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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
10 November 2016 (10.11.2016)

WIPO | PCT

(10) International Publication Number
WO 2016/178150 A1

(51) International Patent Classification:
A61K 31/4375 (2006.01)

(21) International Application Number:
PCT/IB2016/052530

(22) International Filing Date:
4 May 2016 (04.05.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2270/CHE/2015 5 May 2015 (05.05.2015) IN

(71) Applicant: **SHILPA MEDICARE LIMITED** [IN/IN]; 10/80,Second Floor,Rajendra Gunj, Raichur,karnataka 584102 (IN).

(72) Inventors: **PIPAL, Bhagat Raj**; Shilpa Medicare Limited, 10/80; Second Floor;, Rajendra Gunj, Raichur, Raichur 584102 (IN). **SINGH, Vinod Kumar**; Shilpa Medicare Limited, 10/80; Second Floor;, Rajendra Gunj, Raichur, Raichur 584102 (IN). **CHATURVEDI, Akshay Kant**; 10/80,Second Floor,Rajendra Gunj, Raichur,karnataka 584102 (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, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, 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:

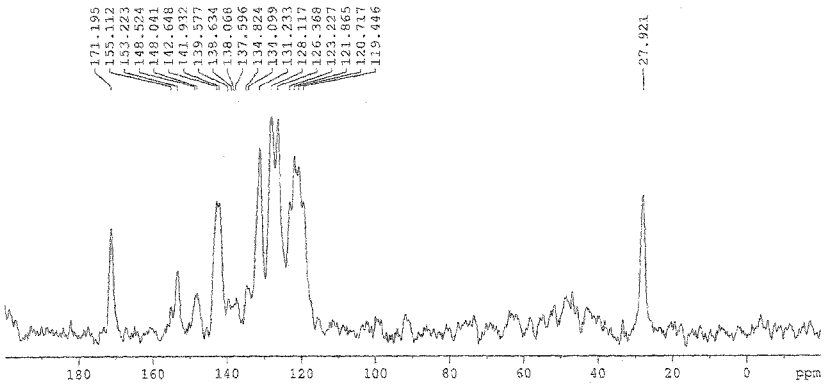
— *as to the identity of the inventor (Rule 4.17(i))*

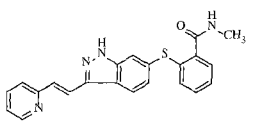
— *of inventorship (Rule 4.17(iv))*

[Continued on next page]

(54) Title: NOVEL POLYMORPHS OF AXITINIB

FIGURE 12





(I)

(57) Abstract: The present invention relates to novel crystalline polymorphic forms of Axitinib Formula (I). Said crystalline forms may be useful in the improved preparation of oral dosage forms for the treatment of cancer.

WO 2016/178150 A1

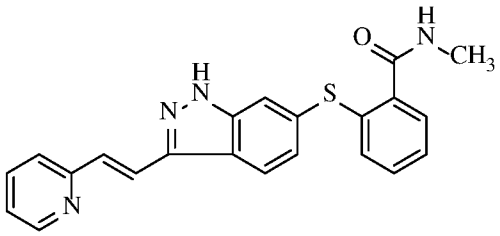
Published:

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

NOVEL POLYMORPHS OF AXITINIB

FIELD OF THE INVENTION

The present invention relates to novel stable crystalline polymorphic forms of Axitinib Formula (I).



(I)

said crystalline forms may be commercially viable and lead to consistently produce as the stable material as per the processes according to the present invention.

BACKGROUND OF THE INVENTION

Axitinib is chemically known as N-methyl-2-[3-((E)-2-pyridin-2-yl-vinyl)-1H-indazol-6-ylsulfanyl]-benzamide (I).

N-methyl-2-[3-((*E*)2-pyridin-2-yl-vinyl)-1*H*-indazol-6-ylsulfanyl]-benzamide or Axitinib is reported as tyrosine kinase inhibitor of vascular endothelial growth factor receptors (VEGFR)-1, VEGFR-2 and VEGFR-3 in US6,534,524. These receptors are implicated in pathologic angiogenesis, tumour growth, and metastatic progression of cancer. Axitinib has been shown to potently inhibit VEGF-mediated endothelial cell proliferation and survival. Axitinib inhibited the phosphorylation of VEGFR-2 in xenograft tumor vasculature that expressed the target in vivo and produced tumor growth delay, regression, and inhibition of metastases in many experimental models of cancer.

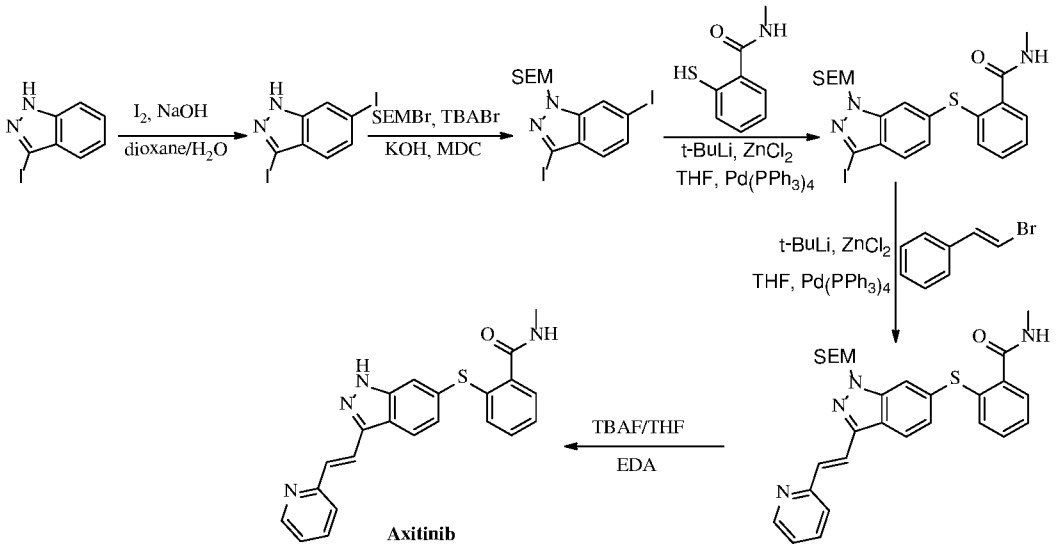
Axitinib is weak base, non-hygrospic, classified as Bio pharmaceutics Classification System (BCS) class II (low solubility, high permeability), and exhibits polymorphism.

Axitinib was approved by USFDA in 2012 and is marketed under the brand name Inlyta®, and is indicated for the treatment of adult patients with advanced renal cell carcinoma (RCC) after failure of prior systemic treatment. Axitinib is marketed in a crystalline Form XLI, which is reported by Campeta et al in US8791140. Axitinib is a white to light yellow powder with the empirical formula C_{22} H_{18} N_4OS and a molecular weight of 386.47 Daltons.

As per the EMEA scientific discussion of Axitinib- it provides "*Five crystalline anhydrous forms have been identified (Form I, Form IV, Form VI, Form XXV and Form*

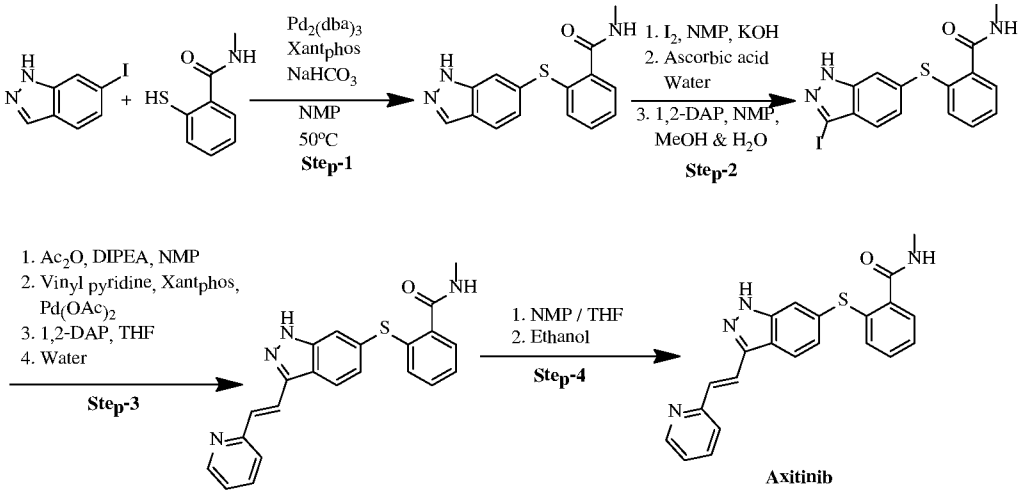
XLI). A number of crystalline solvates and hydrate forms have been observed and an amorphous form has been prepared. The polymorphic form intended for marketing is Form XLI."

Axitinib is generically and specifically disclosed in US 6,534,524.The process disclosed for the preparation of Axitinib is delineated below:



This patent has not provided any insight about the impurity concern as well as disclosure of any purity of the final product. The process appears cumbersome and involves the formation of large number of impurities as disclosed in Organic process Research and development 2014 18(1), 266-274. In view of this, it was apparent to develop a process/or crystallization process resulting in the product, which is complying with the ICH requirements of quality parameters.

US 7,232,910 and Organic process Research and development (OPRD) 2014 18(1), 266-274 discloses a process for the preparation of Axitinib. The process is as disclosed below:



US patent 7,232,910 further disclosed two more route of synthesis for the preparation of Axitinib. However, this patent has not disclosed any generalized impurities formed during the process development. This patent also not disclosed exact purity obtained as per this process. It broadly mentioned the purity as ≥ 99 % and does not disclosed the content of total impurities formed in the final active pharmaceutical ingredient (API).

Organic Process Research and development 2014 18(1), 266-274 disclosed that condensation of 6-iodoindazole with 2-Mecapto N-methyl benzamide in presence of palladium catalyst leads to the formation of Xantphos impurities. The proposed mechanism for exchange of aryl groups on Xantphos and the observed side products are clearly disclosed in scheme 5 of this Journal. Further, this Journal clearly discloses that the formation of these impurities due to incompletion of reaction.

Ye et al in US 2006/0094763 disclosed different crystalline forms like crystalline Form I, Form II, Form III, Form IV, Form VI, Form VII and Form VIII of Axitinib. Further, this patent not disclosed any specific synthesis for the preparation of Axitinib.

Campeta et al in US 2010/0179329 disclosed some more different crystalline forms like crystalline Form XLI, Form XXV, Form IX, Form XII, Form XV and amorphous form of Axitinib. Further, this patent has not disclosed any specific synthesis for the preparation of Axitinib. Specifics for Form-XLI mentioned in this patent requires ethanol solvent to be utilized [as per Example 1(d)] for its preparation. Form-XLI shall essentially contain XRPD peaks at 6.0, 11.5,11.9 and 21.0 +/- 0.1°2θ. Further, within large number of reported crystalline forms in the same patent, these essential peaks are also found to be present. E.g. Form VIII and XXV possess peaks at 21.0, Form XVI possess peak at 5.9 and 11.9+/- 0.1°2θ. In view of this, it is materially questionable- whether single peak becomes the essential feature for distinguishing a particular crystalline form.

Journal of Pharmaceutical Sciences 99(9) 3874-3886 disclosed many solvates, hydrates and anhydrates of Axitinib. However, this journal disclosed that "solvates may be anticipated to be thermodynamically stable in their corresponding mother liquor and may resist further solvent mediated transformation to an anhydrous form"

In view of the above it is pertinent to note that there exists an inherent need to develop stable crystalline form of Axitinib having further improved physical and/or chemical properties besides high purity levels. Hence it was thought worthwhile by the inventors of the present application to explore novel process/crystallization process for the preparation of Axitinib, which may further improve the characteristics of drug Axitinib and in developing

the substantially pure stable crystalline forms of Axitinib consistently obtainable and amenable to scale up.

As polymorphism has been given importance in the recent literatures owing to its relevance to the drugs having oral dosage forms due to its apparent relation to dose preparation/suitability in composition steps/ bioavailability and other pharmaceutical profiles, stable polymorphic form of a drug has often remained the clear choice in compositions due to various reasons of handling, mixing and further processing including bioavailability and stability.

Exploring new polymorphic form for developing a stable and pure form of Axitinib, which are amenable to scale up for pharmaceutically active useful compounds in the preparation of Axitinib may thus provide an opportunity to improve the drug performance characteristics of products such as purity and solubility. Hence, inventors of the present application report a new polymorphic form, which is a stable and substantially pure form of Axitinib, which may be industrially amenable and usable for preparing the corresponding pharmaceutical compositions.

The present invention provides an improved process for the preparation of substantially pure novel crystalline forms of Axitinib, wherein substantially pure material having a purity of greater than 99.5% by HPLC and meeting the quality of ICH guidelines. Axitinib crystalline material obtained by the process of the present invention is chemically stable and has been found with good dissolution properties.

In view of the above and to overcome the prior-art problems the present inventors had now developed a new polymorphic forms of Axitinib, which are substantially pure, stable produced by using industrially friendly solvents, which does not include tedious work up and time lagging steps.

OBJECTIVE OF THE INVENTION

The main objective of the invention relates to new stable polymorphic forms of Axitinib.

Yet another objective of the invention relates to crystalline forms of Axitinib, which is a stable and substantially pure form of Axitinib, which may be industrially amenable and usable for preparing the corresponding pharmaceutical compositions.

Yet another objective of the invention relates a process for the preparation of crystalline forms of Axitinib.

Yet another objective of the invention relates a process for the preparation of crystalline form of Axitinib, which is free of process related impurities.

SUMMARY OF THE INVENTION

Aspects of the present invention relates to the new stable polymorphic forms of Axitinib.

In one aspect of present invention, it relates to Non-solvated Axitinib crystalline Form-SAB-I characterized by X-ray powder diffraction pattern comprising at least 5 characteristic 2θ° peaks selected from 8.3, 9.3, 15.6, 16.5, 17.6, 21.0, 24.1 and 26.0 ±0.2 2θ°; liquid state NMR in DMSO spectrum comprising ^{13}C chemical shift at 26.1±0.2, 114.7±0.2, 154.8±0.2 and 167.8±0.2 ppm and solid state NMR spectrum comprising ^{13}C chemical shift at 171.1, 153.2, 142.6, 139.5, 131.2, 128.1 and 126.3 ± 0.5

This non-solvated Axitinib crystalline Form-SAB-I, is further characterized by DSC isotherm comprising two endothermic peaks ranging between-

a. Peak -1- Between 213 to 217°C
b. Peak -2- Between 219 to 224°C

Further aspect of the present invention relates to process for the preparation of Non-solvated Axitinib crystalline Form-SAB-I comprising the steps of:

a) dissolving Axitinib in Dimethylsulfoxide;
b) heating the reaction mixture to about 60-80°C followed by cooling;
c) adding methanol;
d) recover the crystalline material; and
e) drying the crystalline material between 40-70°C.

Another aspect of the present invention relates to Axitinib monohydrate crystalline Form-SAB-II characterized by X-ray powder diffraction pattern comprising at least 5characteristic 2θ° peaks selected from 7.5, 8.0, 14.2, 14.7, 15.7, 18.1, 20.1, 24.4, 29.8 and 32.0 ±0.2 2θ°.

Said Axitinib monohydrate crystalline Form-SAB-II, is further characterized by DSC isotherm comprising three endothermic peaks ranging between-

a. Peak -1- Between 48 to 86°C
b. Peak -2- Between 213 to 217°C
c. Peak -2- Between 219 to 224°C

Further aspect of the present invention relates to process for the preparation of Axitinib monohydrate crystalline Form-SAB-II comprising the steps of:

a) adding Axitinib in water;

b) stirring the contents of step a) at 25-30 °C; and

c) filtered to recover crystalline Axitinib monohydrate

Another aspect of the present invention relates to Axitinib crystalline Form-SAB-III characterized by X-ray powder diffraction pattern comprising at least 4 characteristic 2θ° peaks selected from 10.1, 10.4, 15.3, 18.3, 18.7, 19.7and 24.6 ±0.2 2θ° and methanol contents ranging between 1.5 -4.0% w/w (by GC).

Said Axitinib crystalline Form-SAB-III, is further characterized by DSC isotherm comprising three endothermic peaks ranging between-

a. Peak -1- Between 53 to 73°C

b. Peak -2- Between 214 to 218°C

c. Peak -2- Between 222 to 225°C

Further aspect of the present invention relates to process for the preparation of Axitinib crystalline Form-SAB-III comprising the steps of:

a) dissolving Axitinib in Dimethylsulfoxide;

b) heating the reaction mixture to about 60-80°C;

c) adding methanol;

d) isolating crystalline material; and

e) drying at 40-45°C

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is an example of X-ray powder diffraction ("XRPD") pattern of Non-solvated Axitinib crystalline Form-SAB-I obtained according the present invention.

Fig. 2 is an example of liquid state ^{13}C NMR spectrum of Non-solvated Axitinib crystalline Form-SAB-I obtained according the present invention.

Fig. 3 is an example of DSC endotherm of Non-solvated Axitinib crystalline Form-SAB-I obtained according the present invention.

Fig. 4 is an example of TGA thermogram of Non-solvated Axitinib crystalline Form-SAB-I obtained according the present invention.

Fig. 5 is an example of X-ray powder diffraction ("XRPD") pattern of Axitinib monohydrate crystalline Form-SAB-II obtained according the present invention.

Fig. 6 is an example of DSC endotherm of Axitinib monohydrate crystalline Form-SAB-II obtained according the present invention.

Fig. 7 is an example of TGA thermogram of Axitinib monohydrate crystalline Form-SAB-II obtained according the present invention.

Fig. 8is an example of X-ray powder diffraction ("XRPD") pattern of Axitinib crystalline Form-SAB-III obtained according the present invention.

Fig. 9 is an example of DSC endotherm of Axitinib crystalline Form-SAB-III obtained according the present invention.

Fig. 10 is an example of TGA thermogram of Axitinib crystalline Form-SAB-III obtained according the present invention.

Fig. 11is an example of X-ray powder diffraction ("XRPD") pattern of Axitinib crystalline Form obtained according to example-1.

Fig. 12 is an example of solid state ^{13}C NMR spectrum of Non-solvated Axitinib crystalline Form-SAB-I obtained according the present invention.

DETAILED DESCRIPTION OF THE INVENTION

Although several polymorphs of Axitinib have been identified and well known in the literature, each polymorphic form can be distinguished using several different analytical parameters, alone or in combination, such as, but not limited to, powder X-ray diffraction pattern peaks or combinations of two or more peaks. However, the present inventors now developed a new stable crystalline polymorphic form, which are different from the prior-art polymorphic forms disclosed in the literature.

In one embodiment of the present invention relates to a novel Non-solvated Axitinib crystalline Form-SAB-I characterized by X-ray powder diffraction pattern comprising at least 5 characteristic 2θ° peaks selected from 8.3, 9.3, 15.6, 16.5, 17.6, 21.0, 24.1 and 26.0 ±0.2 2θ°; liquid state NMR spectrum comprising ^{13}C chemical shift at 26.1±0.2, 114.7±0.2, 154.8±0.2 and 167.8±0.2, ppm and solid state NMR spectrum comprising ^{13}C chemical shift at 171.1, 153.2, 142.6, 139.5, 131.2, 128.1 and 126.3 ± 0.5

Non-solvated Axitinib crystalline Form-SAB-I is further characterized by X-ray powder diffraction pattern comprising at 2θ° peaks selected from 13.7, 16.1, 18.6, 22.6, 23.1, and 23.4 ±0.2 2θ°.

Non-solvated Axitinib crystalline Form-SAB-I is further characterized by DSC isotherm comprising two endothermic peaks ranging between-

a. Peak -1- Between 213 to 217°C
b. Peak -2- Between 219 to 224°C

The present invention further provides a process for the preparation of Non-solvated Axitinib crystalline Form-SAB-I characterized by X-ray powder diffraction pattern comprising at least 4 characteristic 2θ° peaks selected from 8.3, 9.3, 15.6, 16.5, 17.6, 21.0, 24.1 and 26.0 ±0.2 2θ°, comprising the steps of:

a) dissolving Axitinib in Dimethylsulfoxide;
b) heating the reaction mixture to about 60-80°C followed by cooling;
c) adding methanol;
d) recover the crystalline material; and
e) drying the crystalline material between 40-70°C.

Non-solvated Axitinib crystalline Form-SAB-I obtained by the above process is anhydrous and having a moisture content of less than 1.0 %. The Axitinib crystalline Form-SAB-I obtained by this process is stable and free of process related impurities.

In one embodiment of the present invention, said Non-solvated Axitinib crystalline Form-SAB-I obtained according to the process was found to possess moisture content about 0.44% w/w (By KF).

The present inventors analyzed Non-solvated Axitinib crystalline Form-SAB-I for Hygroscopic study. However, the present inventors found that the Non-solvated Axitinib crystalline Form-SAB-I obtained by the present invention is stable at all temperature ranging between 0-80°C.

Further, the study of Non-solvated Axitinib crystalline Form-SAB-I at 90% relative humidity in desiccator at 25°C containing saturated potassium chloride solution are kept in glass petri-dish and placed it into desiccator, the samples were withdrawn and analyzed at different time intervals, the results are as follows:

S.No	Time (in Hours)	Water content (%)
1	Initial	0.40%
2	2 hours	4.31%
3	4 hours	4.35%
4	6 hours	4.47%
5	8 hours	4.40%

S.No	Time (in Hours)	Water content (%)
6	24 hours	4.52%
7	48 hours	4.51%
8	72 hours	4.49%

The above results indicates that the Non-solvated Axitinib crystalline Form-SAB-I was observed to absorb moisture at about 90% relative humidity. The sample obtained after 72 hours was dried at 60-80°C and further sent for PXRD analysis. The PXRD obtained was found to resembles with the Non-solvated Axitinib crystalline Form-SAB-I. This data shows that the Non-solvated Axitinib crystalline Form-SAB-I is a stable form of Axitinib and may be utilized in the preparation of pharmaceutical composition. On normal atmospheric conditions, there was no moisture absorption observed in Form-SAB-I. At room temperature condition and humidity of about 50%, there was no weight gain observed as moisture. Hence, under normal atmosphere conditions, Form-SAB-I was found to be thermodynamically stable form.

It was also observed by inventors of the present application that Form-SAB-II also becomes stable as monohydrate form. This form may also be produced consistently at industrial scale quantities. However, due to anticipated degradation in presence of moisture said form may be utilized with caution and further studies of stabilities in preparing any solid oral dosage form.

Further embodiment of the present invention provides Non-solvated crystalline Axitinib Form-SAB-I obtained by the present invention is free of other polymorphic impurities, wherein said crystalline form is present in a solid form greater than 99.9 %by weight.

Non-solvated Axitinib crystalline Form-SAB-Iis found to be a very stable crystal lattice which is adequately stable to handle and store for longer time without any significant or measurable change in its morphology and physicochemical characteristics. Non-solvated Axitinib crystalline Form-SAB-Iretains its nature even on exposure to uncontrolled environmental conditions. This stable form thus, offers various advantages in terms of storage, shelf life and favorable impurity profile.

Any form of Crude or Pure Axitinib obtained by any process may be used for preparing Non-solvated Axitinib crystalline Form-SAB-I. Non-solvated Axitinib crystalline Form-SAB-I of the present invention may have one or more advantageous and desirable properties compared to the known Crystalline Axitinib forms, which are not limited to better

stability, hygroscopicity, high solubility and high purity leading to improved storage and distribution.

The process related impurities, including degradation products and other medium dependent impurities like residual solvent, that appear in the impurity profile of the Axitinib can be substantially removed by the process of the present invention resulting in the formation pure Non-solvated Axitinib crystalline Form-SAB-I. A substantially pure product i.e. Non-solvated Axitinib crystalline Form-SAB-I having purity more than 99.9% (by HPLC) can be obtained in high yield by the process of the present invention.

The Non-solvated Axitinib crystalline Form-SAB-I described herein may be characterized by X-ray powder diffraction pattern (XRPD) and IR absorption spectra and Thermal techniques such as differential scanning calorimetric (DSC) Analysis and TGA and solid state NMR. The samples of Non-solvated Axitinib crystalline Form-SAB-I were analyzed by XRPD on a Bruker AXS D8 Advance Diffractometer using X-ray source - Cu Kα radiation using the wavelength 1.5418 Å. DSC was done on a Perkin Elmer Pyris 7.0 instrument. Illustrative example of analytical data for the Non-solvated Axitinib crystalline Form-SAB-I obtained in the Examples is set forth in the Figures 1-4 and 12.

In an another embodiment of the present invention relates to Axitinib monohydrate crystalline Form-SAB-II characterized by X-ray powder diffraction pattern comprising at least 4 characteristic 2θ° peaks selected from 7.5, 8.0, 14.2, 14.7, 15.7, 18.1, 20.1, 24.4, 29.8 and 32.0 ±0.2 2θ°.

Axitinib monohydrate crystalline Form-SAB-II is further characterized by X-ray powder diffraction pattern comprising at 2θ° peaks selected from 8.4, 13.3, 13.9, 15.2, 18.6, 20.9, 21.2, 21.9, 22.3, 23.0, 24.0, 25.6 and 28.1 ±0.2 2θ°.

Axitinib monohydrate crystalline Form-SAB-II is further characterized by DSC isotherm comprising three endothermic peaks ranging between-

a. Peak -1- Between 48 to 86°C
b. Peak -2- Between 213 to 217°C
c. Peak -2- Between 219 to 224°C

In another embodiment of the present invention relates to a process for the preparation of Axitinib monohydrate crystalline Form-SAB-II comprising the steps of:

a) adding Axitinib in water;
b) stirring the contents of step a) at 25-30 °C; and
c) filtered to recover crystalline Axitinib monohydrate

Axitinib monohydrate crystalline Form-SAB-II obtained by the above process appears to be hydrate and having a moisture content of about 4.6 %. The Axitinib monohydrate crystalline Form-SAB-II obtained by this process is stable and free of process related impurities.

In another embodiment, the present invention provides crystalline Axitinib Form-SAB-II obtained by the present invention is free of other polymorphic impurities, wherein said crystalline form is present in a solid form greater than 99.9 %by weight.

The present inventors found that Axitinib monohydrate crystalline Form-SAB-II, when heated to extreme conditions it loses the water molecule and converted in to Non-solvated Axitinib crystalline Form-SAB-I. It clearly shows that the Axitinib crystalline Form-SAB-II is unstable at extreme conditions.

The Axitinib monohydrate crystalline Form-SAB-II is a monohydrate form, which is evident from the moisture content results. A sample of the Axitinib monohydrate crystalline Form-SAB-II prepared by the inventors of this application showed moisture content up to about 4.6 % w/w by KF method, which confirms the monohydrate nature of the compound. While the invention is not limited to any specific theory, it should be understood however that the Axitinib monohydrate crystalline Form-SAB-II may contain additional residual or unbound moisture without losing its character and/or its monohydrate crystalline characteristics. Nevertheless, person having skill in the art should be able to determine whether they are same crystalline forms or not, by looking at the overall shape of the X-ray powder diffraction pattern optionally with help of other thermal data like DSC or TGA.

The thermo gravimetric analysis of Axitinib monohydrate crystalline Form-SAB-II clearly shows the existence of water molecule and it is about 4.5%, which is depicted in Fig.7

The Axitinib monohydrate crystalline Form-SAB-II described herein may be characterized by X-ray powder diffraction pattern (XRPD) and IR absorption spectra and Thermal techniques such as differential scanning calorimetric (DSC) Analysis and TGA. The samples of Axitinib monohydrate crystalline Form-SAB-II were analyzed by XRPD on a Bruker AXS D8 Advance Diffractometer using X-ray source - Cu Kα radiation using the wavelength 1.5418 Å. DSC was done on a Perkin Elmer Pyris 7.0 instrument. Illustrative example of analytical data for the Axitinib monohydrate crystalline Form-SAB-II obtained in the Examples is set forth in the Figures 5-7.

In another embodiment of the invention relates to Axitinib crystalline Form-SAB-III characterized by X-ray powder diffraction pattern comprising at least 4 characteristic 2θ° peaks selected from 10.1, 10.4, 15.3, 18.3, 18.7, 19.7and 24.6 ±0.2 2θ°and methanol content ranging between 1.5 to 4% w/w..

Axitinib crystalline Form-SAB-III is further characterized by X-ray powder diffraction pattern comprising at 2θ° peaks selected from 7.7, 8.2, 8.5, 10.1, 14.9, 15.3, 15.9, 18.3, 18.7, 20.2, 21.0, 21.4, 23.1, 24.6, 30.0 and 32.2 ± 0.2 2θ°.

Axitinib crystalline Form-SAB-III is further characterized by DSC isotherm comprising three endothermic peaks ranging between-

a. Peak -1- Between 53 to 73°C
b. Peak -2- Between 214 to 218°C
c. Peak -2- Between 222 to 225°C

In another embodiment of the present invention relates to process for the preparation Axitinib crystalline Form-SAB-III comprising the steps of:

a) dissolving Axitinib in Dimethylsulfoxide;
b) heating the reaction mixture to about 60-80°C;
c) adding methanol;
d) isolating crystalline material; and
e) drying at 40-45°C

Axitinib crystalline Form-SAB-III obtained by the above process is having methanol content in the range between 1-4 %. The Axitinib crystalline Form-SAB-III obtained by this process is stable and free of process related impurities.

The present inventors analyzed Axitinib crystalline Form-SAB-III for Hygroscopic study. However, the present inventors found that the Axitinib crystalline Form-SAB-III obtained by the present invention is stable at room temperature as well as at 0-5°C.

The Axitinib crystalline Form-SAB-III described herein may be characterized by X-ray powder diffraction pattern (XRPD) and IR absorption spectra and Thermal techniques such as differential scanning calorimetric (DSC) Analysis and TGA. The samples of Axitinib crystalline Form-SAB-III were analyzed by XRPD on a Bruker AXS D8 Advance Diffractometer using X-ray source - Cu Kα radiation using the wavelength 1.5418 Å. DSC was done on a Perkin Elmer Pyris 7.0 instrument. Illustrative example of analytical data for the Axitinib crystalline Form-SAB-III obtained in the Examples is set forth in the Figures 8-10.

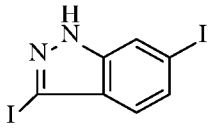
The Axitinib of Formula (I) used in the present invention is prepared by comprising the steps of charging2-((3-iodo-1H-indazol-6-yl)thio)-N methylbenzamidewith N-methylpyrrolidonein presence of Palladium (II) acetate and Xantphos at 25-30 °C in nitrogen atmosphere. Diisopropylethylamine was added under stirring. The reaction mixture was heated to 50°C. Acetic anhydride was slowly added and stirred for 2-3 hrs at 50°C. 2-Vinylpyridine was added slowly, raised the temperature of reaction mass to 90-95°C and maintained for 12 hrs. Cooled the reaction mixture to 50°C under stirring, diluted with THF and filtered the reaction mass. To the obtained reaction mass 1,2-diaminopropane was added. Stirred at 50°C for 30 min. Water was added slowly added for 30 min to 1hr followed by maintaining temperature 50°C under stirring for 12 hrs. Reaction mass cooled to 15°C and further maintained for 2 hrs, filtered the solid, washed with water and THF. The obtained solid was dried under vacuum to afford crude Axitinib. The samples of Axitinib crystalline Form-SAB-IIIwere analyzed by XRPD on a Bruker AXS D8 Advance Diffractometer using X-ray source - Cu Kα radiation using the wavelength 1.5418 Å. The diffractogram resembles with the PXRD pattern as disclosed in Fig.11.

The crude Axitinib of the compound of the formula (I) obtained from the above stage may be purified by treating the compound of the formula (I) or a reaction mixture or a solvated form thereof is treated with an acid selected from methane sulphonic acid, sulphuric acid, trifluoro-methanesulphonic acid, difluoromethanesulphonic acid, dichloroacetic acid, glucornic acid, gluconic acid, Ferulate, glycols and glycol ethers; to form a salt of the compound of the formula (I) which precipitates from the solution containing the solvated compound of the formula (I), the salt of the compound of the formula (I) is then treated with an aqueous basic solution to precipitate the pure form of compound of the formula (I), preferably at a temperature of from 15° C. to 45° C., most preferably from 25° C. to 35° C. If required, repeat again the acidification followed by basification to obtained desired purity, which is greater than 99.5 %.

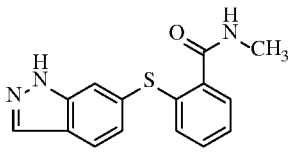
The Axitinib of the compound of the formula (I) is dissolved in a solvent selected from solvent selected from alcohol (C1-3) or Ketones (C3-6) or organic solvents (C1-8 alkanes, dimethyl formamide) or halogenated organic solvents (Methylene dichloride, Ethylene dichloride) or Ethers (Methyl tertiary butyl ether, tetrahydrofuran) or sulphoxides (dimethyl sulphoxide) or esters (Ethyl acetate, benzyl acetate, isoamyl acetate) or water or mixtures thereof. To the obtained solution acid was added at a temperature ranging from -10 to 30°C for 30 min to 2 hrs to yield wet product, which was dried under vacuum at 50-55°C for 2hrs to yield Axitinib acid salt.

The obtained Axitinib acid saltis dissolved in a solvent selected from solvent selected from alcohol (C1-4) or Ketones (C3-6) or organic solvents (C1-8 alkanes, dimethyl formamide, toluene, xylene) or halogenated organic solvents (Methylene dichloride, Ethylene dichloride) or Ethers (Methyl tertiary butyl ether, tetrahydrofuran, Di-isopropyl ether) or sulphoxides (dimethyl sulphoxide) or esters (Ethyl acetate, benzyl acetate, isoamyl acetate) or water or mixtures thereof at a temperature ranging from 25-30°C and stirred for 30min to get clear solution. The obtained solution was treated with an alkaline solution, wherein alkaline solution used is prepared using a base selected from organic base such as triethylamine, methylamine, pyridine, imidazole, benzimidazole; or inorganic base selected from carbonates such as sodium carbonate, potassium carbonate, calcium carbonate, ammonium carbonate; hydroxides such as sodium hydroxide, potassium hydroxide, calcium hydroxide, ammonium hydroxide, barium hydroxide, magnesium hydroxide, lithium hydroxide, zinc hydroxide; bicarbonates such as sodium bicarbonate, potassium bicarbonate, ammonium bicarbonate, calcium bicarbonate, magnesium bicarbonate; in a solvent selected from organic solvent or water. The reaction mass was stirred for 30 min to 4 hrs depending on the acid used. After completion of the reaction, the reaction mass was cooled to a temperature ranging from 0-10°C and maintained the reaction mass under stirring for 30min to 4 hrs. The precipitated product was filtered, washed with organic solvent or a mixture of organic solvent or mixture of organic solvent and water to get wet cake, which was dried under vacuum at 50-85°C for 3 hrs to 6hrs to yield pure Axitinib.

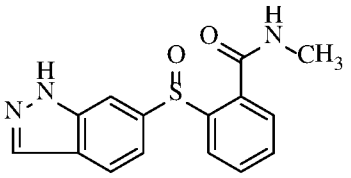
The obtained pure Axitinib was analyzed, if it is not matching with the desired purity; again repeat the process by treating the Axitinib with acid to prepare the corresponding salt, followed by treating with an alkali solution to obtain substantially pure Axitinib having a purity of greater than 99.5% and meeting the ICH guidelines.



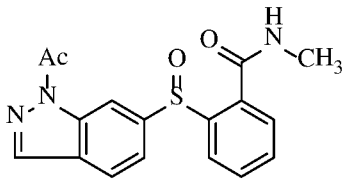
Impurity-A



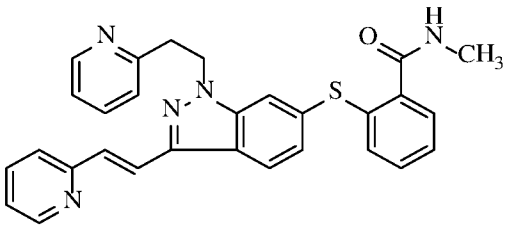
Impurity-B



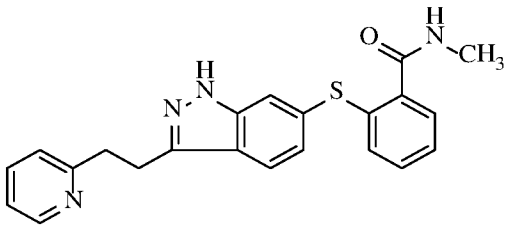
Impurity-C



Impurity-D



Impurity-E



Impurity-F

Axitinib obtained by this process is substantially pure Axitinib, wherein substantially pure Axitinib contains the process related impurities A, B, C, D, E and F collectively below 0.3% and meeting the ICH guidelines.

The use of pure Axitinib in the preparation of new polymorphic form parallel results in the formation of substantially pure crystalline forms of Axitinib having a purity of greater than 99.5 %, wherein substantially pure Axitinib is having an impurity profile meeting the ICH guidelines. The polymorph related impurities formed during the crystallization of crude Axitinib has been successfully removed by the present process, which yields in the formation of highly pure crystalline forms of Axitinib

Another embodiment of the present invention relates to substantially pure crystalline Axitinib having a purity of greater than 99.5 %, wherein substantially pure Axitinib contains the process related impurities A, B, C, D, E and F collectively below 0.3% area percentage by HPLC and meeting the ICH guidelines.

The process related impurities that appear in the impurity profile of the Axitinib (I) may be substantially removed by the process of the present invention resulting in the formation of substantially Axitinib (I), which meets the ICH guidelines.

The merit of the process according to the present invention resides in that product isolated after drying is stable and having a purity of greater than 99.5% purity by HPLC, which was not disclosed in any of the prior-art. The product obtained as per the present invention is highly pure than the any of the prior-art products obtained. Still now no-publication discloses a purity of greater than 99.5%.

Solubility is one of the important parameters to achieve desired concentration of drug in systemic circulation for achieving required pharmacological response. Poorly water soluble drugs often require high doses in order to reach therapeutic plasma concentrations after oral administration. Low aqueous solubility is the major problem encountered with formulation development of new chemical entities as well as generic formulation development. Most of the drugs are either weakly acidic or weakly basic having poor aqueous solubility. The improvement of drug solubility thereby its oral bio-availability remains one of the most challenging aspects of drug development process especially for oral-drug delivery system. The poor solubility and low dissolution rate of poorly water soluble drugs in the aqueous gastrointestinal fluids often cause insufficient bioavailability. The enhancement in the purity of Axitinib and crystalline arrangement of novel polymorphic forms (Axitinib Form-SAB-I,Axitinib Form-SAB-II, Axitinib Form-SAB-III) which is free of process related impurities inherently, increases the solubility of Axitinib, which plays a major role for enhancement of drug dissolution rate in solid oral dosage forms.

The present invention also relates to a process for the preparation of Axitinib, which is substantially pure having a purity of greater 99.5 % and meeting the ICH guidelines, by limiting the content of each impurity less than 0.3%. Further, the Axitinib obtained as per the present process is found devoid of any other process related impurities and is adequately stable to handle and store for longer time (at least up to more than 6 months) without any significant or measurable change in its morphology and physicochemical characteristics.

Drying may be also be performed by any conventional process not limited to spray drying or distillation to remove the solvent. Drying may be performed under reduced pressure conditions also. Reduced pressure conditions may be suitably utilized by person skilled in the art in order to obtain the dried material. The drying may be performed at a temperature ranging from 50-85°C for a time ranging from 5 to 10 hours depending upon the physical attributes of the end product obtained i.e. Pure Axitinib, which is obtained according to the present invention is having purity greater than 99.5%.

In another embodiment of the present invention the substantially pure Axitinib obtained by the processes of the present application may be taken as such in crystalline form for manufacture of solid dosage forms like tablets, capsules and/or for manufacture of oral liquids.

In another embodiment of the present invention the substantially pure crystalline form of Axitinib (Axitinib Form-SAB-I, Axitinib Form-SAB-II, Axitinib Form-SAB-III) obtained

by the processes of the present application may be manufactured as the amorphous form by processing with polymers like hydroxypropyl methylcellulose acetate succinate (HPMC-AS).

In another embodiment, the substantially pure crystalline form of Axitinib (Axitinib Form-SAB-I, Axitinib Form-SAB-II, Axitinib Form-SAB-III) obtained by the processes of the present application may be formulated as solid compositions for oral administration in the form of capsules, tablets, pills, powders or granules. In these compositions, the active product is mixed with one or more pharmaceutically acceptable excipients. The drug substance can be formulated as liquid compositions for oral administration including solutions, suspensions, syrups, elixirs and emulsions, containing solvents or vehicles such as water, sorbitol, glycerin, propylene glycol or liquid paraffin.

In one embodiment of the present invention, it also includes premix comprising one or more pharmaceutically acceptable excipients in the range of 1 to 50% w/w with the substantially pure Axitinibor its acid addition salt, while retaining the crystalline nature of the premix.

The compositions for parenteral administration can be suspensions, emulsions or aqueous or non-aqueous sterile solutions. As a solvent or vehicle, propylene glycol, polyethylene glycol, vegetable oils, especially olive oil, and injectable organic esters, e.g. ethyl oleate, may be employed. These compositions can contain adjuvants, especially wetting, emulsifying and dispersing agents. The sterilization may be carried out in several ways, e.g. using a bacteriological filter, by incorporating sterilizing agents in the composition, by irradiation or by heating. They may be prepared in the form of sterile compositions, which can be dissolved at the time of use in sterile water or any other sterile injectable medium.

Pharmaceutically acceptable excipients used in the compositions comprising substantially pure Axitinib or its acid addition salt obtained as per the present application process- include, but are but not limited to diluents such as starch, pregelatinized starch, lactose, powdered cellulose, microcrystalline cellulose, di-calcium phosphate, tri-calcium phosphate, mannitol, sorbitol, sugar and the like; binders such as acacia, guar gum, tragacanth, gelatin, pre-gelatinized starch and the like; disintegrants such as starch, sodium starch glycolate, pregelatinized starch, Croscarmellose sodium, colloidal silicon dioxide and the like; lubricants such as stearic acid, magnesium stearate, zinc stearate and the like; glidants such as colloidal silicon dioxide and the like; solubility or wetting enhancers such as anionic or cationic or neutral surfactants, waxes and the like. Other pharmaceutically acceptable excipients that are of use include but not limited to film formers, plasticizers,

colorants, flavoring agents, sweeteners, viscosity enhancers, preservatives, antioxidants and the like.

Pharmaceutically acceptable excipients used in the compositions derived from substantially pure Axitinib or its acid addition salt of the present application may also comprise to include the pharmaceutically acceptable carrier used for the preparation of solid dispersion, wherever utilized in the desired dosage form preparation.

The following examples illustrate the nature of the invention and are provided for illustrative purposes only and should not be construed to limit the scope of the invention.

EXAMPLES

Example-1

Preparation of Axitinib (I)

Take N-methylpyrrolidone (379.11 ml), Palladium (II) acetate (3.64 g, 0.0162 mol) and Xantphos (9.32 g, 0.0161mol) into a RB flask at 25-30 °C in nitrogen atmosphere. Charged 2-((3-iodo-1H-indazol-6-yl)thio)-N methylbenzamide (HPLC Purity: 99.29%; 165.0 g, 0.4031mol) and diisopropylethylamine(156.62 g, 1.21 mol)under stirring. The reaction was heated to 50°C. Acetic anhydride (83.77 g, 0.8195 mol) was slowly added and stirred for 2-3 hrs at 50°C. 2-Vinylpyridine (254.97 g, 2.4250 mol) was added slowly, raised the temperature of reaction mass to 90-95°C and maintained for about 12 hrs. Cooled the reaction mixture to 50°C under stirring, diluted with THF (495 ml) and filtered. To the reaction mass 1,2-diaminopropane (120.20 g) was added. Stirred at 50°C for 30 min. Water (1815 ml) was added slowly for 30 min followed by maintaining temperature 50°C under stirring for 12 hrs. Reaction mass cooled to 15°C and further maintained for 2 hrs, filtered the solid, washed with purified water (495 ml) and THF (163.69 ml). The obtained solid was dried under vacuum to afford crude Axitinib.

Yield: 110 g (70.68%)

Chromatographic Purity (By HPLC): 96.3%;

XRPD resembles with Fig. 11

Example-2

Preparation of polymorph Non-solvated Axitinib crystalline Form-SAB-I

Charge Dimethylsulfoxide (500 ml) and Axitinib (100 g, 0.2588mol- prepared as per example-1) in to the reaction vessel at 25-30 °C under nitrogen atmosphere. The reaction mixture was heated to about 70-80°C for 30 min under stirring. The reaction mixture was cooled to 60-65°C and methanol (1000 ml) added under stirring. The reaction mixture cooled

to 25-30°C, filtered and washed with methanol (200 ml) and dried under vacuum at 50-65°C to obtain title product.

Yield: 85.0 g (85.00% w/w),

Chromatographic Purity (By HPLC): 99.91%.

XRPD resembles with Fig. 1

Moisture content: 0.443 %

Example-3

Preparation of polymorph Non-solvated Axitinib crystalline Form-SAB-I

Take Axitinib (10.0 g, 0.0258mol- Form-IV prepared as per US20060094763) and DMSO solvent (50.0 ml) into the reaction vessel at room temperature. The reaction mixture was heated to about 70-75°C for 30 min under stirring. The reaction mixture was cooled to 60-65°C and slowly methanol (100 ml) was added under continued stirring. This reaction mixture was cooled to 25-30°C. Subsequently, it was filtered and washed with methanol (20 ml) and dried under vacuum at 60-65°C to obtain title product.

Yield: 8.3 g (83.00% w/w), Moisture content: 0.4 %

Example-4

Preparation of polymorph SAB-II (Hydrate)

Take water (70 ml) and Axitinib (3.0 g, 0.0078 mol) in to the reaction vessel at 25-30 °C. The reaction mixture was stirred at 25-30 °C for 2 hrs. The reaction mixture was filtered and washed with water (10 ml) and suck dried at 25-30°C for 1 hr to obtain title product.

Yield: 2.8 g (93.33% w/w),

Chromatographic Purity (By HPLC): 99.91%.

XRPD resembles with Fig. 5

Moisture content: 4.6 %

Example-5

Preparation of polymorph SAB-II (Hydrate) by exposing Axitinib to high humidity

By exposing Non-solvated Axitinib crystalline Form-SAB-I(about 5 gms) at 90% relative humidity in desiccator at 25°C containing saturated potassium chloride solution kept in glass petri-dish and placed it into desiccator.

Samples were withdrawn and analyzed at different time intervals, the results are as follows:

S.No	Time (in Hours)	Water content (%)	Crystalline Form
1	Initial	0.40%	SAB-I
2	2 hours	4.31%	SAB-II
3	4 hours	4.35%	-
4	6 hours	4.47%	-
5	8 hours	4.40%	-
6	24 hours	4.52%	SAB-II
7	48 hours	4.51%	ND
8	72 hours	4.49%	SAB-II

Axitinib crystalline Form-SAB-II is obtained as stable monohydrate form. XRay Poweder Diffraction study reveals that samples after 2 hours resembles in diffraction pattern with no significant variations.

Example-6

Preparation of polymorph SAB-III (Methanol solvate)

Take Dimethylsulfoxide (385 ml) and Axitinib (77 g, 0.1992 mol) in to the reaction vessel at 25-30 °C under nitrogen purged atmosphere. The reaction mixture was heated to about 70-80°C for 30 min under stirring. The reaction mixture was cooled to 60-65°C and methanol (770 ml) added under stirring. The reaction mixture cooled to 25-30°C, filtered and washed with methanol (154 ml) and suck dried the material for 30 min. Finally material dried under vacuum at 40-45°C to obtain title product.

Yield: 65.45 g (85.00% w/w),

Chromatographic Purity (By HPLC): 99.89%. TGA weight loss: 3.53% w/w

XRPD resembles with Fig. 8 and TGA –Fig.10

Methanol content (By GC): ~ 3.4%

While the foregoing pages provide a detailed description of the preferred embodiments of the invention, it is to be understood that the summary, description and examples are for illustrative purpose only of the core of the invention and non-limiting in their scope. Furthermore, as many changes may be made to the invention without departing from the scope of the invention, it is intended that all material contained herein be interpreted as illustrative of the invention and not in a limiting sense.

We Claim:

1) Non-solvated Axitinib crystalline Form-SAB-I characterized by X-ray powder diffraction pattern comprising at least 5 characteristic 2θ° peaks selected from 8.3, 9.3, 15.6, 16.5, 17.6, 21.0, 24.1 and 26.0 ±0.2 2θ°; liquid state NMR in DMSO spectrum comprising ^{13}C chemical shift at 26.1±0.2, 114.7±0.2, 154.8±0.2 and 167.8±0.2 ppm and solid state NMR spectrum comprising ^{13}C chemical shift at 171.1, 153.2, 142.6, 139.5, 131.2, 128.1 and 126.3 ± 0.5

2) Non-solvated Axitinib crystalline Form-SAB-I according to claim 1, further characterized by X-ray powder diffraction pattern comprising at 2θ° peaks selected from 13.7, 16.1, 18.6, 22.6, 23.1, and 23.4 ±0.2 2θ°.

3) Non-solvated Axitinib crystalline Form-SAB-I according to claim 1, further characterized by DSC isotherm comprising two endothermic peaks ranging between-
   a. Peak -1- Between 213 to 217°C
   b. Peak -2- Between 219 to 224°C

4) Non-solvated Axitinib crystalline Form-SAB-I characterized by X-ray powder diffraction pattern comprising at least 5characteristic 2θ° peaks selected from 8.3, 9.3, 15.6, 16.5, 17.6, 21.0, 24.1 and 26.0 ±0.2 2θ° according to claim 1, wherein process for the preparation of Axitinib crystalline Form-SAB-I comprising the steps of:
   a) dissolving Axitinib in Dimethylsulfoxide;
   b) heating the reaction mixture to about 60-80°C followed by cooling;
   c) adding methanol;
   d) recover the crystalline material; and
   e) dryingthe crystalline material between40-70°C.

5) Axitinib monohydrate crystalline Form-SAB-II characterized by X-ray powder diffraction pattern comprising at least 5characteristic 2θ° peaks selected from 7.5, 8.0, 14.2, 14.7, 15.7, 18.1, 20.1, 24.4, 29.8 and 32.0 ±0.2 2θ°.

6) Axitinib monohydrate crystalline Form-SAB-II according to claim 5, further characterized by X-ray powder diffraction pattern comprising at 2θ° peaks selected from 8.4, 13.3, 13.9, 15.2, 18.6, 20.9, 21.2, 21.9, 22.3, 23.0, 24.0, 25.6 and 28.1 ±0.2 2θ°.

7) Axitinib monohydrate crystalline Form-SAB-II according to claim 5, further characterized by DSC isotherm comprising three endothermic peaks ranging between-

a. Peak -1- Between 48 to 86°C
b. Peak -2- Between 213 to 217°C
c. Peak -2- Between 219 to 224°C

8) Axitinib monohydrate crystalline Form-SAB-II according to claim 5, wherein process for the preparation of Axitinib crystalline Form-SAB-II comprising the steps of:

a) adding Axitinib in water;
b) stirring the contents of step a) at 25-30 °C; and
c) filtered to recover crystalline Axitinib monohydrate

9) Axitinib crystalline Form-SAB-III characterized by X-ray powder diffraction pattern comprising at least 4 characteristic 2θ° peaks selected from 10.1, 10.4, 15.3, 18.3, 18.7, 19.7and 24.6 ±0.2 2θ° and methanol content ranging between 1.5 to 4% w/w.

10) Axitinib crystalline Form-SAB-III according to claim 9, further characterized by X-ray powder diffraction pattern comprising at 2θ° peaks selected from 7.7, 8.2, 8.5, 10.1, 14.9, 15.3, 15.9, 18.3, 18.7, 20.2, 21.0, 21.4, 23.1, 24.6, 30.0 and 32.2 ± 0.2 2θ°.

11) Axitinib crystalline Form-SAB-III according to claim 9, further characterized by DSC isotherm comprising three endothermic peaks ranging between-

a. Peak -1- Between 53 to 73°C
b. Peak -2- Between 214 to 218°C
c. Peak -2- Between 222 to 225°C

12) Axitinib crystalline Form-SAB-III according to claim 9, wherein process for the preparation of Axitinib crystalline Form-SAB-III comprising the steps of:

a) dissolving Axitinib in Dimethylsulfoxide;

b) heating the reaction mixture to about 60-80°C;

c) adding methanol;

d) isolating crystalline material; and

e) drying at 40-45°C

FIGURE 1

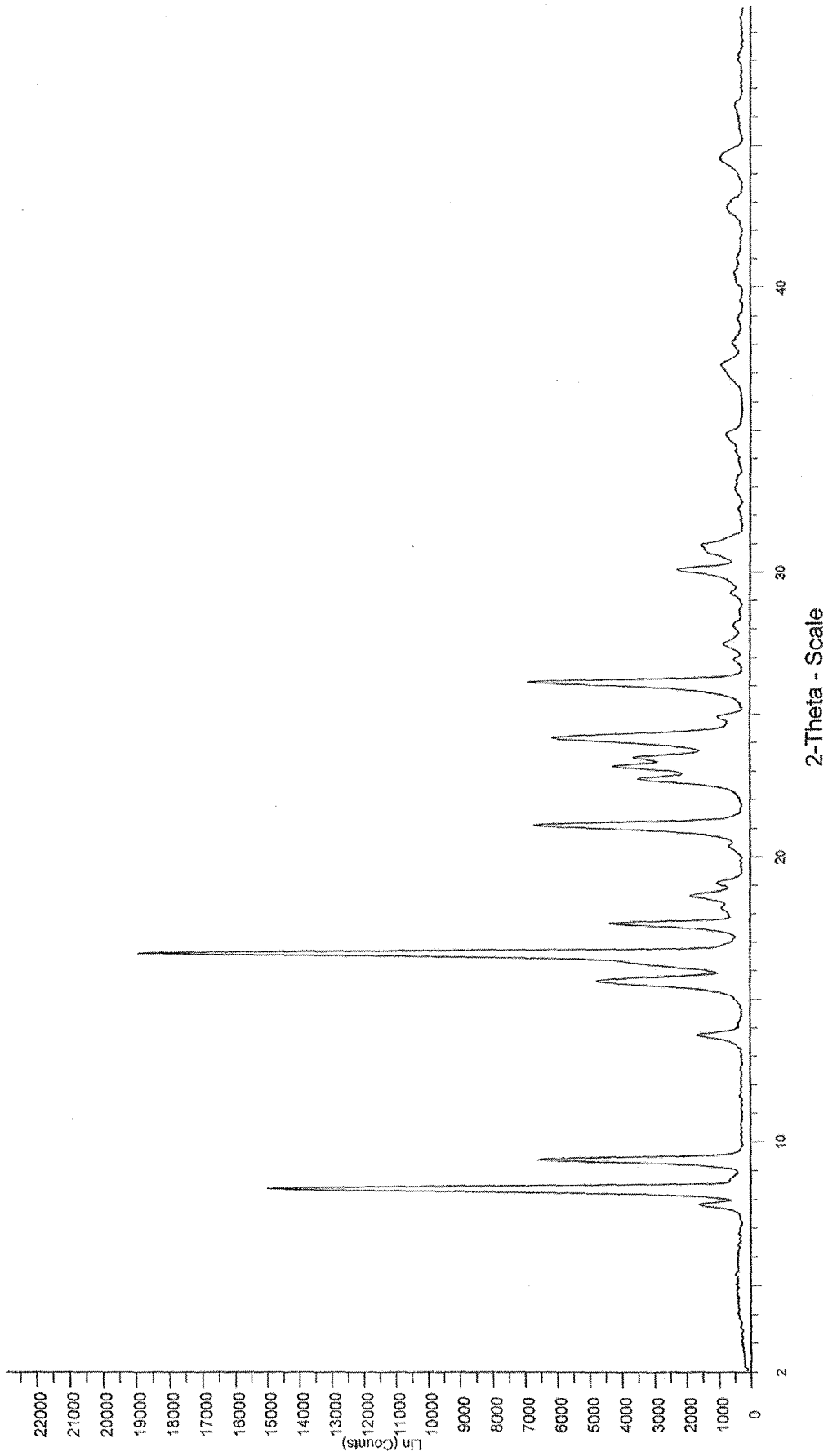

Lin (Counts)
22000
21000
20000
19000
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
2
10
20
30
40
2-Theta - Scale

FIGURE 2

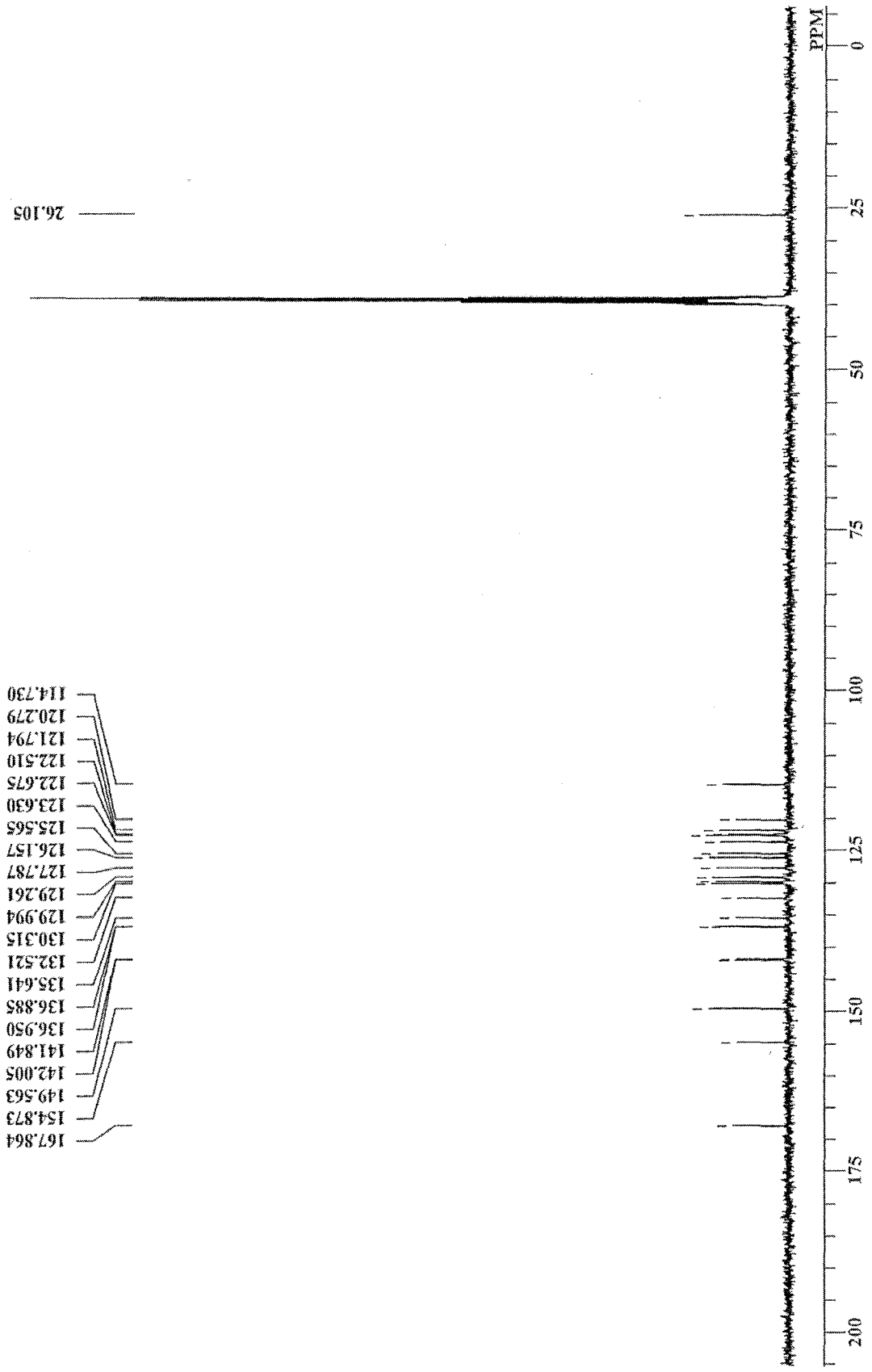

26.105
114.730
120.279
121.794
122.510
122.675
123.630
125.565
126.157
127.787
129.261
129.994
130.315
132.521
135.641
136.885
136.950
141.849
142.005
149.563
154.873
167.864
PPM
0
25
50
75
100
125
150
175
200

FIGURE 3

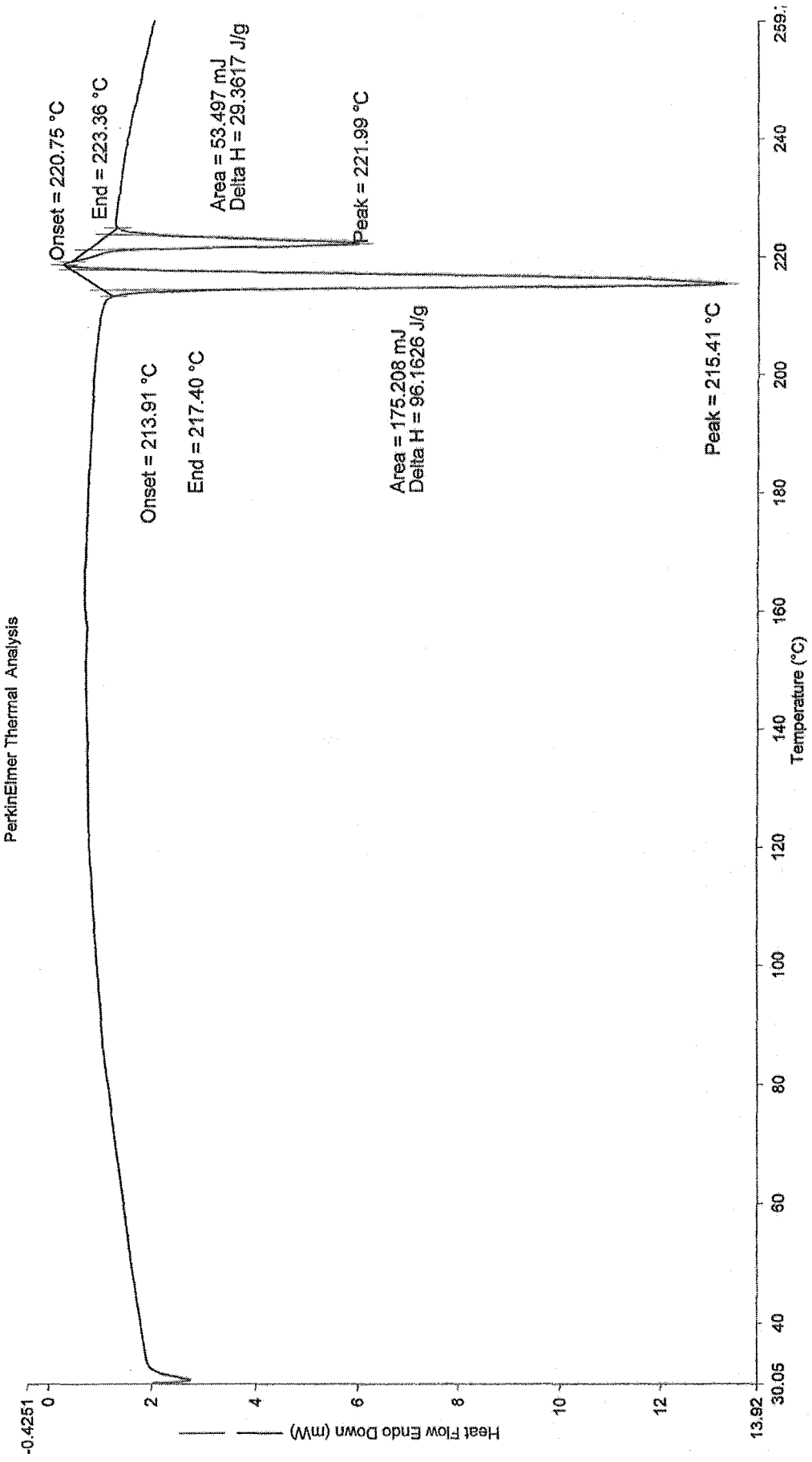

PerkinElmer Thermal Analysis
Onset = 220.75 °C
End = 223.36 °C
Area = 53.497 mJ
Delta H = 29.3617 J/g
Peak = 221.99 °C
Onset = 213.91 °C
End = 217.40 °C
Area = 175.208 mJ
Delta H = 96.1626 J/g
Peak = 215.41 °C
Heat Flow Endo Down (mW)
Temperature (°C)
-0.4251
13.92
30.05
0
2
4
6
8
10
12
40
60
80
100
120
140
160
180
200
220
240

FIGURE 4

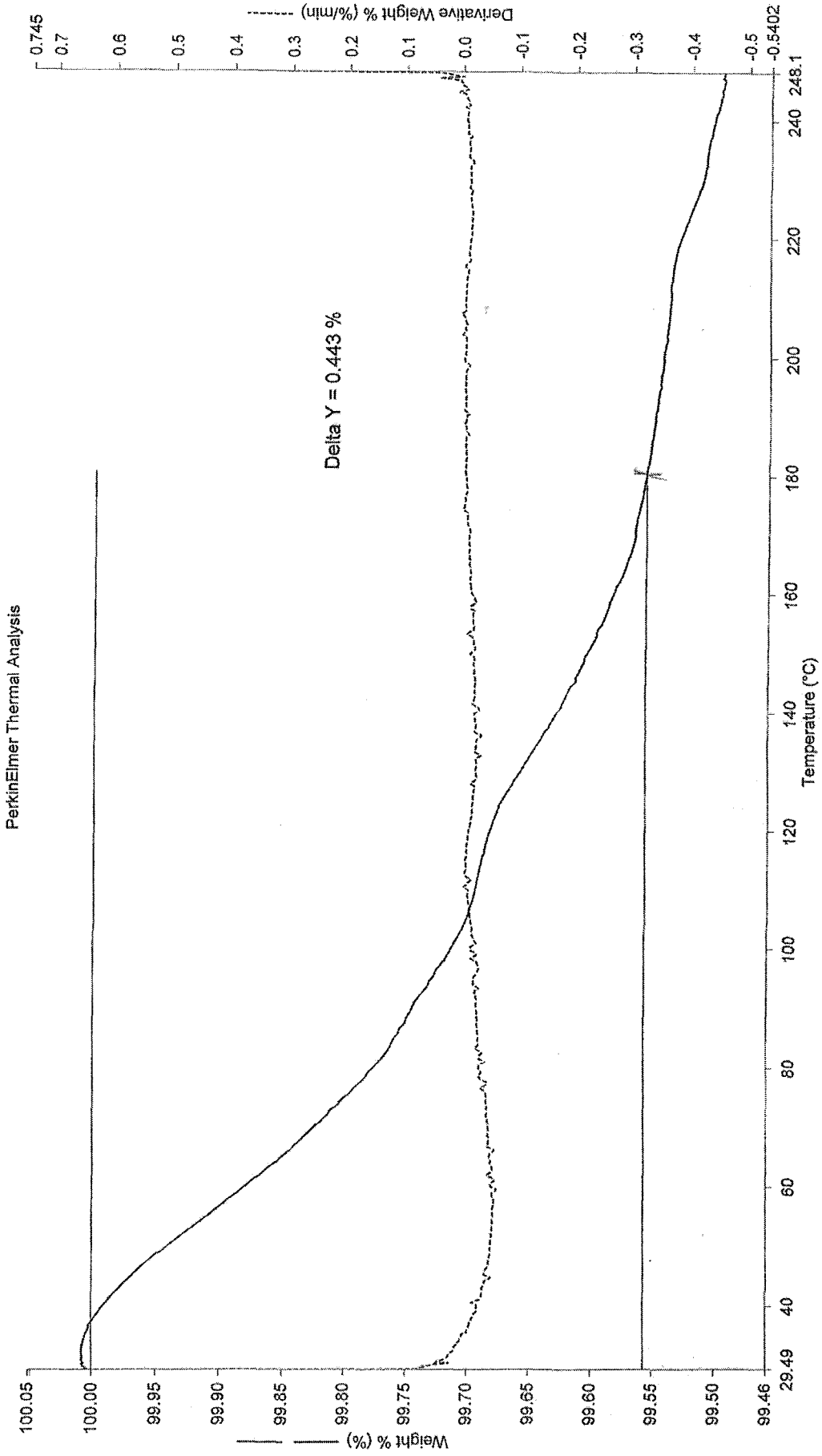

PerkinElmer Thermal Analysis
Delta Y = 0.443 %
Derivative Weight % (%/min)
Weight % (%)
Temperature (°C)
0.745
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
-0.1
-0.2
-0.3
-0.4
-0.5
-0.5402
100.05
100.00
99.95
99.90
99.85
99.80
99.75
99.70
99.65
99.60
99.55
99.50
99.46
29.49
40
60
80
100
120
140
160
180
200
220
240
248.1

FIGURE 5

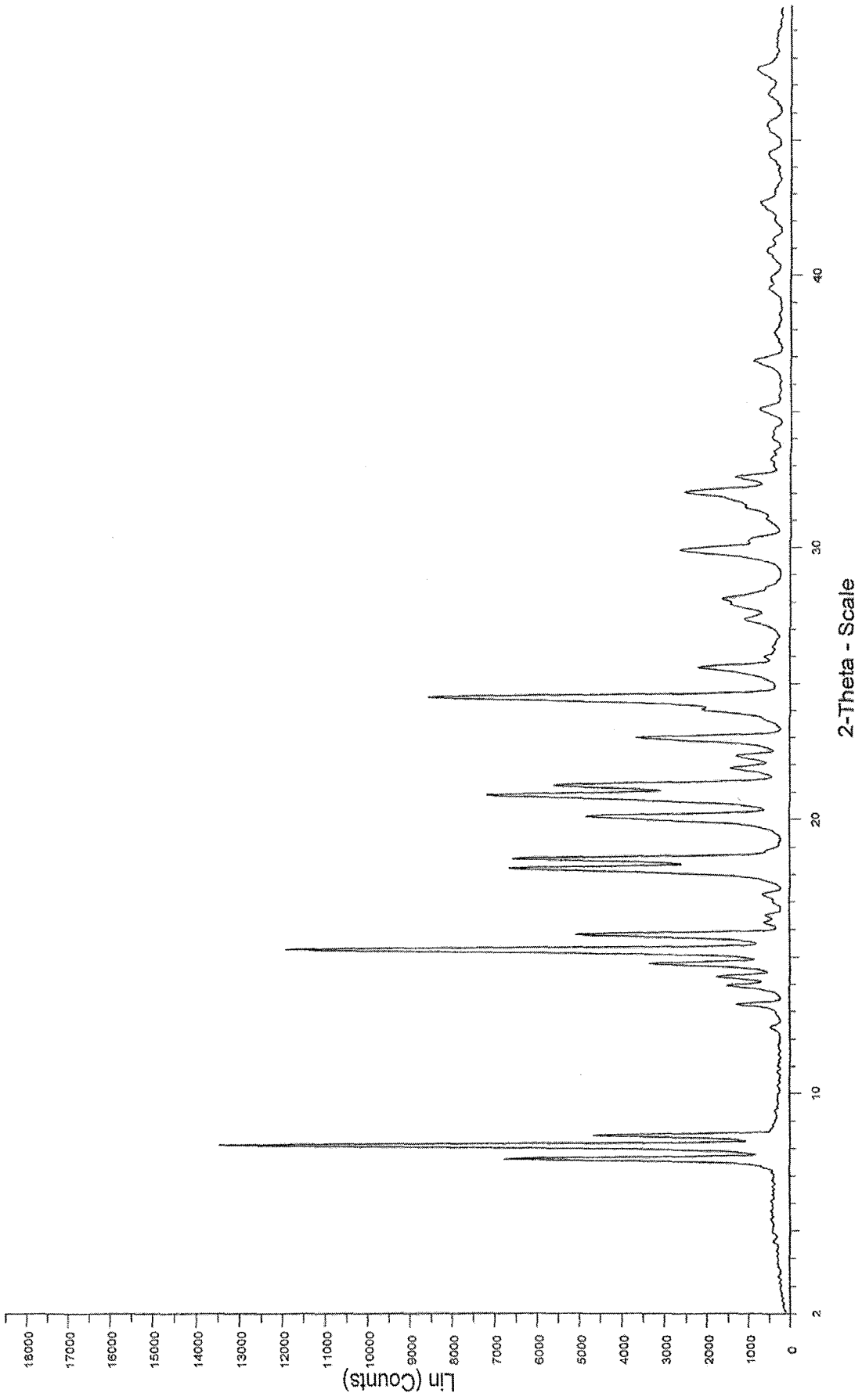

Lin (Counts)
0
1000
2000
3000
4000
5000
6000
7000
8000
9000
10000
11000
12000
13000
14000
15000
16000
17000
18000
2
10
20
30
40
2-Theta - Scale

FIGURE 6

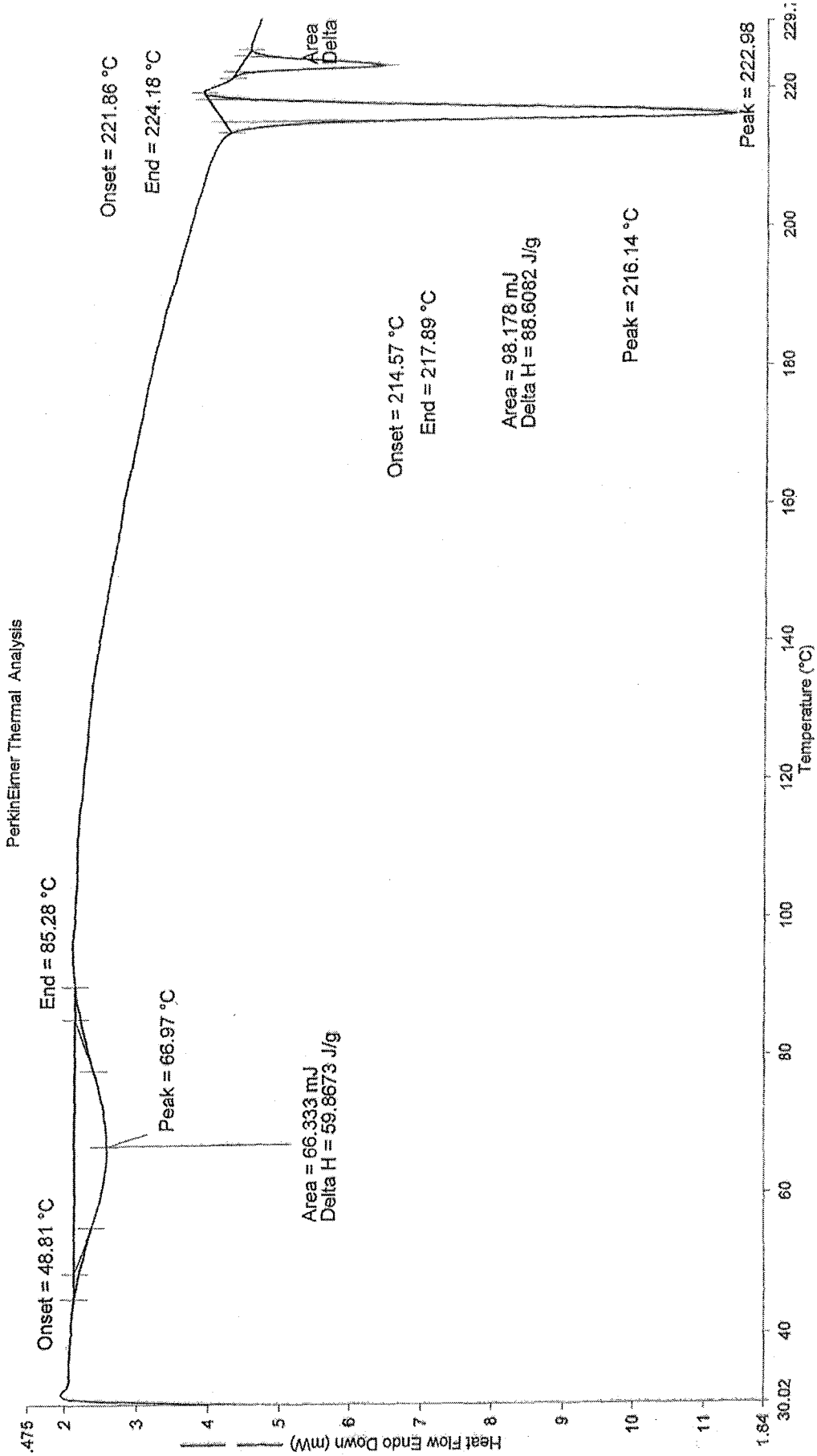

PerkinElmer Thermal Analysis
Onset = 48.81 °C
End = 85.28 °C
Peak = 66.97 °C
Area = 66.333 mJ
Delta H = 59.8673 J/g
Onset = 214.57 °C
End = 217.89 °C
Area = 98.178 mJ
Delta H = 88.6082 J/g
Peak = 216.14 °C
Onset = 221.86 °C
End = 224.18 °C
Area
Delta
Peak = 222.98
Heat Flow Endo Down (mW)
Temperature (°C)

FIGURE 7

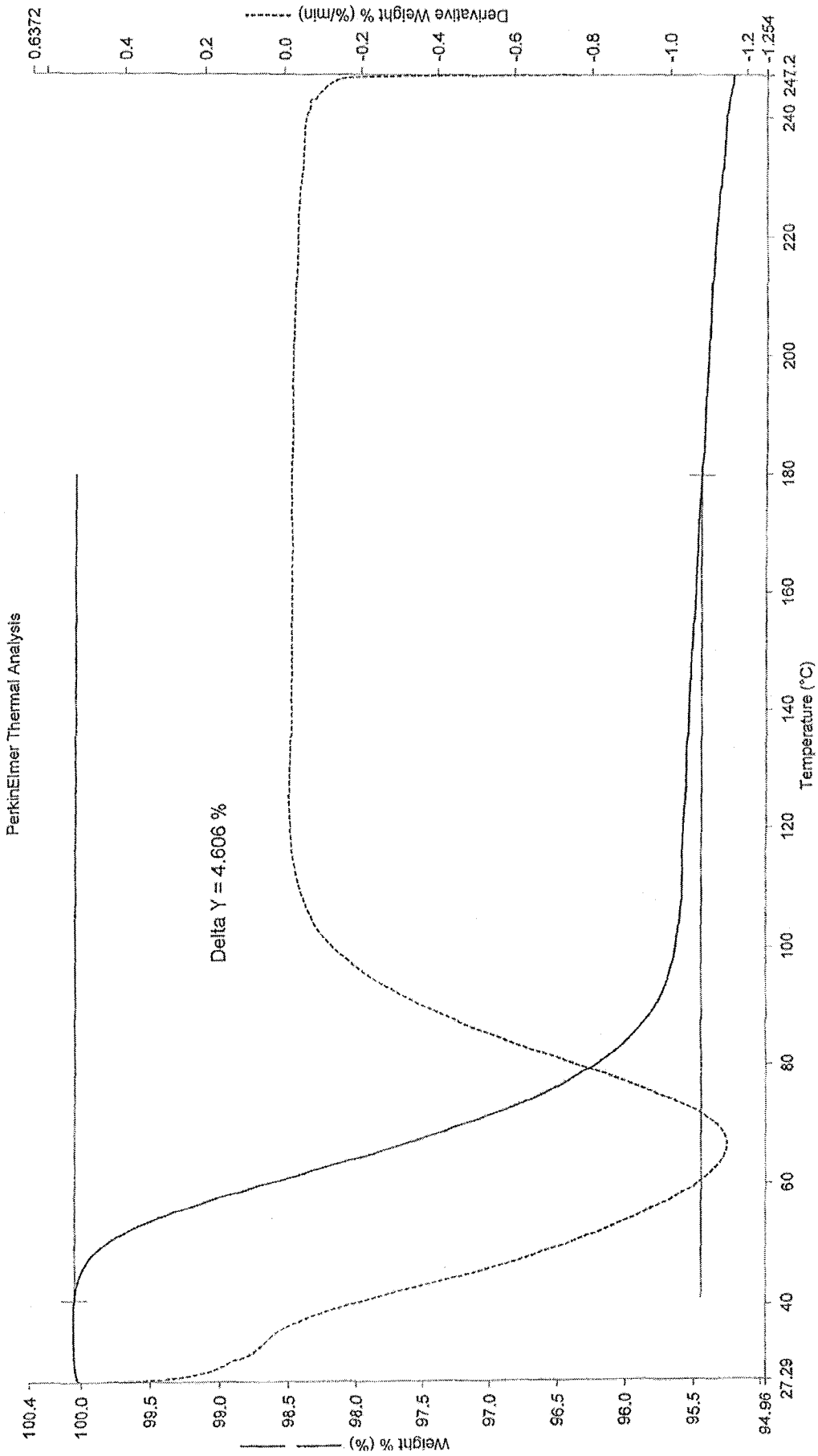

PerkinElmer Thermal Analysis
Delta Y = 4.606 %
Weight % (%)
Derivative Weight % (%/min)
Temperature (°C)
100.4
100.0
99.5
99.0
98.5
98.0
97.5
97.0
96.5
96.0
95.5
94.96
0.6372
0.4
0.2
0.0
-0.2
-0.4
-0.6
-0.8
-1.0
-1.2
-1.254
27.29
40
60
80
100
120
140
160
180
200
220
240
247.2

FIGURE 8

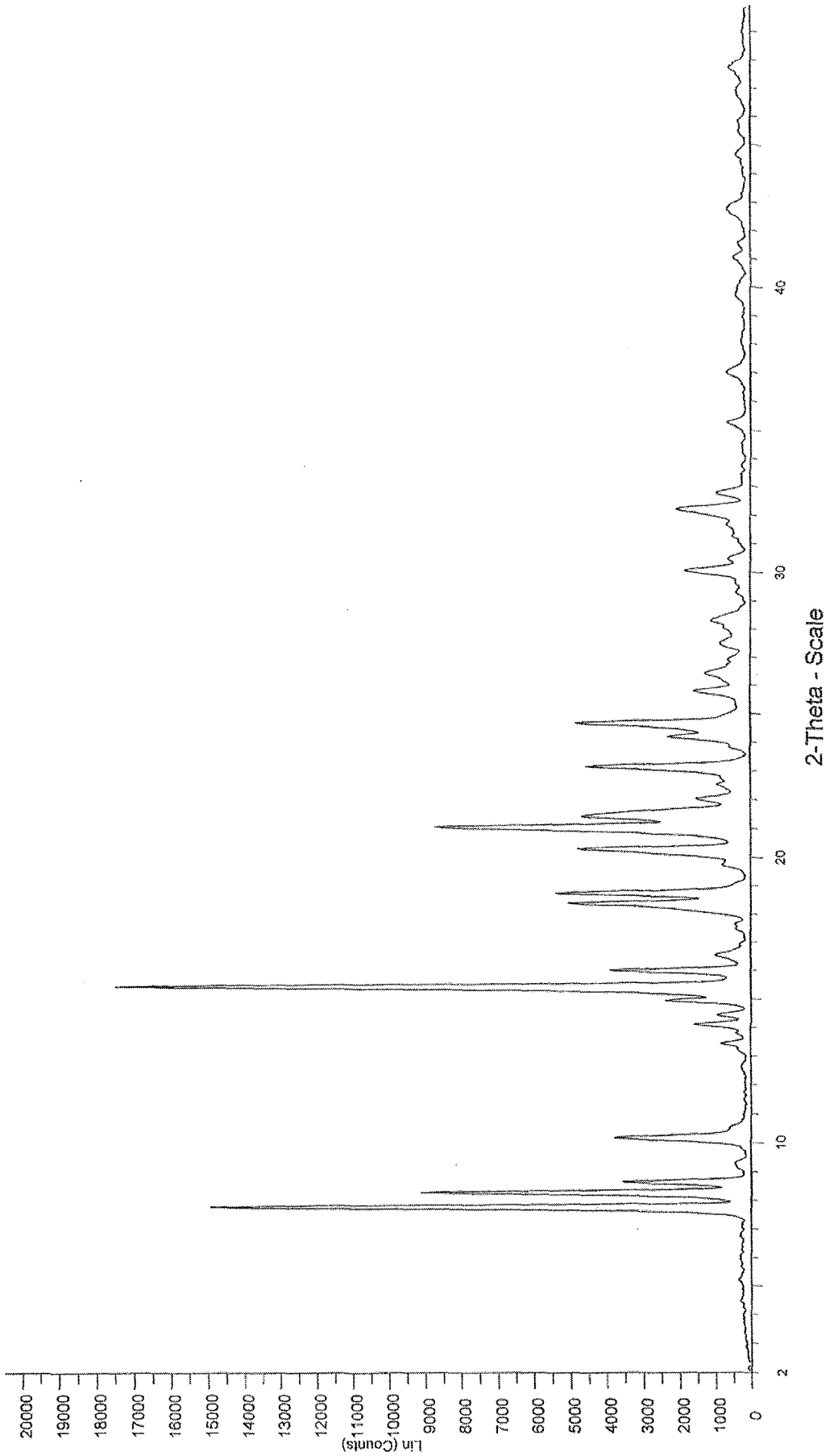

Lin (Counts)
20000
19000
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
2
10
20
30
40
2-Theta - Scale

FIGURE 9

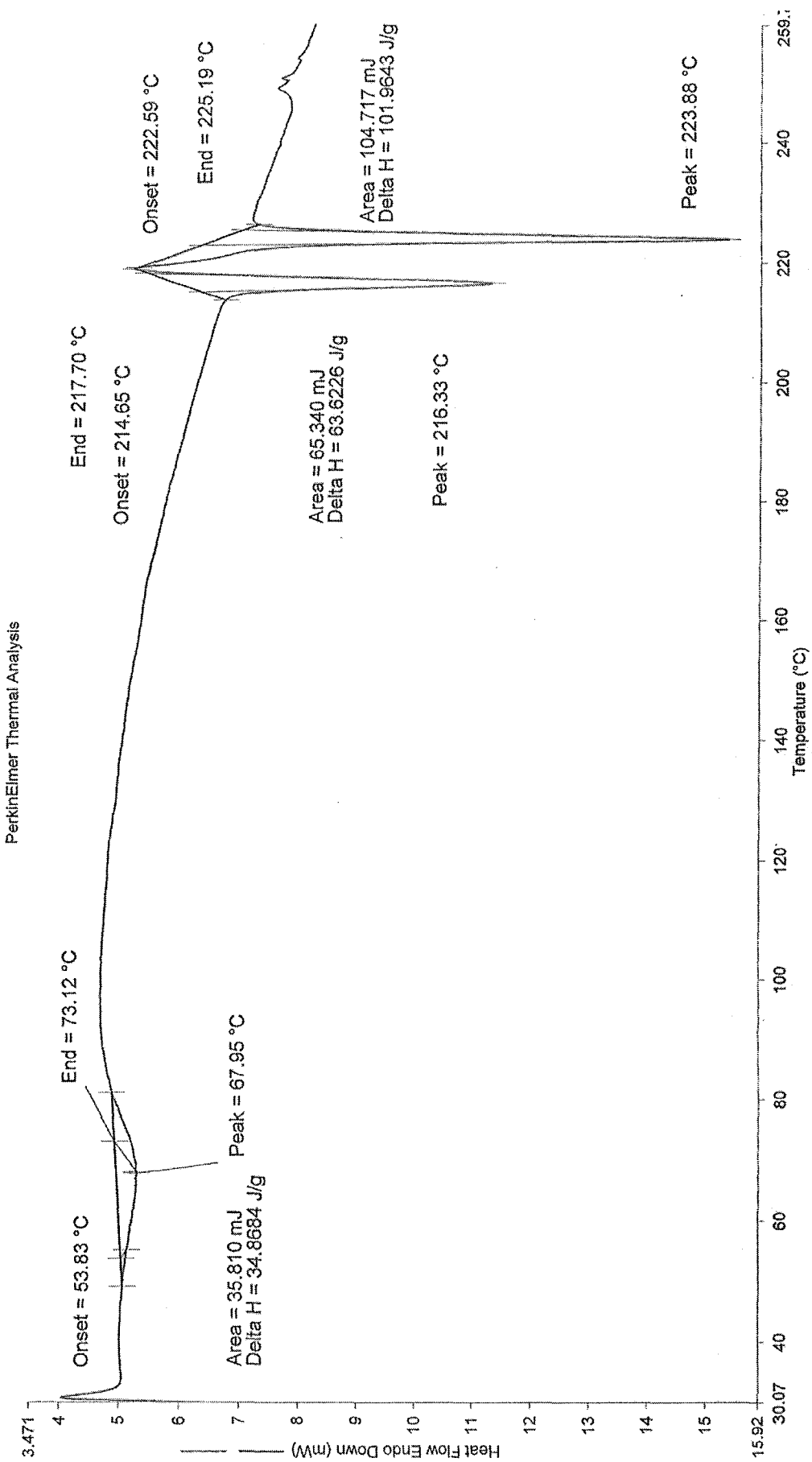

PerkinElmer Thermal Analysis
Onset = 53.83 °C
End = 73.12 °C
Peak = 67.95 °C
Area = 35.810 mJ
Delta H = 34.8684 J/g
Onset = 214.65 °C
End = 217.70 °C
Peak = 216.33 °C
Area = 65.340 mJ
Delta H = 63.6226 J/g
Onset = 222.59 °C
End = 225.19 °C
Peak = 223.88 °C
Area = 104.717 mJ
Delta H = 101.9643 J/g
Heat Flow Endo Down (mW)
Temperature (°C)
3.471
15.92
30.07
259.

FIGURE 10

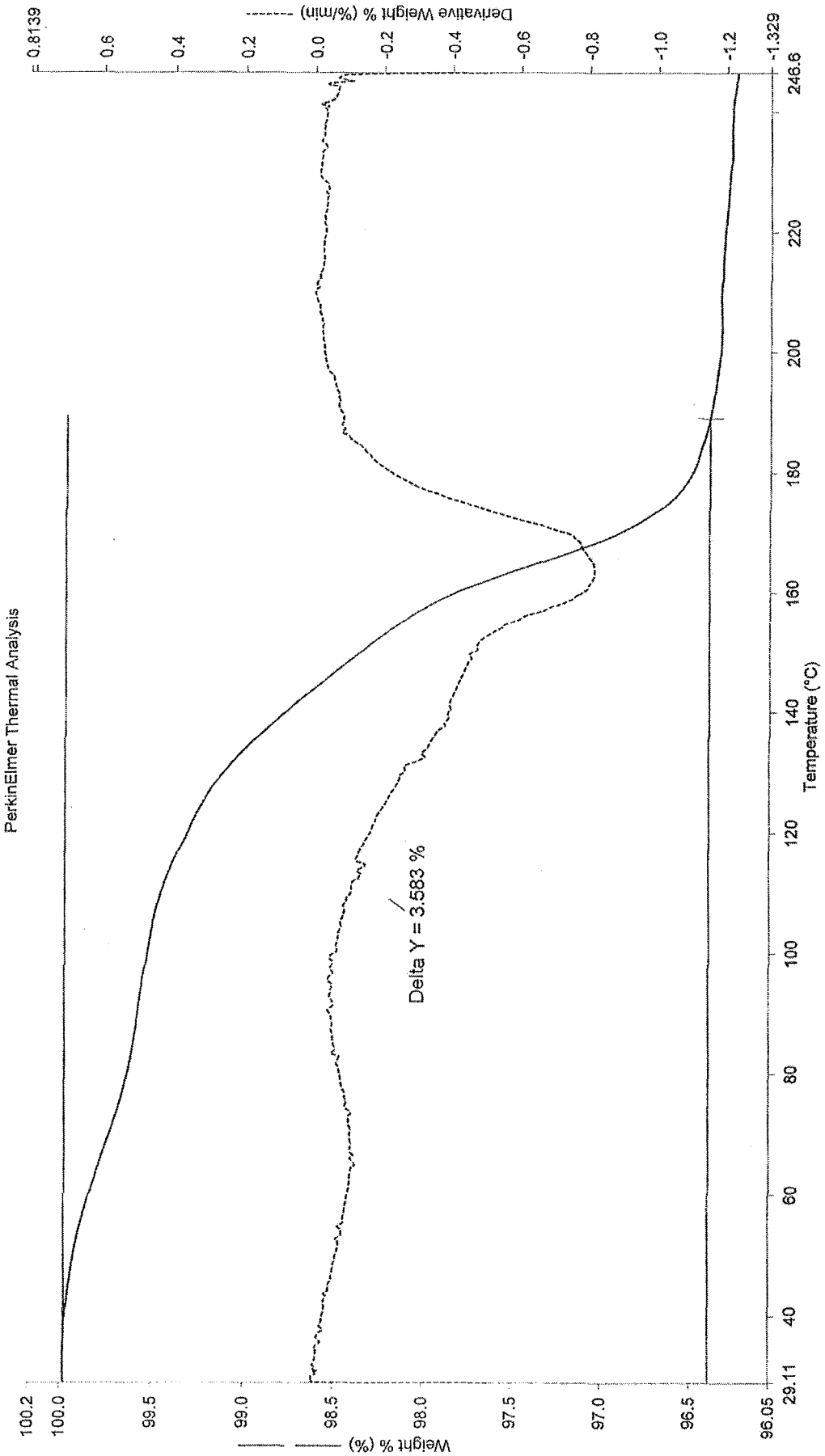

PerkinElmer Thermal Analysis
Derivative Weight % (%/min)
Weight % (%)
Temperature (°C)
Delta Y = 3.583 %
0.8139
-1.329
100.2
96.05
29.11
246.6

FIGURE 11

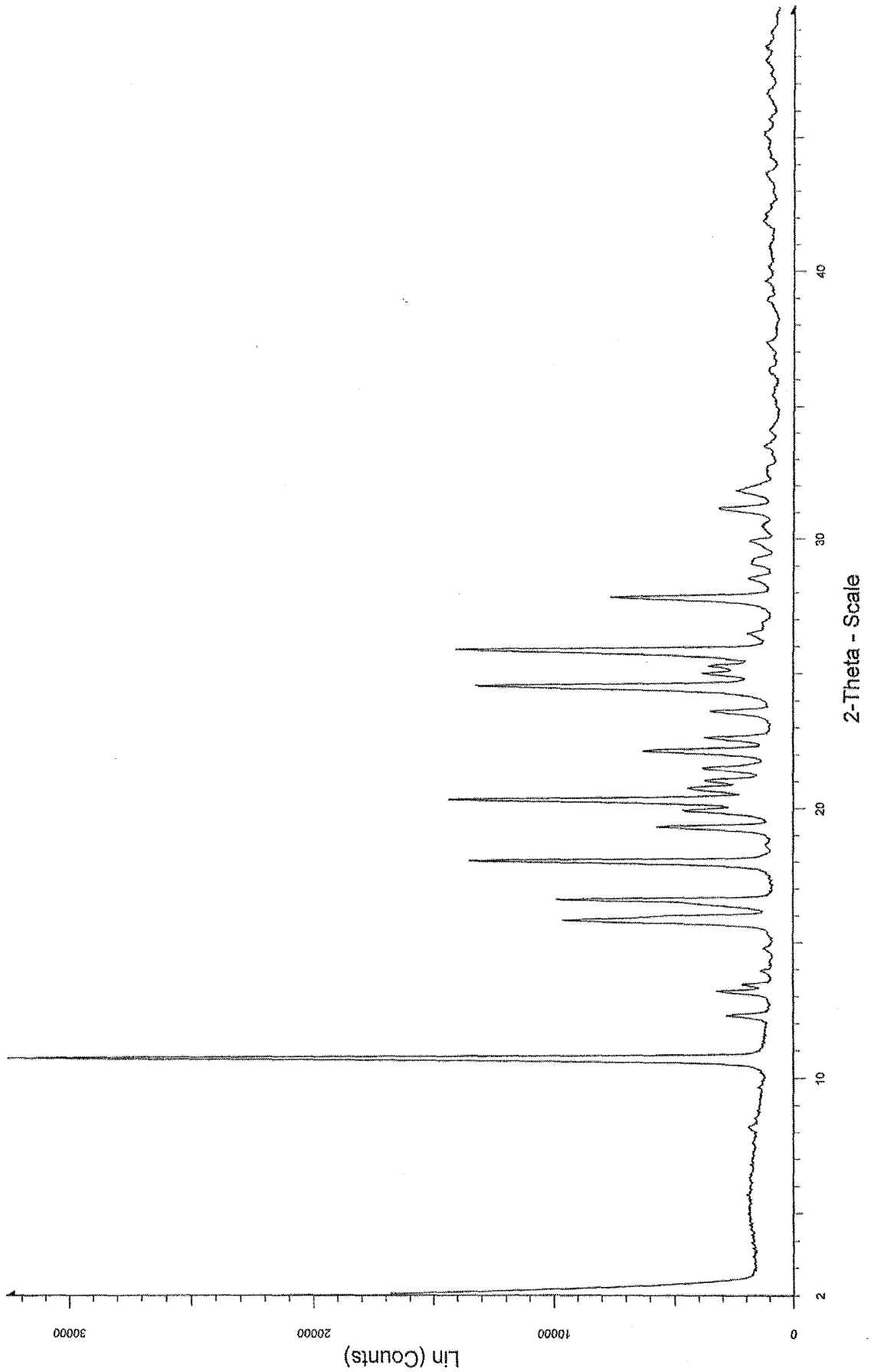
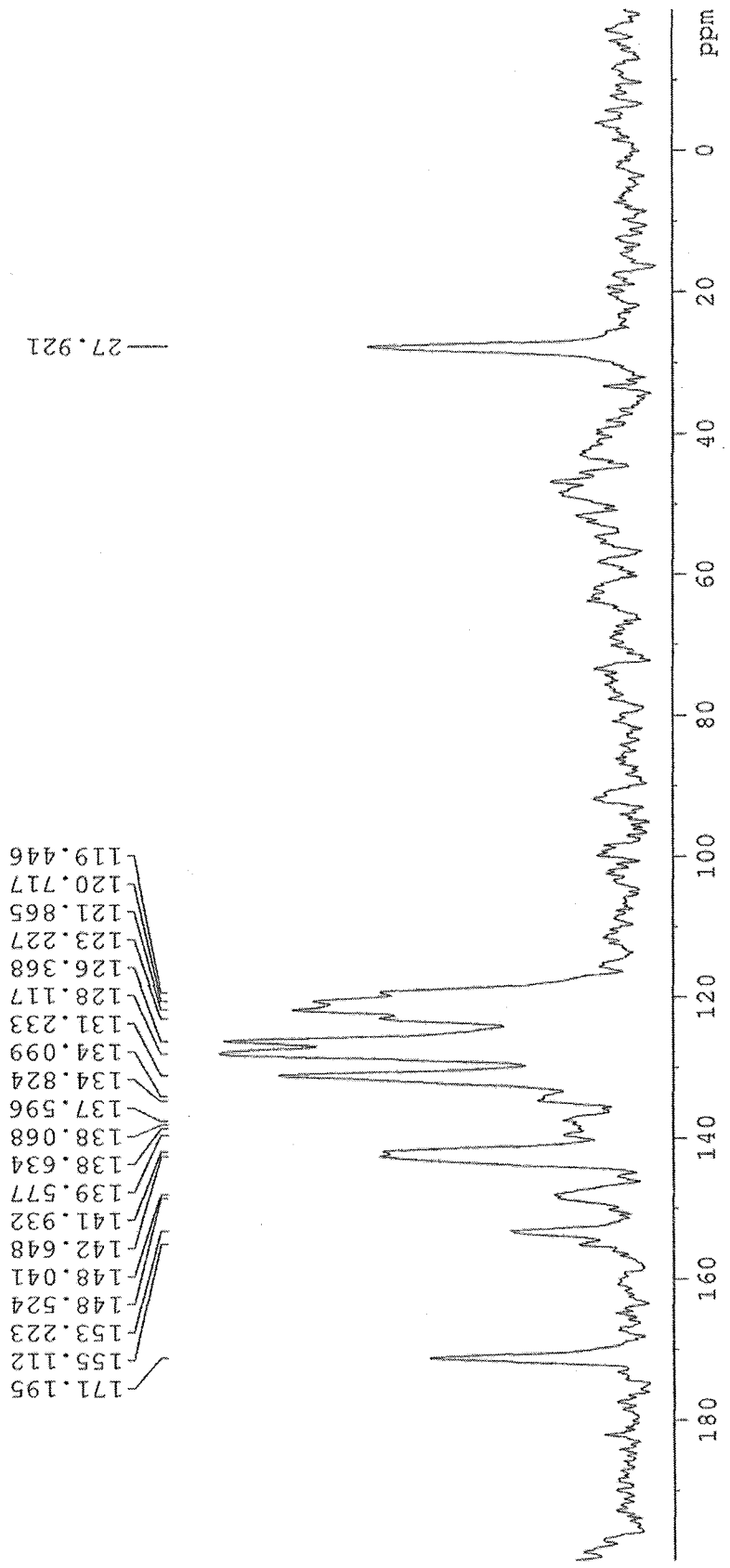


FIGURE 12


27.921
119.446
120.717
121.865
123.227
126.368
128.117
131.233
134.099
134.824
137.596
138.068
138.634
139.577
141.932
142.648
148.041
148.524
153.223
155.112
171.195
ppm
0
20
40
60
80
100
120
140
160
180

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2016/052530

A. CLASSIFICATION OF SUBJECT MATTER
A61K31/4375 Version=2016.01

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)

A61K

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

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

Patseer, IPO Internal Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2010/0179329 (Anthony Michael Campeta et al.) 15/July/2010 whole document	1-12
Y	WO 2006048751 (PFIZER INC.) 11/May/2006 whole document	1-12

☐ 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
08-08-2016	08-08-2016
Name and mailing address of the ISA/ Indian Patent Office Plot No.32, Sector 14,Dwarka,New Delhi-110075 Facsimile No.	Authorized officer Dr. Manmeet Kumar Telephone No. +91-1125300200

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IB2016/052530

Citation	Pub.Date	Family	Pub.Date
US 2010/0179329 A1	15-07-2010	WO 2008122858 A2	25-03-2008
		EP 2134702 A2	23-12-2009
		CN 101679356 A	24-03-2010
WO 2006048751 A1	11-05-2006	US 20060094763 A1	31-10-2005
		EP 1819696 A1	22-08-2007