therefore, crystalline stability of API has a critical role on satisfying the essentialities of qualified pharmaceutical product and stable polymorphs of API should be used in pharmaceutical formulations.

For this aspect, crystalline stability of Form S of vismodegib was investigated under the following conditions: a sample was kept in an open flask at 90 °C for 10 days, packed samples were kept at 40 °C under 75% relative humidity (RH) and at 25 °C under 60% relative humidity (RH) for 6 months. The crystalline stability referred here, is the stability of a polymorphic form of API with respect to polymorph transformations, hydration, desolvation or amorphization through time under these conditions.

The crystalline stability of vismodegib Form S was investigated and determined by X-ray powder diffraction method. Results showed that any polymorphic transformation to another crystal form or any degradation in crystalline Form S did not occur. Crystalline Form S showed crystalline stability under dry heating at 90 °C for 10 days, at 40 °C / 75% RH and at 25 °C / 60% RH for 6 months.

The chemical stability of crystalline Form S of vismodegib is also important and its stability in finished product at room-temperature storage can be predicted from shorter-term storage under accelerated conditions of high temperature and humidity. In the present invention, crystalline vismodegib Form S samples were kept under dry heating in open flask at 90 °C for 10 days in an oven, and in LDPE pack at 40 °C & 75% RH and at 25 °C & 60% RH for 6 months in stability chambers to test chemical stability. The chemical stability of the samples was determined by HPLC method.

Table 1 shows the stability results of vismodegib Form S prepared according to the present invention. Form S samples stayed stable under all conditions without any change in the impurity profile and without increase in the impurity amounts.

Table 1. Vismodegib Form S stability test results

Test		**Acceptance Criteria**	**Initial**	**10 days at 90 °C in open flask**	**6 months at 40 °C, 75% RH**	**6 months at 25 °C, 60% RH**
X-Ray Diffraction Pattern		Form S	Form S	Form S	Form S	Form S
Related Substances (HPLC)	Any impurity	NMT 0.10% (for each impurity)	< 0.05%	< 0.05%	< 0.05%	< 0.05%
	Total impurities	NMT 0.50%	< 0.05%	< 0.05%	< 0.05%	< 0.05%

Table 2 shows the stability results of vismodegib Form B under the same conditions. Form B samples also stayed stable under all conditions without any change in the polymorphic form, without any significant change in the impurity profile and without increase in the impurity amounts.

Table 2. Vismodegib Form B stability test results

Test		**Acceptance Criteria**	**Initial**	**10 days at 90 °C in open flask**	**6 months at 40 °C, 75% RH**	**6 months at 25 °C, 60% RH**
X-Ray Diffraction Pattern		Form B	Form B	Form B	Form B	Form B
Related Substances (HPLC)	Any impurity	NMT 0.10% (for each impurity)	< 0.05%	< 0.05%	< 0.05%	< 0.05%
	Total impurities	NMT 0.50%	< 0.05%	< 0.05%	< 0.05%	< 0.05%

It can be concluded that there is no difference between vismodegib Form S and Form B in terms of stability. Both are physically and chemically stable under normal and accelerated stability conditions.

A sixth aspect of the present invention relates to pharmaceutical compositions comprising crystalline Form S of vismodegib along with a pharmaceutically acceptable carrier.

Instrumental parameters:

PXRD Method of Analysis:

X-Ray powder diffractograms were measured using a Shimadzu LabX XRD-6100 X-ray diffractometer (Shimadzu Corporation, Japan) by using following instrument parameters:
The measurement conditions were as follows:

Radiation: Cu (1.5406 Å)
Filter for Kβ: Nickel
Voltage: 40.0 kV
Current: 30.0 mA
Auto slit: not used
Divergence slit: 1.0°
Scatter slit: 1.0°
Receiving slit: 0.30 mm with a Graphite monochromator
Drive axis: Theta-2Theta
Scan range: 3.00 – 40.00°
Scan mode: continuous scan
Scan speed: 2.0°/min
Sampling pitch: 0.02°

FTIR:

Samples were measured as neat by ATR (attenuated total reflectance) on Shimadzu FTIR Spectrometer IR Prestige-21 (Shimadzu Corporation, Kyoto, Japan) in the range of 400 – 4000 cm^{-1} with 20 scans and 4 cm^{-1} resolution.

DSC:

Differential scanning calorimetry (DSC) thermograms were obtained using a differential scanning calorimeter (TA instruments DSC 250, USA) by using following instrument parameters: Start temperature: 25 °C, final temperature: 350 °C, heating rate: 10 °C/min.

TGA:

Thermogravimetric analysis (TGA) thermograms were obtained by using a thermogravimetric analyzer (TA instruments TGA 550, USA) by using the following instrument parameters: Start temperature: 25 °C, final temperature: 150 °C, heating rate: 10 °C/min, isothermal: 15 min or 10 min.

Following examples are provided to enable one skilled in the art to practice the invention and are merely illustrative of the invention. The examples should not be read as limiting the scope of the invention.

EXAMPLES

Preparation of new crystalline Form S of vismodegib

Example 1

HBTU (17.0 kg, 44.8 mol, 1.5 equiv.) and triethylamine (9.0 kg, 88.9 mol, 3.0 equiv.) were added into a dichloromethane (80 kg) mixture of 2-chloro-4-(methylsulfonyl)benzoic acid (9.0 kg, 38.4 mol, 1.3 equiv.) and stirred at 20 – 25 °C for 20 min. Then, 4-chloro-3-(pyridin-2-yl)aniline (6.1 kg, 29.8 mol, 1.0 equiv.) was added and the reaction mixture was stirred at 20 – 25 °C. After completion of the reaction, water (20 kg) was added and the solvent was evaporated in vacuo. Methanol (10 kg) was added onto the residue and the mixture was heated and stirred at 65 °C for 3 h. After cooling and stirring for 3 h at 20 – 25 °C, the mixture was filtered and product crystals were washed with methanol. Methanol (30 kg) mixture of crude product was prepared, heated to 65 °C and stirred at this temperature for 3 h. After cooling and stirring for 3 h at 20 – 25 °C, the mixture was filtered, the product crystals were washed with methanol and dried to afford white to off-white crystalline Form S of vismodegib (11.0 kg, 87.6%; purity by HPLC: 99.9%, LOD by TGA: 6.2%, methanol content by GC: 66,166 ppm). XRD, FTIR, DSC, and TGA of vismodegib Form S are presented in Fig. 1, 3, 5, and 7, respectively.

Example 2

HBTU (17.0 kg, 44.8 mol, 1.5 equiv.) and triethylamine (9.0 kg, 88.9 mol, 3.0 equiv.) were added into a dichloromethane (80 kg) mixture of 2-chloro-4-(methylsulfonyl)benzoic acid (9.0 kg, 38.4 mol, 1.3 equiv.) and stirred at 20 – 25 °C for 20 min. Then, 4-chloro-3-(pyridin-2-yl)aniline (6.1 kg, 29.8 mol, 1.0 equiv.) was added and the reaction mixture was stirred at 20 – 25 °C. After completion of the reaction, water (20 kg) was added and the solvent was evaporated in vacuo. Methanol (10 kg) was added onto the residue and the mixture was heated and stirred at 65 °C for 3 h. After cooling and stirring for 3 h at 20 – 25 °C, the mixture was filtered and product crystals were washed with methanol. Methanol (20 kg) and water (10 kg) mixture of crude product was prepared, heated to 65 °C and stirred at this temperature for 3 h. After cooling and stirring for 3 h at 20 – 25 °C, the mixture was filtered, the product crystals were washed with methanol and dried to afford white to off-white crystalline Form S of vismodegib (11.5 kg, 91.6%; purity by HPLC: 99.9%, LOD by TGA: 6.5%).

Preparation for Form B of vismodegib from Form S of vismodegib

Example 3

The mixture of vismodegib Form S (11.0 kg, 26.1 mol) in water (30 kg) is heated to 90 – 95 °C and stirred for 2 h. Product was isolated by filtration, washed with water and dried to afford white to off-white crystalline Form B of vismodegib (10.0 kg, 90.9%; purity by HPLC: 99.9%, water content by KF: 0.1%). XRD, FTIR, and DSC of vismodegib Form B are presented in Fig. 2, 4, and 6, respectively.

Example 4

Vismodegib Form S (10.0 g, 23.7 mmol) is dissolved in N,N-dimethylformamide (10 mL) by heating to 70 °C and then water (30 mL) is added. The mixture is stirred for 1 h at 70 °C and then cooled to 20 – 25 °C and stirred for 2 h at this temperature. Product was isolated by filtration, washed with water and dried to afford white to off-white crystalline Form B of vismodegib (8.5 g, 85.0%; purity by HPLC: 99.9%, water content by KF: 0.3%).

Example 5

Vismodegib methanol solvate (Form S) was dried in vacuo at 135 °C for 1 h to obtain anhydrous crystalline vismodegib (Form B) as an off-white crystalline solid (100%; purity by HPLC: 99.9%, water content by KF: 0.05%). This experiment was done by using 1 g and 10 g vismodegib methanol solvate (Form S) and both afforded anhydrous crystalline vismodegib (Form B).

CLAIMS

1. Crystalline Form S of vismodegib.

2. The crystalline Form S of vismodegib of claim 1, characterized by an XRPD pattern having characteristic peaks at 7.1 ± 0.2, 14.0 ± 0.2, 16.7 ± 0.2, 19.1± 0.2, 22.3 ± 0.2, 24.6 ± 0.2 and 28.0 ± 0.2 degree 2-theta; and further characterized by having peaks at 14.7 ± 0.2, 16.0 ± 0.2, 17.0 ± 0.2, 17.6 ± 0.2, 21.7 ± 0.2, 22.9 ± 0.2, 23.6 ± 0.2, 25.6 ± 0.2, 26.1 ± 0.2, 27.5 ± 0.2, and 29.0 ± 0.2 degree 2-theta.

3. The crystalline Form S of vismodegib of claim 1, characterized by a XPRD pattern having 2-theta values as shown in Fig. 1.

4. The crystalline Form S of vismodegib of claim 1, characterized by an IR spectrum as shown in Fig. 3.

5. The crystalline Form S of vismodegib of claim 1, characterized by a DSC thermogram as shown in Fig. 5 and characterized by a TGA thermogram as shown in Fig. 7.

6. A method of preparation of crystalline vismodegib Form S of claim 1, comprising crystalline Form B of vismodegib.

7. A method of preparation of crystalline vismodegib Form B, comprising crystalline vismodegib Form S of claim 1.

8. A pharmaceutical composition comprising crystalline Form S of vismodegib and optionally at least one pharmaceutically acceptable excipient.

9. A method of treating basal cell carcinoma comprising administering therapeutically effective amount of crystalline Form S of vismodegib, wherein the crystalline Form S of vismodegib is characterized by an XPRD pattern having 2-theta values as shown in Fig. 1.

10. The method of claim 9, comprising administering therapeutically effective amount of crystalline Form S of vismodegib according to any one of the claims 1 to 9.

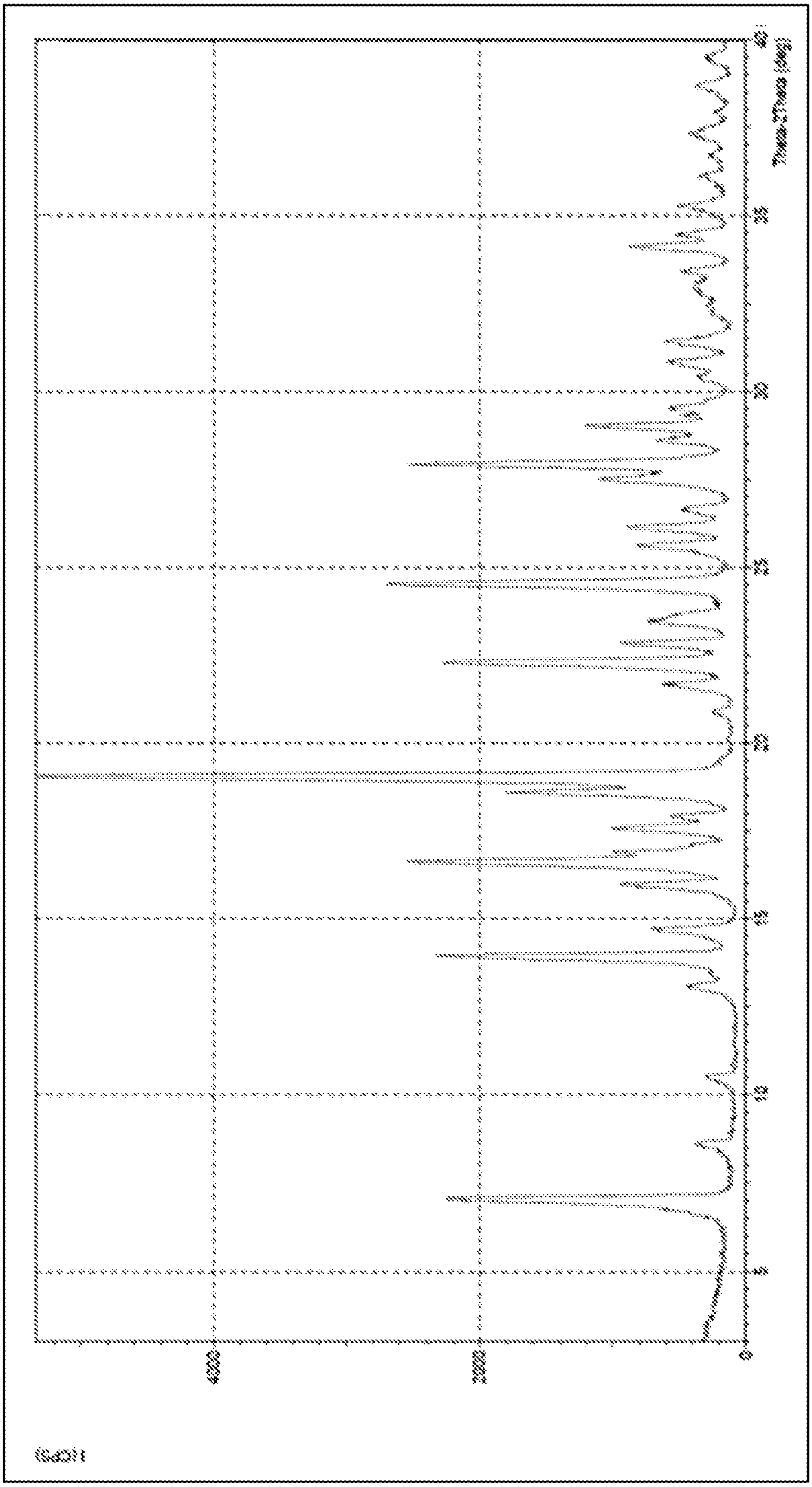


Figure 1

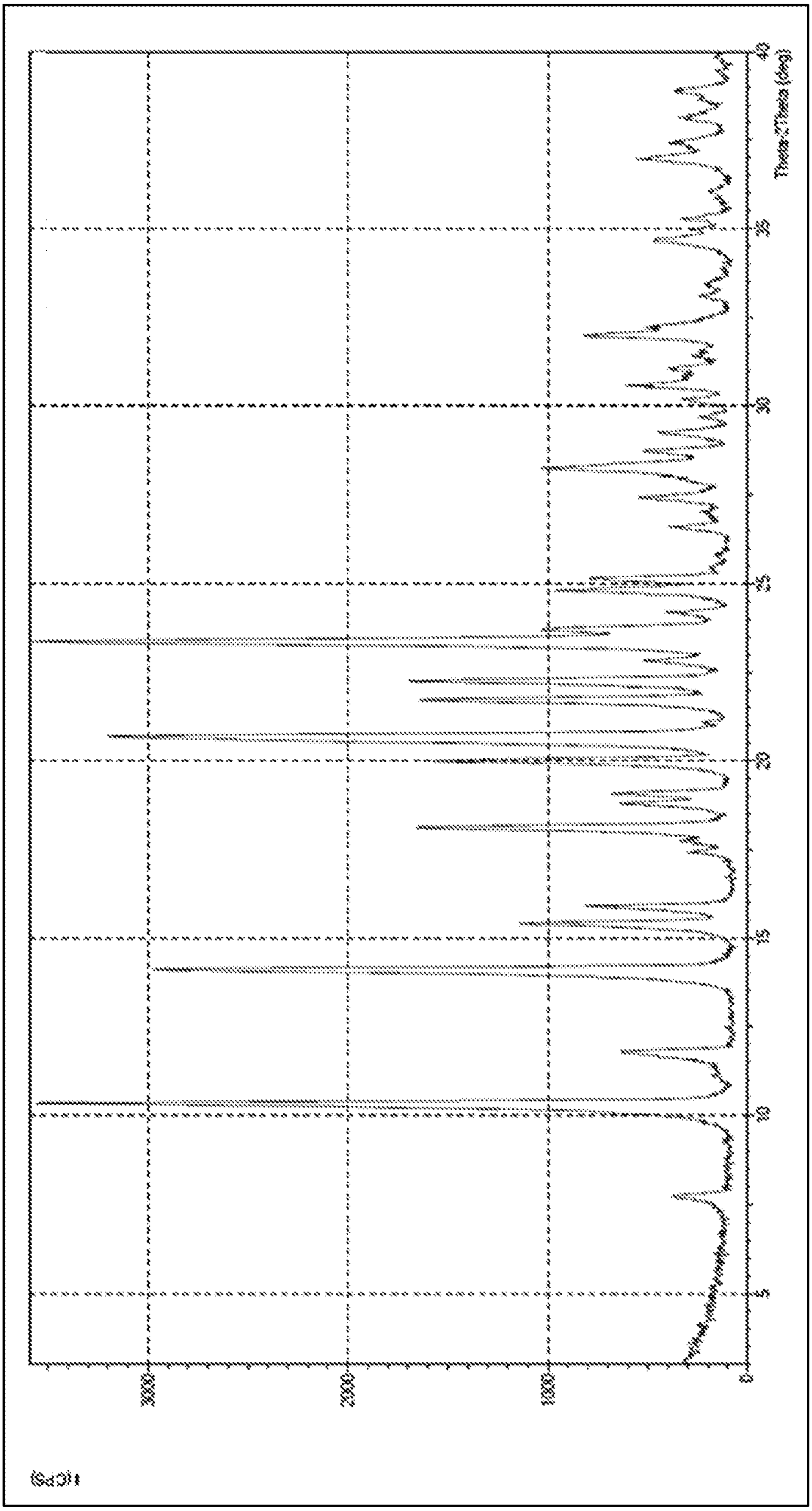


Figure 2

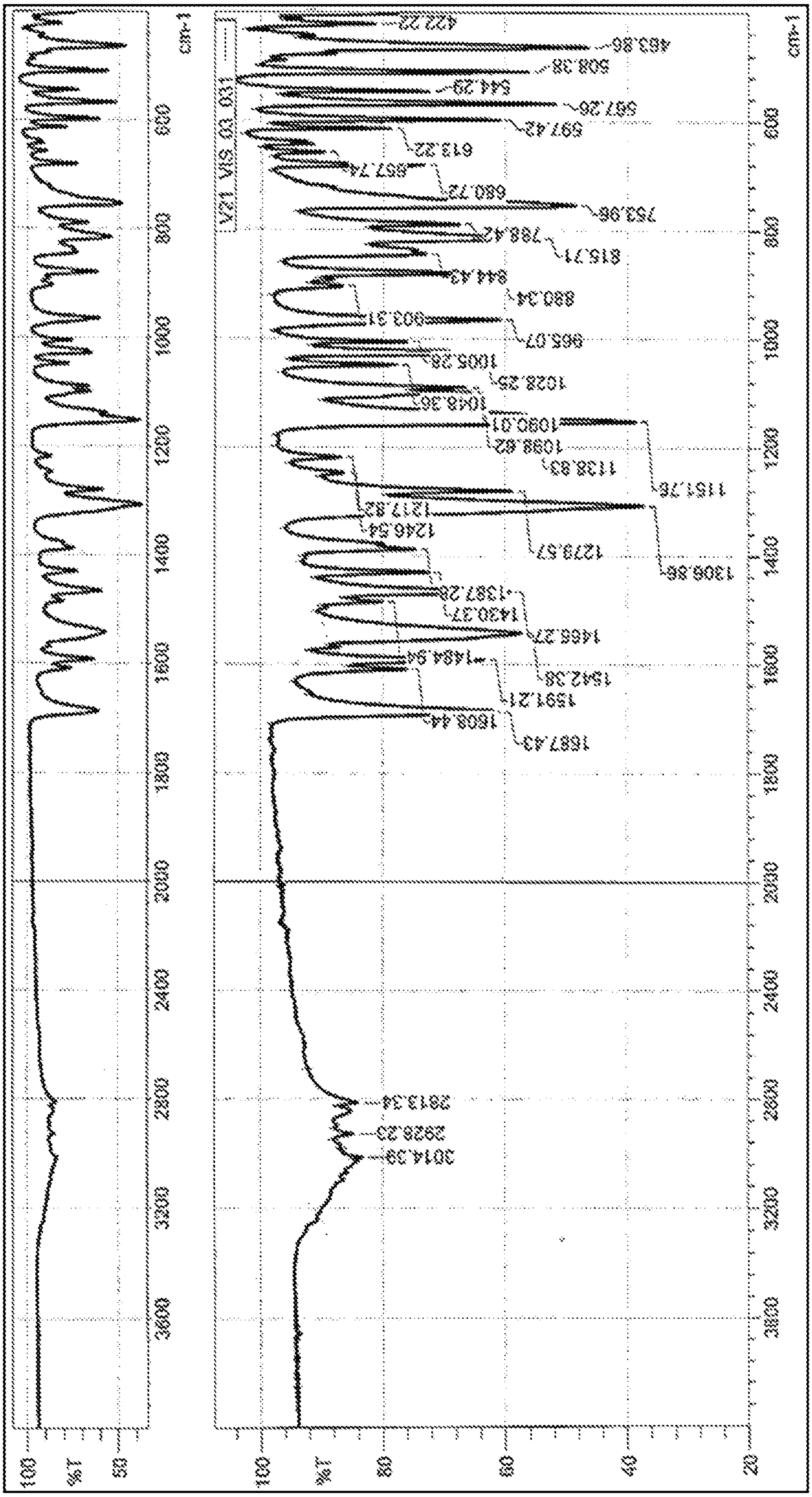

V21 VIS 03 031
cm-1
100
%T
50
80
60
40
20
600
800
1000
1200
1400
1600
1800
2000
2400
2800
3200
3600
422.22
463.86
508.38
544.29
567.26
597.42
613.22
657.74
680.72
753.06
788.42
816.71
844.43
880.34
903.31
965.07
1005.28
1028.25
1048.36
1080.01
1098.62
1138.83
1151.76
1217.82
1246.54
1278.57
1306.86
1387.28
1430.37
1465.27
1484.94
1542.38
1591.21
1608.44
1687.43
2813.34
2928.23
3014.39

Figure 3

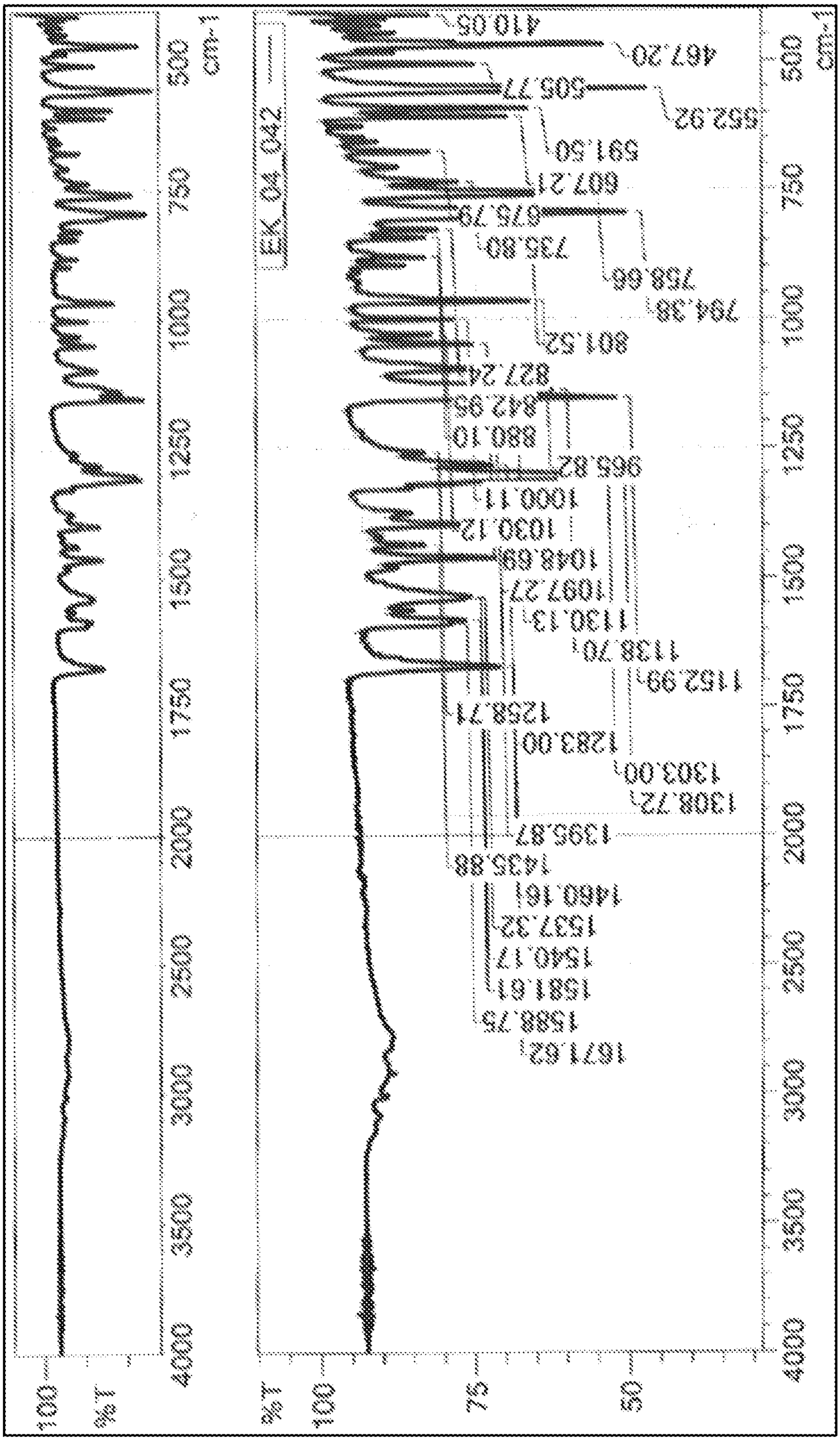

EK_04_042
%T
100
75
50
4000
3500
3000
2500
2000
1750
1500
1250
1000
750
500
cm-1
410.05
467.20
505.77
552.92
591.50
607.21
675.79
735.80
758.66
794.38
801.52
827.24
842.95
880.10
965.82
1000.11
1030.12
1048.69
1097.27
1130.13
1138.70
1152.99
1258.71
1283.00
1303.00
1308.72
1395.87
1435.88
1460.16
1537.32
1540.17
1581.61
1588.75
1671.62

Figure 4

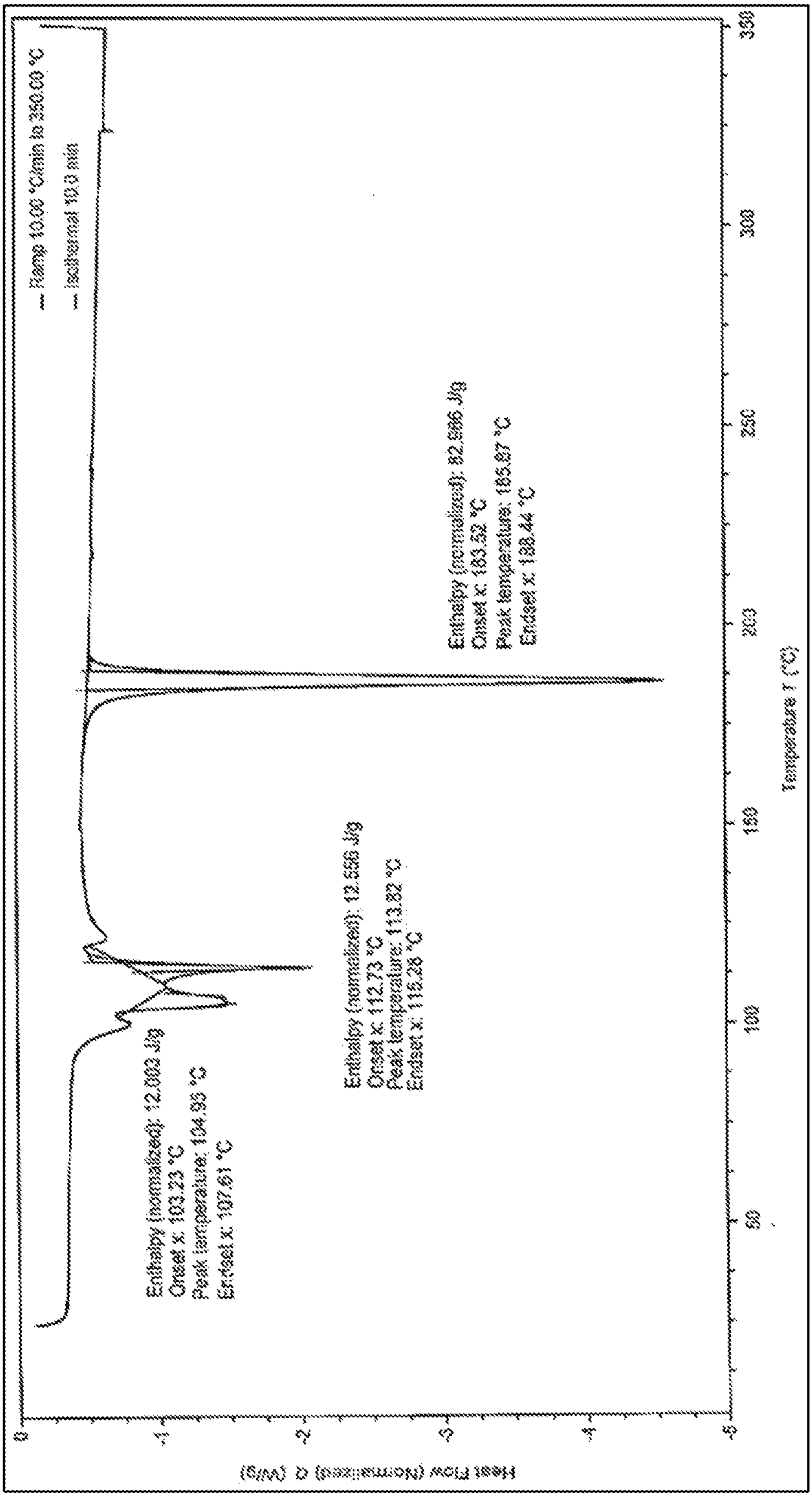

— Ramp 10.00 °C/min to 350.00 °C
— Isothermal 10.0 min
Enthalpy (normalized): 12.002 J/g
Onset x: 103.23 °C
Peak temperature: 104.95 °C
Endset x: 107.61 °C
Enthalpy (normalized): 12.556 J/g
Onset x: 112.73 °C
Peak temperature: 113.82 °C
Endset x: 115.28 °C
Enthalpy (normalized): 82.586 J/g
Onset x: 183.53 °C
Peak temperature: 185.87 °C
Endset x: 188.44 °C
Temperature T (°C)
50
100
150
200
250
300
350
Heat Flow (Normalized) Q (W/g)
0
-1
-2
-3
-4
-5

Figure 5

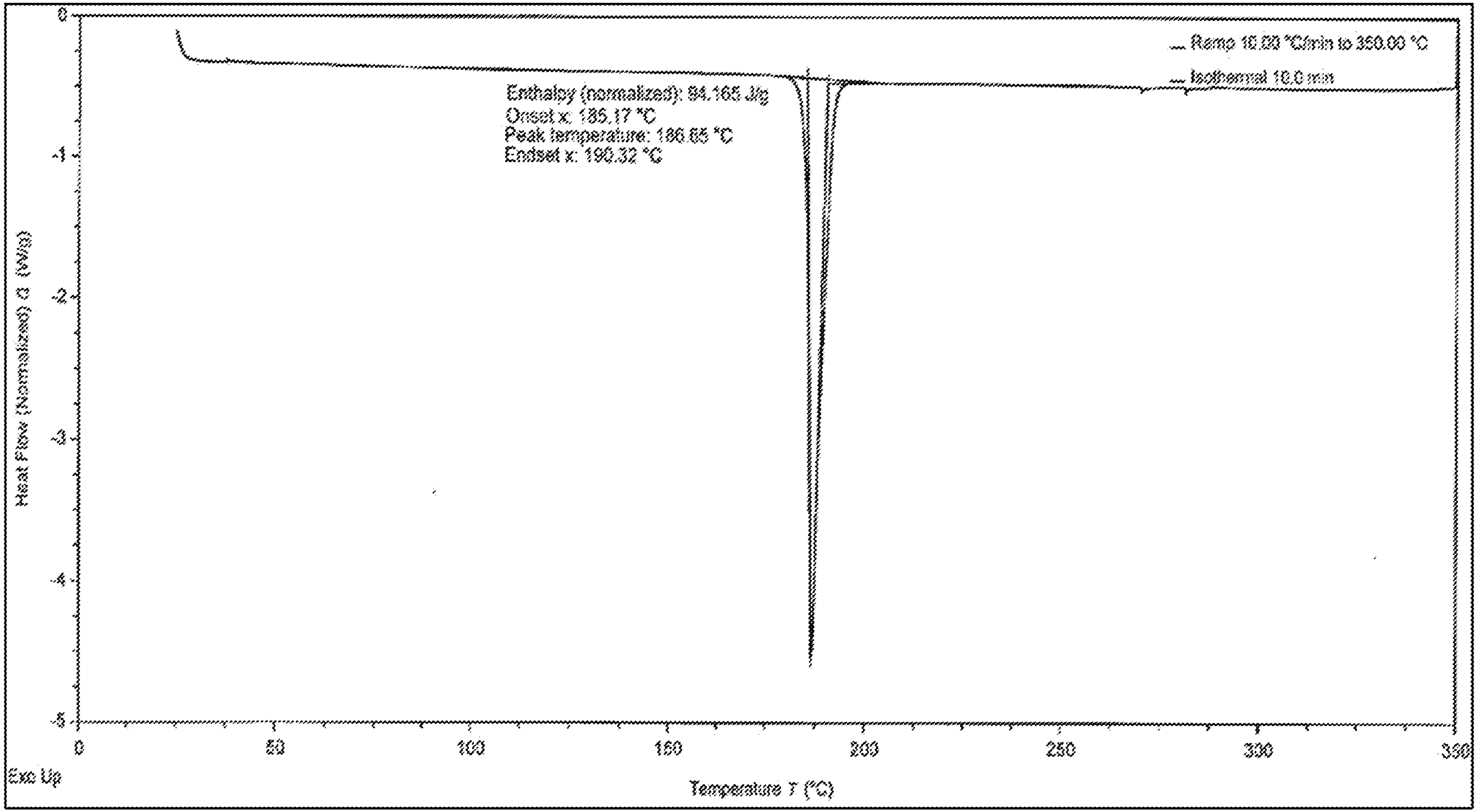

Enthalpy (normalized): 94.165 J/g
Onset x: 185.17 °C
Peak temperature: 186.85 °C
Endset x: 190.32 °C
Ramp 10.00 °C/min to 350.00 °C
Isothermal 10.0 min
Heat Flow (Normalized) Q (W/g)
0
-1
-2
-3
-4
-5
Exo Up
0
50
100
150
200
250
300
350
Temperature T (°C)

Figure 6

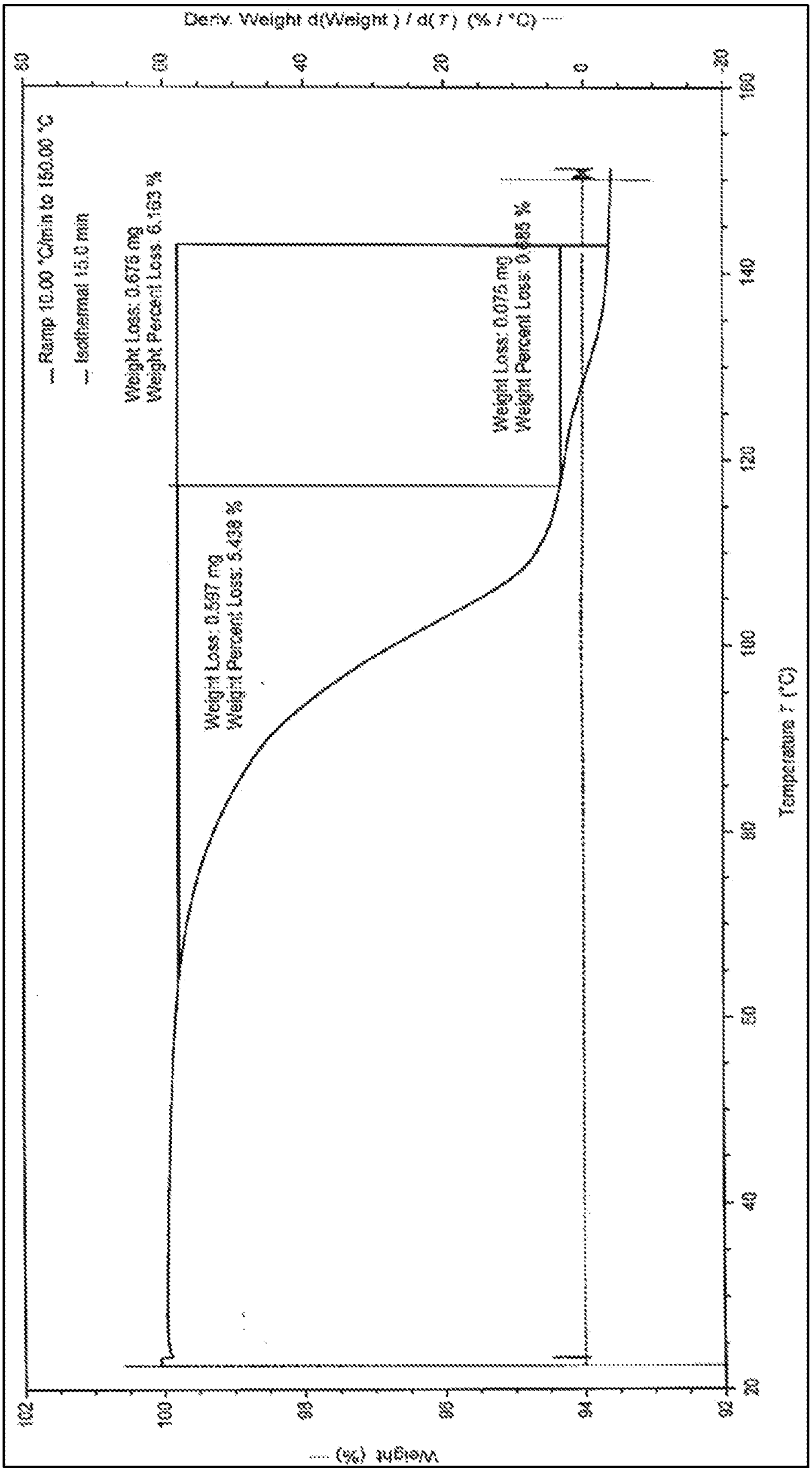

Deriv. Weight d(Weight) / d(T) (% / °C) ·····
80
60
40
20
0
-20
— Ramp 10.00 °C/min to 150.00 °C
— Isothermal 15.0 min
Weight Loss: 0.675 mg
Weight Percent Loss: 6.153 %
Weight Loss: 0.597 mg
Weight Percent Loss: 5.438 %
Weight Loss: 0.075 mg
Weight Percent Loss: 0.685 %
Weight (%) ·····
102
100
98
96
94
92
Temperature T (°C)
20
40
60
80
100
120
140
160

Figure 7

INTERNATIONAL SEARCH REPORT

International application No.
PCT/TR2022/050047

A. CLASSIFICATION OF SUBJECT MATTER

A61P 35/00 (2006.01)i; C07D 213/40 (2006.01)i

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)

A61P 35/00; C07D 213/40

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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2016020324 A1 (BASF SE [DE]) 11 February 2016 (2016-02-11) Desc. examples 7,8 figure 6,7	1-10
A	WO 2014195977 A2 (HETERO RESEARCH FOUNDATION [IN]) 11 December 2014 (2014-12-11) All document	1-10
A	EP 3381900 A1 (AZAD PHARMACEUTICAL INGREDIENTS AG [CH]) 03 October 2018 (2018-10-03) All document	1-10

☐ Further documents are listed in the continuation of Box C. ☑ See patent family annex.

*	Special categories of cited documents:	"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
"A"	document defining the general state of the art which is not considered to be of particular relevance	"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
"D"	document cited by the applicant in the international application	"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
"E"	earlier application or patent but published on or after the international filing date	"&"	document member of the same patent family
"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		

Date of the actual completion of the international search	Date of mailing of the international search report
14 November 2022	**14 November 2022**

Name and mailing address of the ISA/TR
Turkish Patent and Trademark Office (Turkpatent)
Hipodrom Caddesi No. 13
06560 Yenimahalle
Ankara
Turkey
Telephone No. **+903123031000**
Facsimile No. **+903123031220**

Authorized officer
Nurgül SIKI
Telephone No. **+903123031622**

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/TR2022/050047

Patent document cited in search report			Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
WO	2016020324	A1	11 February 2016	CA	2955570	A1	11 February 2016
				CN	106573888	A	19 April 2017
				EP	3177591	A1	14 June 2017
				JP	2017524004	A	24 August 2017
				US	2017216266	A1	03 August 2017
				US	10105355	B2	23 October 2018
WO	2014195977	A2	11 December 2014	WO	2014195977	A3	12 November 2015
EP	3381900	A1	03 October 2018	GB	201704801	D0	10 May 2017
				GB	2560903	A	03 October 2018
				US	2018273477	A1	27 September 2018
				US	10343998	B2	09 July 2019