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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
4 July 2013 (04.07.2013)

WIPO | PCT

(10) International Publication Number
WO 2013/098773 A1

(51) International Patent Classification:
C07D 215/14 (2006.01) *A61P 9/00* (2006.01)
A61K 31/47 (2006.01)

(21) International Application Number:
PCT/IB2012/057752

(22) International Filing Date:
27 December 2012 (27.12.2012)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
4634/CHE/2011 28 December 2011 (28.12.2011) IN
61/596,835 9 February 2012 (09.02.2012) US

(71) Applicant: **DR. REDDY'S LABORATORIES LIMITED** [IN/IN]; 8-2-337, Road No.3, Banjara Hills, Andhra Pradesh, Hyderabad 500034 (IN).

(72) Inventors: **PEDDY, Vishweshwar**; Plot No. 341,Vasavi Colony, Green Hills Road No. 1, Saroornagar, Andhra Pradesh, Hyderabad 500035 (IN). **CHENNURU, Ramanaiah**; Sulluru pet (MDL), Nellore (Dt), Andhra Pradesh, Velagala Ponnuru 524121 (IN). **KAMBHAMPATI, Anil Kumar**; H.No:12-26/A, Adarshnagar, IDPL, Andhra Pradesh, Hyderabad 500032 (IN). **TUMMALA, Arjun Kumar**; H. No. 39-26-25, Rajeev Nagar, NH-5, Marripalem, Andhara Pradesh, Visakhapatnam 530018 (IN). **RANGINENI, Srinivasulu**; Machinenipalli (Village), Yenmenvetla (post), Kollapur, Andhra Pradesh, Mahabubnagar 509102 (IN). **DOOSA, Hima Bindu**; H. No. 12-10-587/50/1E, Flat No. 102, Warasiguda, Andhra Pradesh, Secunderabad 500061 (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, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, 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, 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, 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, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *of inventorship (Rule 4.17(iv))*

Published:

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

[Continued on next page]

(54) Title: CRYSTALLINE FORMS OF PITAVASTATIN CALCIUM

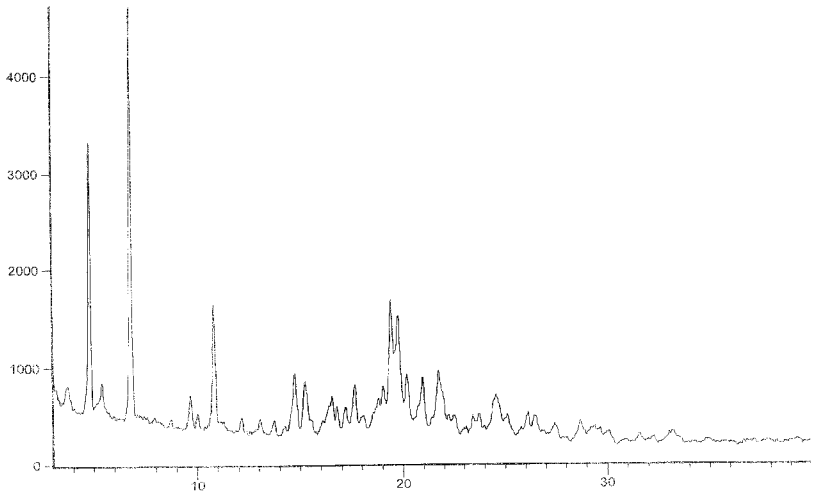


Fig. 2

(57) Abstract: Disclosed are crystalline forms of pitavastatin calcium and processes for their preparation and isolation. Pharmaceutical compositions comprising said crystalline forms are provided also.

WO 2013/098773 A1

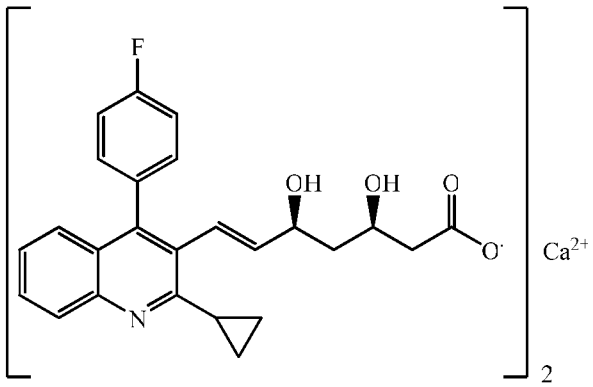
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

CRYSTALLINE FORMS OF PITAVASTATIN CALCIUM

INTRODUCTION

Aspects of the present application relate to crystalline forms of pitavastatin calcium and processes for their preparation and isolation. Aspects of the application further relate to pharmaceutical compositions comprising crystalline forms of the present application as well as methods for treating hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia.

Pitavastatin calcium is a common chemical name for bis[(E)-3*R*,5*S*-dihydroxy-7-[4'-(4"-fluorophenyl)-2'-cyclopropyl-quinolin-3'-hept-6-enoic acid] calcium salt, is represented by formula (1):



(1)

Pitavastatin is a cholesterol-lowering agent (HMG-Co A reductase inhibitor). The HMG-Co A reductase enzyme catalyzes the conversions of HMG-Co A to mevalonate. Inhibitors of HMG-Co A reductase are commonly referred to as "statins." Statins are therapeutically effective drugs used for reducing low density lipoprotein (LDL) particle concentrations in the blood of patients at risk for cardiovascular disease. The calcium salt, having a chemical name (+)monocalcium *bis*{(3*R*,5*S*,6*E*)-7-[2-cyclopropyl-4-(4-fluorophenyl)-3-quinolyl]-3,5-dihydroxy-6-heptanoate}, referred to hereinafter as “pitavastatin calcium,” is the active ingredient in products marketed as LIVALO®.

Pitavastatin and its pharmaceutically acceptable salts are described in U.S. Patent Nos. 5,753,675 and 5,856,336. International patent applications *viz.*, WO 2005/063711 A1 describes crystalline Form A of pitavastatin calcium which contains 5 to 15% of water and WO 2004072040 A1 discloses crystalline Forms A, B, C, D, E, F, and an amorphous form of pitavastatin calcium along with processes for their

preparation. Polymorphism is very common among pharmaceutical substances. Further, Chinese Patent Application Publication 101195603A describes a crystalline form of pitavastatin calcium, wherein the water content is in the range of 0.5-3%. Korean Patent Application Publication No. 2010125124A relates to a crystal form A of pitavastatin hemicalcium salt having peaks with relative intensities above 50%, at 5.2°, 6.2°, 7.7°, 19.9°, and 23.1° 2θ, in an X-ray powder diffraction pattern using copper Kα radiation.

Polymorphism is an unpredictable property of any given compound. This subject has been reviewed in recent articles, including A. Goho, "Tricky Business," *Science News*, August 21, 2004. In general, one cannot predict whether there will be more than one polymorphic form for a compound, how many forms will eventually be discovered, or how to prepare any previously unidentified form.

Pharmaceutical stability is believed to depend on simultaneous influence of various factors, of which some important factors are the water content, residual solvents, and impurities. One or more of these factors may be uniquely addressed by the isolation process of the polymorphic forms of pitavastatin calcium. Therefore, it would be desirable to prepare and characterize new polymorphs of pitavastatin calcium. Further, it would be desirable to have reliable processes for producing these forms.

It is desirable that pharmaceutical products are stable for commercially relevant periods of time, without the need for specialized storage conditions. In the development of pharmaceutical compositions, crystallinity can be a desirable property for an active pharmaceutical ingredient. Discovering new polymorphic forms and solvates of a pharmaceutical product can provide materials having desirable processing properties, such as ease of handling, ease of processing, storage stability, and ease of purification, or as desirable intermediate crystal forms that facilitate conversion to other polymorphic forms. New polymorphic forms and solvates of a pharmaceutically useful compound or salts thereof can also provide an opportunity to improve the performance characteristics of a pharmaceutical product. They enlarge the repertoire of materials that a formulation scientists has available for designing, for example, a pharmaceutical dosage form of a drug with a targeted release profile or other desired characteristics.

Although the known forms of pitavastatin and their polymorphic forms may address some of the deficiencies in terms of formulated product and its manufacturability, there remains a need for yet further improvement in these properties as well as improvements in other properties such as flowability, vapor impermeability, and solubility. Therefore, a need remains to prepare and characterize new crystalline forms of pitavastatin calcium, and to develop reliable processes for producing these crystalline forms.

SUMMARY

Aspects of the present application relate to novel crystalline forms of pitavastatin calcium and processes for their preparation.

BRIEF DESCRIPTION OF THE DRAWING

Fig. 1 is an illustration of a powder X-ray diffraction ("PXRD") pattern of novel crystalline pitavastatin calcium Form IV, as prepared in Example 1.

Fig. 2 is an illustration of a powder X-ray diffraction ("PXRD") pattern of novel crystalline pitavastatin calcium Form V, as prepared in Example 2.

Fig. 3 is an illustration of a powder X-ray diffraction ("PXRD") pattern of novel crystalline pitavastatin calcium Form VI, as prepared in Example 3.

Fig. 4 is an illustration of a powder X-ray diffraction ("PXRD") pattern of novel crystalline pitavastatin calcium Form VII, as prepared in Example 4.

Fig. 5 is an illustration of a powder X-ray diffraction ("PXRD") pattern of novel crystalline pitavastatin calcium Form VIII, as prepared in Example 5.

Fig. 6 is an illustration of a powder X-ray diffraction ("PXRD") pattern of novel crystalline pitavastatin calcium Form IX, as prepared in Example 6.

Fig. 7 is an illustration of a powder X-ray diffraction ("PXRD") pattern of novel crystalline pitavastatin calcium Form X as prepared in Example 7.

Fig. 8 is an illustration of a powder X-ray diffraction ("PXRD") pattern of crystalline pitavastatin calcium as prepared in Example 8.

DETAILED DESCRIPTION

Aspects of the present application relate to novel crystalline forms of pitavastatin calcium that can be characterized by using any of various analytical techniques, such as powder X-ray diffraction (PXRD), differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), or Fourier-transform infrared (FT-IR) spectroscopy.

An aspect of the present disclosure includes novel crystalline form of pitavastatin calcium, designated as "Form IV" characterized by its powder X-ray diffractogram comprising peaks at 3.77, 4.88, 6.84, 10.88, 19.75 and 20.90 degrees of 2θ values, a PXRD pattern with two or more peaks further selected from about 5.41, 10.04, 12.13, 13.70, 14.82, 15.23 and 17.67 degrees of 2θ values.

In an embodiment, there is provided crystalline Form IV of pitavastatin calcium, having a PXRD pattern with peaks located substantially as shown in Fig. 1.

An aspect of the present disclosure includes novel crystalline form of pitavastatin calcium, designated as "Form V" characterized by its powder X-ray diffractogram comprising peaks at 3.76, 4.86, 6.87, 10.87, 19.86, 21.01 and 21.75 degrees of 2θ values, a PXRD pattern with two or more peaks further selected from about 5.43, 10.04, 12.19, 13.77, 14.79, 15.28 and 17.74 degrees of 2θ values.

In an embodiment, there is provided crystalline Form V of pitavastatin calcium, having a PXRD pattern with peaks located substantially as shown in Fig. 2.

An aspect of the present disclosure includes novel crystalline form of pitavastatin calcium, designated as "Form VI" characterized by its powder X-ray diffractogram comprising peaks at 3.79, 4.91 and 6.83 degrees of 2θ values, a PXRD pattern with two or more peaks further selected from about 10.08, 10.89, 15.33, 19.29, 19.77 and 22.08 degrees of 2θ values.

In an embodiment, there is provided crystalline Form VI of pitavastatin calcium, having a PXRD pattern with peaks located substantially as shown in Fig. 3.

An aspect of the present disclosure includes novel crystalline form of pitavastatin calcium, designated as "Form VII" characterized by its powder X-ray diffractogram comprising peaks at 14.69, 15.35, 19.32 and 19.78 degrees of 2θ values, a PXRD pattern with two or more peaks further selected from about 4.88, 6.84 and 10.88 degrees of 2θ values.

In an embodiment, there is provided crystalline Form VII of pitavastatin calcium, having a PXRD pattern with peaks located substantially as shown in Fig. 4.

An aspect of the present disclosure includes novel crystalline form of pitavastatin calcium, designated as "Form VIII" characterized by its powder X-ray diffractogram comprising peaks at 3.92 and 5.34 degrees of 2θ values, a PXRD pattern with two or more peaks further selected from about 11.23, 17.34 and 18.06 degrees of 2θ values.

In an embodiment, there is provided crystalline Form VIII of pitavastatin calcium, having a PXRD pattern with peaks located substantially as shown in Fig. 5.

An aspect of the present disclosure includes novel crystalline form of pitavastatin calcium, designated as "Form IX" characterized by its powder X-ray diffractogram comprising peaks at 4.87, 6.85, 10.91, 19.86, 20.91 and 21.73 degrees of 2θ values, a PXRD pattern with two or more peaks further selected from about 5.43, 10.06, 12.19, 13.75, 14.76, 15.30 and 17.65 degrees of 2θ values.

In an embodiment, there is provided crystalline Form IX of pitavastatin calcium, having a PXRD pattern with peaks located substantially as shown in Fig. 6.

An aspect of the present disclosure includes novel crystalline form of pitavastatin calcium, designated as "Form X" characterized by its powder X-ray diffractogram comprising peaks at 4.95, 6.93, 10.96, 14.88, 15.42 and 19.95 degrees of 2θ values, a PXRD pattern with two or more peaks further selected from about 5.51, 10.15, 12.20, 13.79, 17.75, 19.06 and 19.51 degrees of 2θ values.

In an embodiment, there is provided crystalline Form X of pitavastatin calcium, having a PXRD pattern with peaks located substantially as shown in Fig. 7.

In yet another aspect, there are provided processes for the preparation of above novel crystalline forms of pitavastatin calcium, embodiments including:

a) providing a mixture comprising pitavastatin calcium in a suitable solvent;

b) maintaining the reaction mixture at about reflux temperature of solvent,

c) recovering crystalline pitavastatin calcium.

A mixture comprising pitavastatin calcium may be obtained by providing isolated pitavastatin calcium in any form in a suitable solvent or such a mixture may be obtained directly from a reaction in which pitavastatin calcium is formed.

Suitable solvents used in this step include, but are not limited to, alcohols, such as, for example, ethanol, 1-butanol, 2-butanol, iso-butanol, tert-butanol; esters,

such as, for example, ethyl acetate, isopropyl acetate, and iso-butyl acetate; ketones, such as acetone and methyl isobutyl ketone; hydrocarbons, such as heptane, hexane, cyclohexane, methyl cyclohexane; aromatic hydrocarbons such as xylene and toluene; nitriles, such as acetonitrile, or the like; water; and any mixtures of two or more thereof. In preferred embodiments, 1-butanol, 2-butanol, iso-butanol, acetone and ethyl acetate have been employed.

To obtain a clear solution of pitavastatin calcium the reaction mixture can be heated to dissolution temperature that can be any temperature as long as the stability of the pitavastatin calcium is not compromised and a substantially clear solution is obtained. For example, the dissolution temperature may range from about 20°C to about the reflux temperature of the solvent.

The solution can optionally be filtered by passing through paper, glass fiber, or other membrane material, or a bed of a clarifying agent such as Celite®. Depending upon the equipment used and the concentration and temperature of the solution, the filtration apparatus may need to be heated to avoid premature crystallization.

Step b) involves maintenance of the mixture of step a) at about reflux temperature for a time suitable for crystallization of pitavastatin calcium.

In preferred embodiments, the temperature for crystallization in step b) is in the range of 50-120°C.

Suitable time for crystallization can be any time as long as the stability of the pitavastatin calcium is not compromised and a substantial crystallization of pitavastatin calcium occurs. The exact time required for complete solid formation can be readily determined by a person skilled in the art. For example it can range from 2 hours to 24 hours or more.

Step c) involves isolation and drying of crystalline pitavastatin calcium from the reaction mixture.

The pitavastatin calcium may be isolated using conventional techniques known in the art. For example, useful techniques include but are not limited to, decantation, centrifugation, gravity filtration, suction filtration, concentrating, cooling, stirring, shaking. The isolation may be optionally carried out at atmospheric pressure or under reduced pressure. The solid that is obtained may carry a small proportion of occluded mother liquor containing a higher percentage of impurities and, if desired, the solid may be washed with a solvent to wash out the mother liquor.

The wet cake obtained may further be dried. Drying can be suitably carried out in a tray dryer, vacuum oven, air oven, fluidized bed dryer, spin flash dryer, flash dryer, or the like. Drying may be carried out at temperatures less than about 250°C, less than about 200°C, less than about 150°C, less than about 100°C, less than about 50°C or any other suitable temperatures, in the presence or absence of an inert atmosphere such as nitrogen, argon, neon, or helium, with or without applying vacuum. The drying may be carried out for any desired time periods to achieve a desired purity of the product, such as, for example, from about 10 minutes to about 15 hours, or longer.

Once obtained, crystals of pitavastatin calcium may be used as the nucleating agent or "seed" crystals for subsequent crystallizations of pitavastatin calcium from solutions.

Alternately the crystalline forms of the present invention can be obtained by drying the other crystalline forms under suitable conditions.

In yet another aspect, there is provided process for preparation of novel crystalline Form V of pitavastatin calcium comprising;

a) providing a mixture comprising pitavastatin calcium in a suitable solvent;

b) maintaining the reaction mixture at about reflux temperature of solvent,

c) isolating pitavastatin calcium,

d) drying the product of step c) at elevated temperature.

The conditions for steps a) and b) are same as mentioned above for previous aspect of the application.

Step c) involves isolation of Pitavastatin calcium from the reaction mixture.

The pitavastatin calcium may be isolated using conventional techniques known in the art. For example, useful techniques include but are not limited to, decantation, centrifugation, gravity filtration, suction filtration, concentrating, cooling, stirring, shaking. The isolation may be optionally carried out at atmospheric pressure or under reduced pressure. The solid that is obtained may carry a small proportion of occluded mother liquor containing a higher percentage of impurities and, if desired, the solid may be washed with a solvent to wash out the mother liquor.

Step d) involves drying of pitavastatin calcium isolated in step c) at elevated temperature.

Drying can be suitably carried out in a tray dryer, vacuum oven, air oven, fluidized bed dryer, spin flash dryer, flash dryer, or the like. Drying may be carried out at temperatures more than about 80°C, more than about 100°C and preferably at about 120°C in the presence or absence of an inert atmosphere such as nitrogen, argon, neon, or helium, with or without applying vacuum. The drying may be carried out for any desired time periods to achieve a desired purity of the product, such as, for example, from about 10 minutes to about 15 hours, or longer.

Yet another aspect of the present invention provided process for preparation of novel crystalline Form V of pitavastatin calcium comprising drying the novel crystalline Forms IV, VI and VII at any temperature in the range 100-150°C. In a preferred embodiment the drying is performed at about 120°C.

Also provided are pharmaceutical compositions containing a therapeutically effective amount of the crystalline forms of pitavastatin calcium described herein, together with one or more pharmaceutically acceptable excipients. The pharmaceutical compositions that include salts of pitavastatin with one or more pharmaceutically acceptable excipients may be formulated as: solid oral dosage forms such as, but not limited to, powders, granules, pellets, tablets, and capsules; liquid oral dosage forms such as, but not limited to, syrups, suspensions, dispersions, and emulsions; and injectable preparations such as, but not limited to, solutions, dispersions, and freeze dried compositions. Formulations may be in the form of immediate release, delayed release, or modified release. Further, immediate release compositions may be conventional, dispersible, chewable, mouth dissolving, or flash melt preparations, and modified release compositions may comprise hydrophilic or hydrophobic, or combinations of hydrophilic and hydrophobic, release rate controlling substances to form matrix or reservoir systems or combinations of matrix and reservoir systems. The compositions may be prepared using any of techniques such as direct blending, dry granulation, wet granulation, and extrusion and spheronization. Compositions may be presented as uncoated, film coated, sugar coated, powder coated, enteric coated, or modified release coated. Compositions of the present application further comprise one or more pharmaceutically acceptable excipients.

Pharmaceutically acceptable excipients that find use in the present application include, but are not limited to: diluents such as starches, pregelatinized starches, lactose, powdered cellulose, microcrystalline cellulose, dicalcium phosphate, tricalcium phosphate, mannitol, sorbitol, sugar, or the like; binders such as acacia,

guar gum, tragacanth, gelatin, polyvinylpyrrolidones, hydroxypropyl celluloses, hydroxypropyl methylcelluloses, pregelatinized starches, or the like; disintegrants such as starches, sodium starch glycolate, pregelatinized starches, crospovidones, croscarmellose sodium, colloidal silicon dioxide, or the like; lubricants such as stearic acid, magnesium stearate, zinc stearate, or the like; glidants such as colloidal silicon dioxide or the like; solubility or wetting enhancers such as anionic, cationic, and neutral surfactants; complex forming agents such as various grades of cyclodextrins and resins; release rate controlling agents such as hydroxypropyl celluloses, hydroxymethyl celluloses, hydroxypropyl methylcelluloses, ethylcelluloses, methylcelluloses, various grades of methyl methacrylates, waxes, or the like. Other pharmaceutically acceptable excipients that are of use include,but are not limited to, film formers, plasticizers, colorants, flavoring agents, sweeteners, viscosity enhancers, preservatives, antioxidants, or the like.

The processes of the present application are simple, cost-effective, ecologically friendly, reproducible, scalable, and robust, to produce pitavastatin calcium with high purity. Pitavastatin calcium employed as a starting material for generation of pitavastatin free acid can be obtained by any processes known in the art, including processes disclosed in U.S. Patent No. 5,856,336 and International Application Publication No. WO 95/11898 A1, both of which are incorporated herein by reference for their process descriptions, as well as by any other processes.

PXRD data reported herein are obtained using copper Kα radiation, and were obtained using a Bruker AXS D8 Advance Powder X-ray Diffractometer. Crystalline forms are characterized using scattering techniques, *e.g.*, powder or single crystal X-ray diffraction patterns, spectroscopic methods, *e.g.*, infrared absorption spectrophotometry and ^{13}C nuclear magnetic resonance spectroscopy, and by thermal techniques, e.g., differential scanning calorimetry and differential thermal analysis. In general, polymorphic forms are best distinguished by X-ray diffraction patterns, determined in accordance with procedures that are known in the art. For a discussion of these techniques see J. Haleblain, *J. Pharm. Sci.***1975 64**:1269-1288, and J. Haleblain and W. McCrone, *J. Pharm. Sci.***1969 58**:911-929.

Generally, the diffraction angles (2θ) for peaks in powder X-ray diffractometry may have an error in the range of ± 0.2°. Therefore, diffraction angle values should be understood as including values within the range of about ± 0.2°. Although the

intensities of peaks in X-ray powder diffraction patterns of different batches of a compound may vary slightly, the peaks and the peak locations are characteristic for a specific polymorphic form. The relative intensities of the PXRD peaks can vary depending on the sample preparation techniques, crystal size distributions, various filters used, the sample mounting procedure, and the particular instrument employed. Moreover, instrument variation and other factors can affect the 2-theta values. Therefore, the term "substantially" in the context of PXRD is meant to encompass that peak assignments can vary by plus or minus about 0.2°.

DEFINITIONS

The following definitions are used in connection with the present application, unless the context indicates otherwise. Polymorphs are different solids sharing the same molecular structure, yet having distinct physical properties when compared to other polymorphs of the same formula. A pseudopolymorph is a different crystal type that is the result of hydration or solvation.

The acronym ATD means “Air Tray Drier”.

All percentages and ratios used herein are by weight of the total composition, unless the context indicates otherwise. All temperatures are in degrees Celsius unless specified otherwise and all measurements are made at 25°C and atmospheric pressure unless otherwise designated. As used herein, a "room” or “ambient” temperature includes temperature from about 15°C to about 35°C, from about 20°C to about 30°C, or about 25°C.

As used herein, "comprising" means the elements recited, or their equivalents in structure or function, plus any other element or elements which are not recited. The terms "having" and "including" are also to be construed as open ended unless the context suggests otherwise. All ranges recited herein include the endpoints, including those that recite a range "between" two values.

Terms such as "about," "generally," "substantially," or the like are to be construed as modifying a term or value such that it is not an absolute. Such terms will be defined by the circumstances and the terms that they modify, as those terms are understood by those of skill in the art. This includes, at very least, the degree of expected experimental error, technique error, and instrument error for a given technique used to measure a value. Where this document refers to a material, such

as in this instance, crystalline forms of pitavastatin calcium by reference to patterns, spectra or other graphical data, it may do so by qualifying that they are "substantially" shown or as depicted in Figures, or by one or more data points. By "substantially" used in such a context, it will be appreciated that patterns, spectra and other graphical data can be shifted somewhat in their positions, relative intensities and/or values due to a number of factors known to those of skill in the art. For example, in the crystallographic and powder X-ray diffraction arts, such shifts in peak positions or the relative intensities of one or more peaks can occur because of, without limitation: the equipment used, the sample preparation protocol, preferred packing and orientations, the radiation source, operator error, method and length of data collection, or the like. However, those of ordinary skill in the art will be able to compare the figures herein with a pattern generated of an unknown form of, in this case, pitavastatin calcium, and confirm its identity as a form disclosed herein. The same holds true for other techniques which may be reported herein. In addition, where a reference is made to a figure, it is permissible to, and this document includes and contemplates, the selection of any number of data points illustrated in the figure that uniquely define that crystalline form, salt, and/or optical isomer, within any associated and recited margin of error, for purposes of identification.

An “alcohol” is an organic liquid containing a carbon bound to a hydroxyl group, including, but not limited to, methanol, ethanol, 2-nitroethanol, 2-fluoroethanol, 2,2,2-trifluoroethanol, hexafluoroisopropyl alcohol, ethylene glycol, 1-propanol, 2-propanol (isopropyl alcohol), 2-methoxyethanol, 1-butanol, 2-butanol, i-butyl alcohol, t-butyl alcohol, 2-ethoxyethanol, diethylene glycol, 1-, 2-, or 3-pentanol, neo-pentyl alcohol, t-pentyl alcohol, diethylene glycol monomethyl ether, diethylene glycol monoethyl ether, cyclohexanol, benzyl alcohol, phenol, glycerol, C_{1-6}alcohols,or the like.

An “ether” is an organic liquid containing an oxygen atom –O- bonded to two other carbon atoms, including, but not limited to,diethyl ether, diisopropyl ether, methyl t-butyl ether, glyme, diglyme, tetrahydrofuran, 1,4-dioxane, dibutyl ether, dimethylfuran, 2-methoxyethanol, 2-ethoxyethanol, anisole, C_{2-6}ethers, or the like.

A “halogenated hydrocarbon” is an organic liquid containing a carbon bound to a halogen, including, but not limited to, dichloromethane, 1,2-dichloroethane, trichloroethylene, perchloroethylene, 1,1,1-trichloroethane, 1,1,2-trichloroethane, chloroform, carbon tetrachloride, or the like.

A “ketone” is an organic liquid containing a carbonyl group -(C=O)- bonded to two other carbon atoms, including, but not limited to, acetone, ethyl methyl ketone, diethyl ketone, methyl isobutyl ketone, C_{3-6}ketones, or the like.

A “hydrocarbon” is a liquid compound formed from carbon and hydrogen atoms, and may be linear, branched, cyclic, saturated, unsaturated, non-aromatic, or aromatic. Examples include, but are not limited to, n-pentane, isopentane, neopentane, n-hexane, isohexane, 3-methylpentane, 2,3-dimethylbutane, neohexane, n-heptane, isoheptane, 3-methylhexane, neoheptane, 2,3-dimethylpentane, 2,4-dimethylpentane, 3,3-dimethylpentane, 3-ethylpentane, 2,2,3-trimethylbutane, n-octane, isooctane, 3-methylheptane, neooctane, cyclohexane, methylcyclohexane, cycloheptane, C_5-C_8aliphatic hydrocarbons, petroleum ethers, benzene, toluene, ethylbenzene, m-xylene, o-xylene, p-xylene, indane, naphthalene, tetralin, trimethylbenzene, chlorobenzene, fluorobenzene, trifluorotoluene, anisole, C_6-C_{10}aromatic hydrocarbons, or the like.

A “nitrile” is an organic liquid containing a cyano -(C≡N) bonded to another carbon atom, including, but not limited to, acetonitrile, propionitrile, C_{2-6}nitriles, or the like.

A “polar aprotic solvent” has a dielectric constant greater than 15 and includes: amide-based organic solvents, such as hexamethyl phosphoramide (HMPA) and hexamethyl phosphorus triamide (HMPT); nitro-based organic solvents, such as nitromethane, nitroethane, nitropropane, and nitrobenzene; ester-based organic solvents, such as γ-butyrolactone, ethylene carbonate, propylene carbonate, butylene carbonate, dimethyl carbonate, and propiolactone; pyridine-based organic solvents, such as pyridine and picoline; and sulfone-based solvents, such as dimethylsulfone, diethylsulfone, diisopropylsulfone, 2-methylsulfolane, 3-methylsulfolane, 2,4-dimethylsulfolane, 3,4-dimethylsulfolane, 3-sulfolene, and sulfolane.

Any organic solvents may be used alone, or two or more of these may be combined in desired ratios. As used herein, the term "crystalline forms of pitavastatin" encompasses solvates, hydrates, desolvates or the like.

Certain specific aspects and embodiments of the present application will be explained in greater detail with reference to the following examples, which are provided only for purposes of illustration and should not be construed as limiting the scope of the application in any manner.

EXAMPLES

EXAMPLE 1: PREPARATION OF PITAVASTATIN CALCIUM FORM IV.

Pitavastatin calcium (2 g) and 1-butanol (100 mL) were charged into a round bottom flask. The mixture was heated to 80°C to result in clear solution. The said solution was further maintained at the same temperature for about 1 hour 30 minutes and the resulting solid was isolated by filtration. The solid was dried under air at about 40°C for 1 hour to afford the title compound in 85% yield having HPLC purity of 99.80% and 1-butanol content = 2.1%. The said pitavastatin calcium has the PXRD pattern of Fig. 1.

EXAMPLE 2: PREPARATION OF PITAVASTATIN CALCIUM FORM V.

Pitavastatin calcium (6 g) and 1-butanol (300 mL) were charged into a round bottom flask. The mixture was heated to 80°C to result in clear solution. The said solution was further maintained at the same temperature for about 2 hours and the resulted solid was isolated by filtration. The solid was dried in ATD at 120°C for about 2 hours to afford the title compound having HPLC purity of 99.75%. The said pitavastatin calcium has the PXRD pattern of Fig. 2.

EXAMPLE 3: PREPARATION OF PITAVASTATIN CALCIUM FORM VI.

Pitavastatin calcium (3 g) and 2-butanol (150 mL) were charged into a round bottom flask. The mixture was heated to 80°C to result in clear solution. The said solution was further maintained at the same temperature for about 24 hours and the resulting solid was isolated by filtration and divided in two parts. The first part was dried in ATD at about 40°C for 1 hour to afford Pitavastatin calcium Form VI characterized by Fig. 3.

The second part on drying in ATD at about 120°C for about 2 hours resulted in Form V.

EXAMPLE 4: PREPARATION OF PITAVASTATIN CALCIUM FORM VII.

Pitavastatin calcium (3 g) and iso-butanol (150 mL) were charged into a round bottom flask. The mixture was heated to about 80°C to result in clear solution. The said solution was further maintained at the same temperature for about 4 hours and

the resulting solid was isolated by filtration and divided in two parts. The first part was dried in ATD at about 40°C for 1 hour to afford Pitavastatin calcium Form VII characterized by Fig 4.

The second part on drying in ATD at about 120°C for about 2 hours resulted in Form V.

EXAMPLE 5: PREPARATION OF PITAVASTATIN CALCIUM FORM VIII.

Pitavastatin calcium (15 g) and 1-butanol (750 mL) were charged into a round bottom flask. The mixture was heated to 80°C to result in clear solution. The said solution was further maintained at the same temperature for about 2 hours and the resulting solid was isolated by filtration. The solid was dried in ATD at 120°C for about 2 hours followed by drying at 200°C for 15 minutes to afford the title compound. The said pitavastatin calcium has the PXRD pattern of Fig. 5.

EXAMPLE 6: PREPARATION OF PITAVASTATIN CALCIUM FORM IX

Pitavastatin calcium (2 g) and acetone (100 mL) were charged into a round bottom flask. The mixture was heated to 50-55°C and the mixture was further maintained at the same temperature for about 35-45 hours and the obtained solid was isolated by filtration. The solid was dried in ATD at about 40°C for 1 hour to afford the title compound in 72% yield having 99.75% HPLC purity. The said pitavastatin calcium has the PXRD pattern of Fig. 6.

EXAMPLE 7: PREPARATION OF PITAVASTATIN CALCIUM FORM X

Pitavastatin calcium (20 g) and ethyl acetate (300 mL) were charged into a round bottom flask and stirred at room temperature. The mixture was heated to 70°C and was further maintained at the same temperature for about 8 hours for crystallization. The mixture was cooled to room temperature and solid was isolated by filtration followed by drying in VTD at 60°C for 20 hours to afford the title compound having 99.6% HPLC purity. The said pitavastatin calcium has the PXRD pattern of Fig. 7.

EXAMPLE 8: PREPARATION OF PITAVASTATIN CALCIUM

Pitavastatin calcium (2 g) as obtained in example 7 was subjected to drying in ATD at 64°C for about 48 hours to afford crystalline pitavastatin calcium having PXRD pattern as depicted in Fig. 8.

Claims:

1. A crystalline Form IV of pitavastatin calcium characterized by powder X-ray diffractogram comprising peaks at 3.77, 4.88, 6.84, 10.88, 19.75 and 20.90 degrees of 2θ values.

2. The crystalline form of claim 1 characterized by powder X-ray diffractogram with two or more peaks further selected from about 5.41, 10.04, 12.13, 13.70, 14.82, 15.23 and 17.67 degrees of 2θ values.

3. A crystalline Form V of pitavastatin calcium characterized by powder X-ray diffractogram comprising peaks at 3.76, 4.86, 6.87, 10.87, 19.86, 21.01 and 21.75 degrees of 2θ values.

4. The crystalline form of claim 3 characterized by powder X-ray diffractogram with two or more peaks further selected from about 5.43, 10.04, 12.19, 13.77, 14.79, 15.28 and 17.74 degrees of 2θ values.

5. A crystalline Form VI of pitavastatin calcium characterized by powder X-ray diffractogram comprising peaks at 3.79, 4.91, 6.83 degrees of 2θ values.

6. The crystalline form of claim 5 characterized by powder X-ray diffractogram with two or more peaks further selected from about 10.08, 10.89, 15.33, 19.29, 19.77, 22.08 degrees of 2θ values.

7. A crystalline Form VII of pitavastatin calcium characterized by powder X-ray diffractogram comprising peaks at 14.69, 15.35, 19.32 and 19.78 degrees of 2θ values.

8. The crystalline form of claim 7 characterized by powder X-ray diffractogram with two or more peaks further selected from about 4.88, 6.84 and 10.88 degrees of 2θ values.

9. A crystalline Form VIII of pitavastatin calcium characterized by powder X-ray diffractogram comprising peaks at 3.92 and 5.34 degrees of 2θ values.

10. The crystalline form of claim 9 characterized by powder X-ray diffractogram with two or more peaks further selected from about 11.23, 17.34 and 18.06 degrees of 2θ values.

11. A crystalline Form IX of pitavastatin calcium characterized by powder X-ray diffractogram comprising peaks at 4.87, 6.85, 10.91, 19.86, 20.91 and 21.73 degrees of 2θ values.

12. The crystalline form of claim 11 characterized by powder X-ray diffractogram with two or more peaks further selected from about 5.43, 10.06, 12.19, 13.75, 14.76, 15.30 and 17.65 degrees of 2θ values.

13. A crystalline Form X of pitavastatin calcium characterized by powder X-ray diffractogram comprising peaks at 4.95, 6.93, 10.96, 14.88, 15.42 and 19.95 degrees of 2θ values.

14. The crystalline form of claim 13 characterized by powder X-ray diffractogram with two or more peaks further selected from about 5.51, 10.15, 12.20, 13.79, 17.75, 19.06 and 19.51 degrees of 2θ values.

15. A process for the preparation of novel crystalline forms of claims 1-14 of pitavastatin calcium comprising;

a) providing a mixture comprising pitavastatin calcium in a suitable solvent;
b) maintaining the reaction mixture at about reflux temperature of solvent,
c) recovering crystalline pitavastatin calcium.

16. The process of claim 15 wherein in step a) suitable solvent is selected from alcohols, ketones, esters, polar aprotic solvents, hydrocarbons, water and their mixtures.

17. The process of claim 16 wherein suitable solvent is selected from 1-butanol, 2-butanol, iso-butanol, acetone and ethyl acetate.

18. The process of claim 15 wherein the temperature for crystallization in step b) is any temperature in the range of 50-120°C.

19. The process of claim 15 wherein recovery of crystalline pitavastatin calcium in step d) involves drying.

20. The process of claim 19 wherein drying is performed at any temperature in the range 40-200°C.

21. A process for preparation of novel crystalline Form V of pitavastatin calcium comprising;

a) providing a mixture comprising pitavastatin calcium in a suitable solvent;
b) maintaining the reaction mixture at about reflux temperature of solvent,
c) isolating pitavastatin calcium,
d) drying the product of step c) at elevated temperature.

22. The process of claim 21 wherein the temperature for crystallization in step b) is any temperature in the range of 65-120°C.

23. The process of claim 21 wherein drying in step d) is performed at any temperature in the range 80-140°C.

24. A process for preparation of novel crystalline Form V of pitavastatin calcium comprising drying the novel crystalline Forms IV, VI and VII at any temperature in the range 100-150°C.

25. The process of claim 24 wherein the drying temperature is about 120°C.

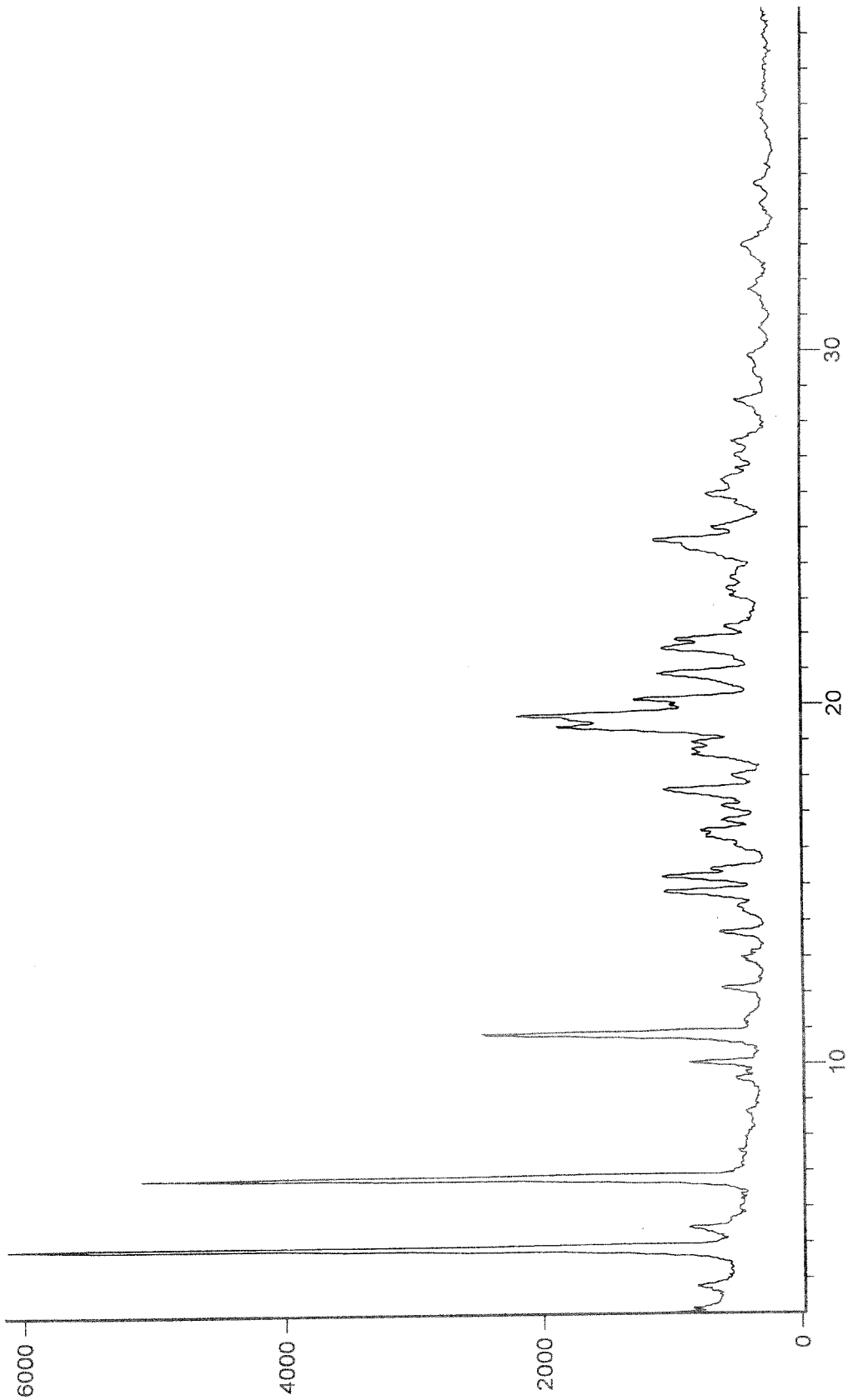


Fig. 1

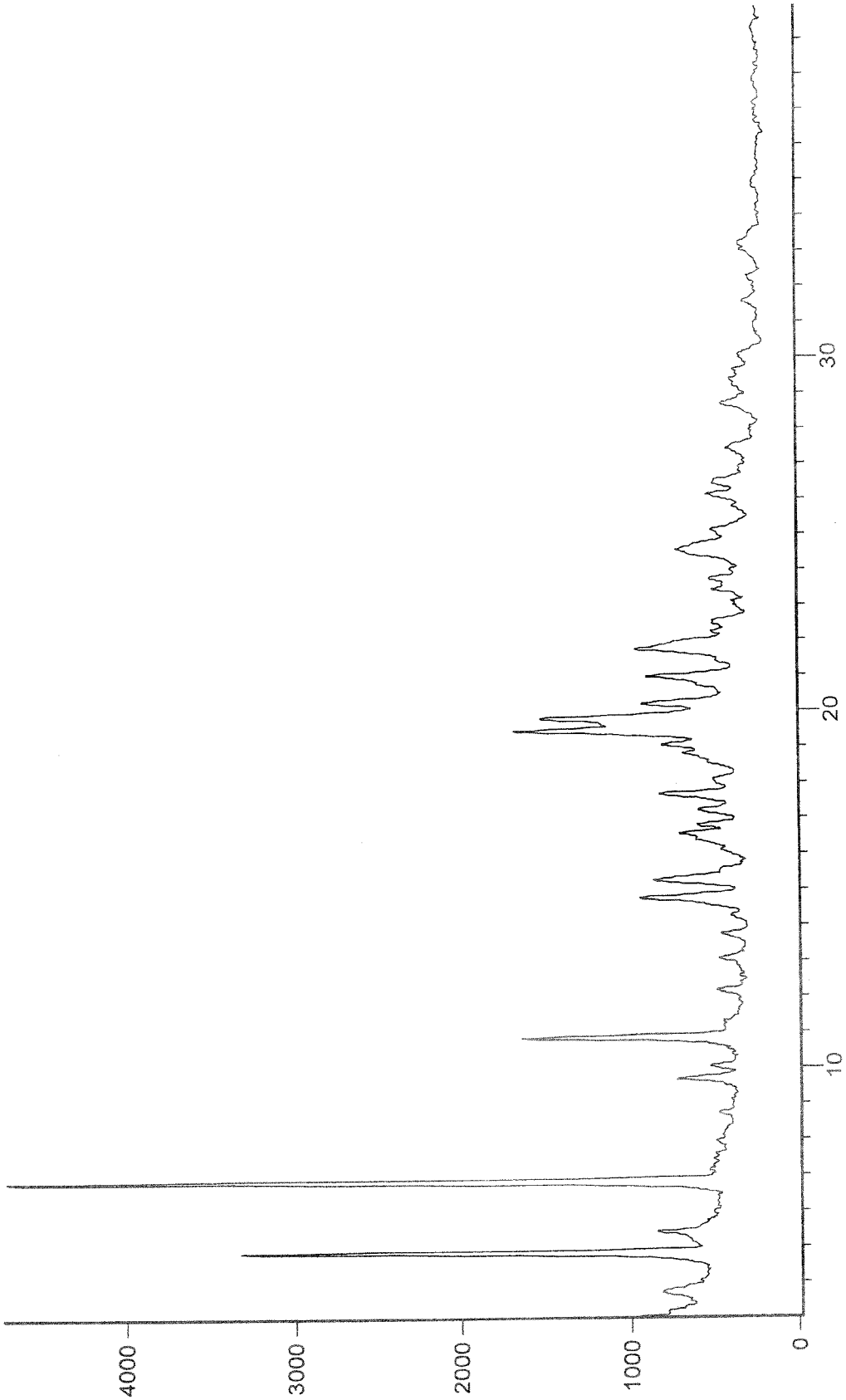


Fig. 2

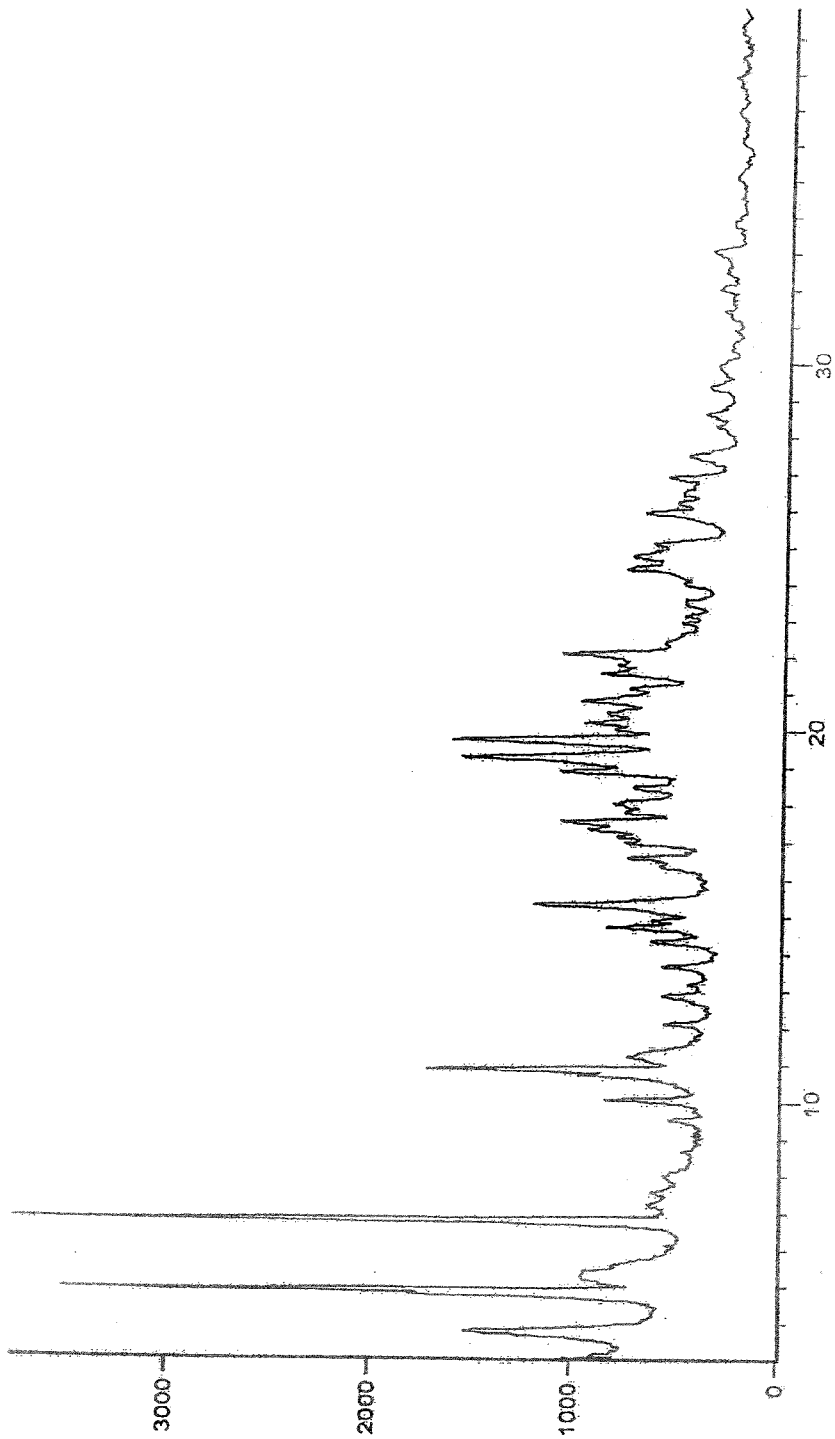


Fig. 3

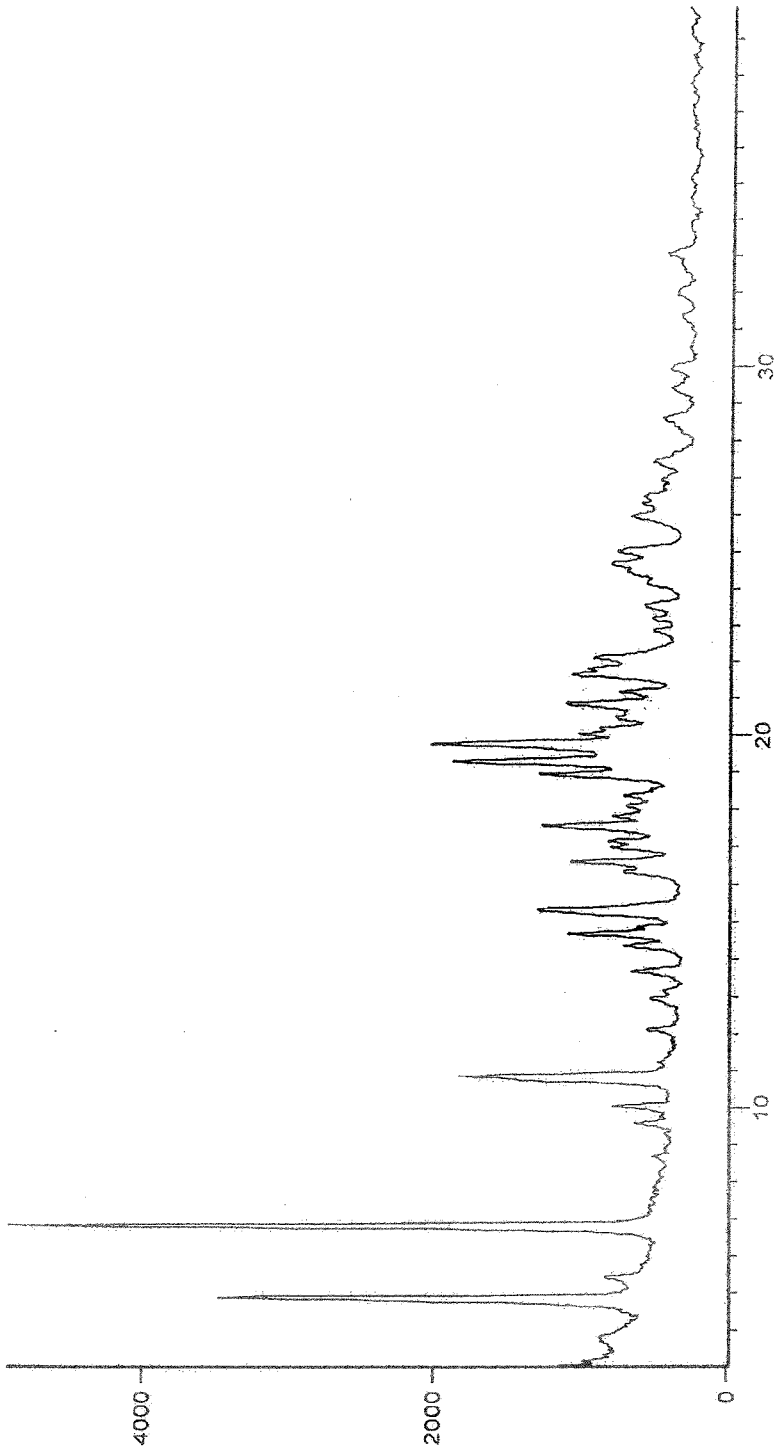


Fig. 4

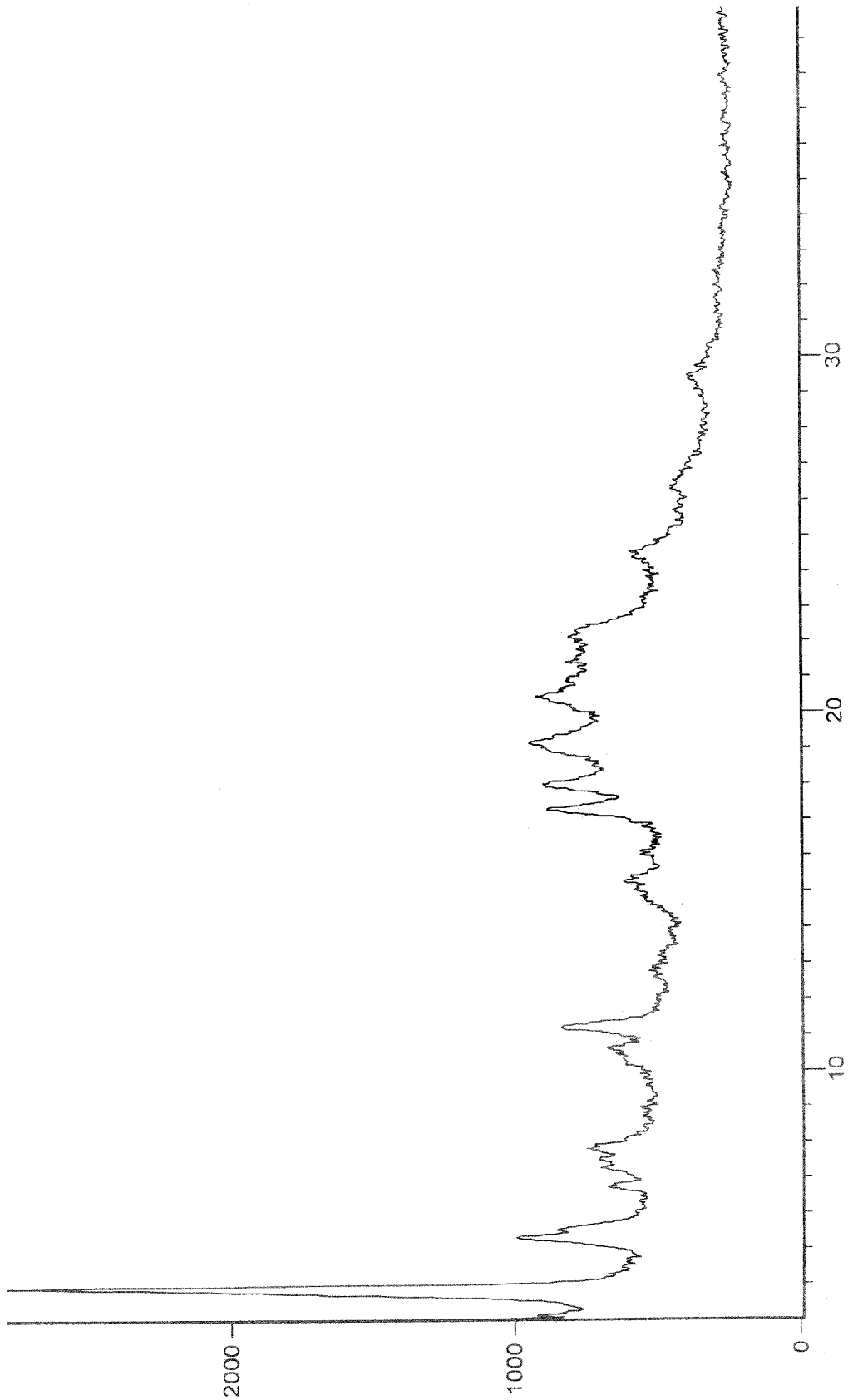


Fig. 5

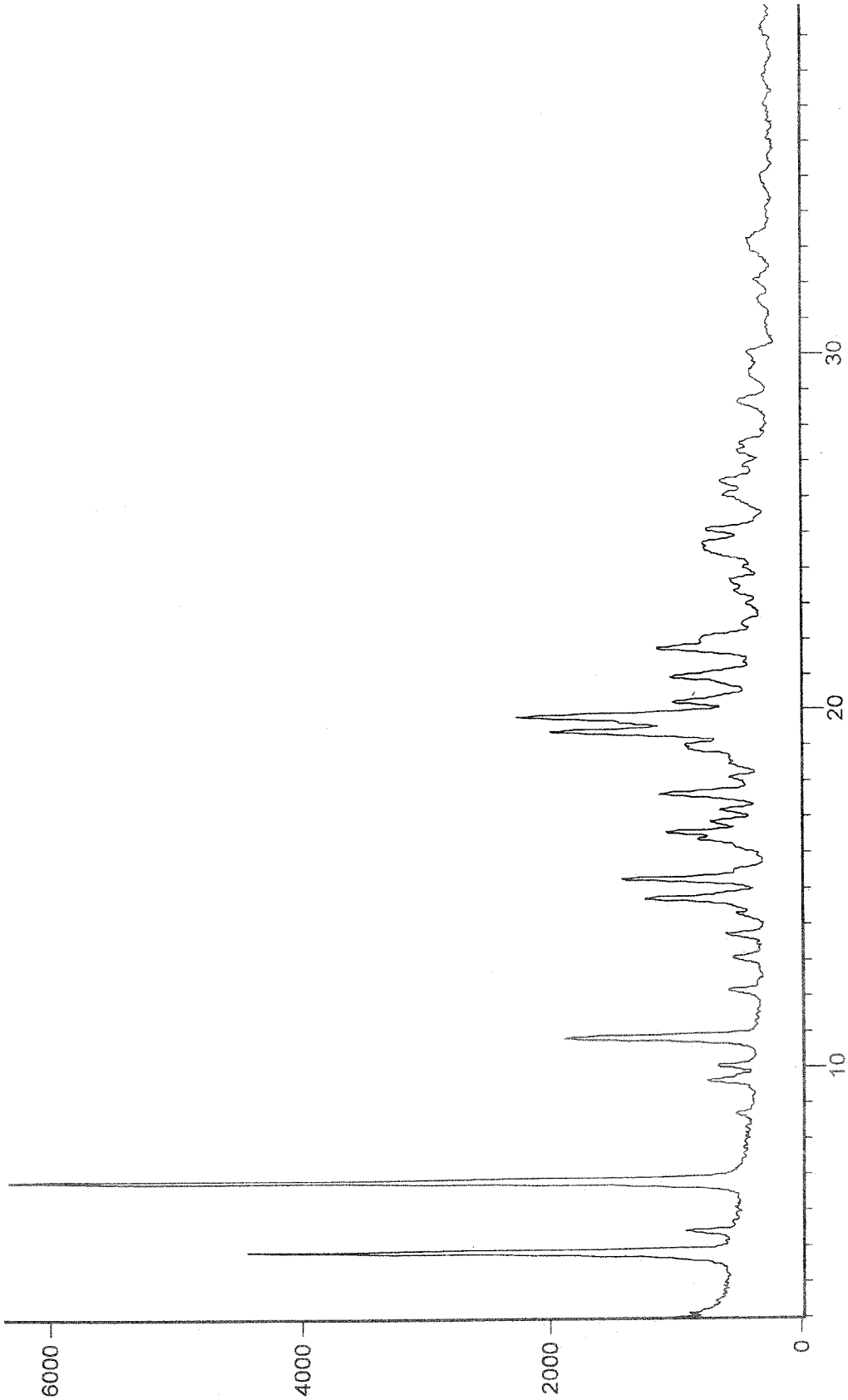


Fig. 6

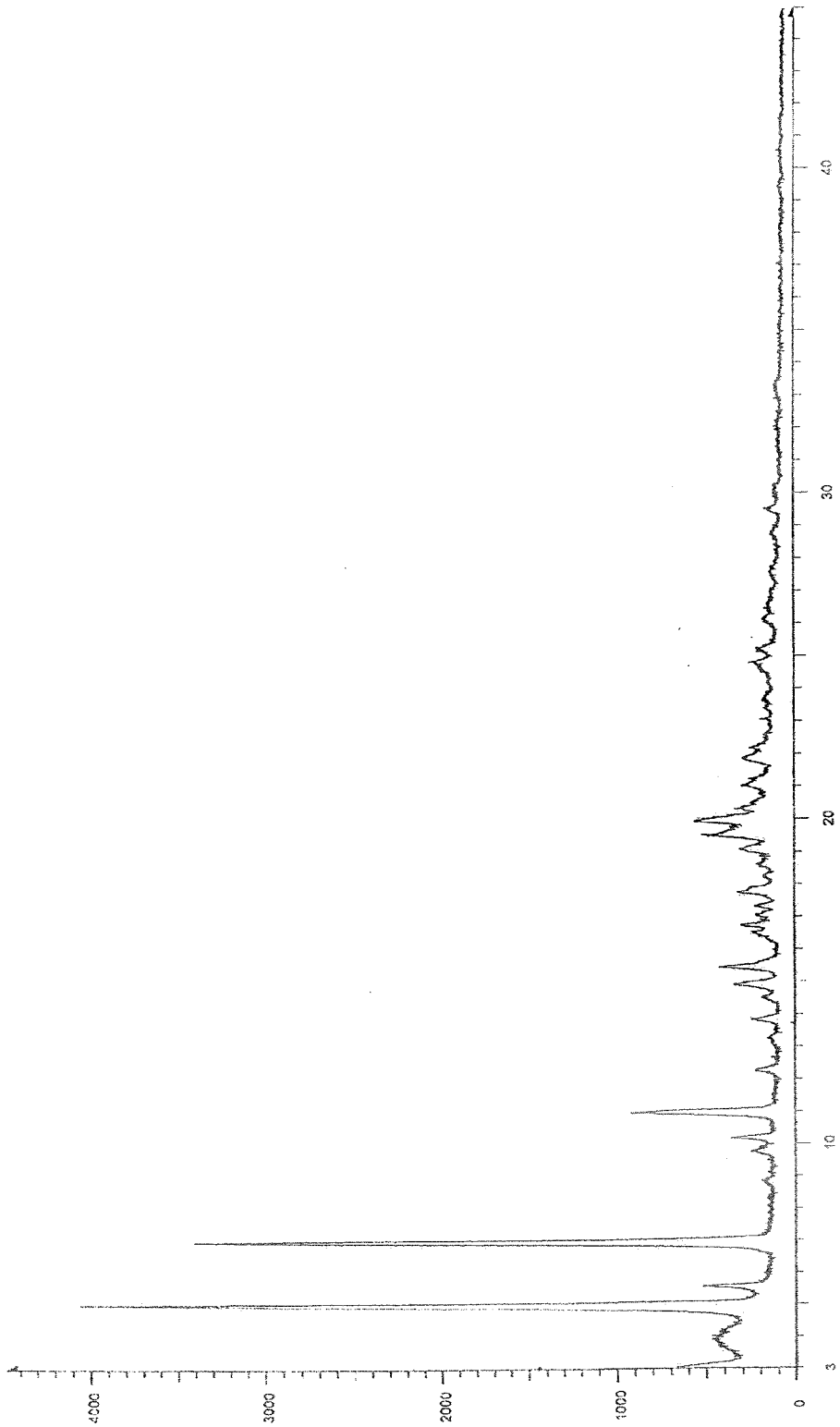


Fig. 7

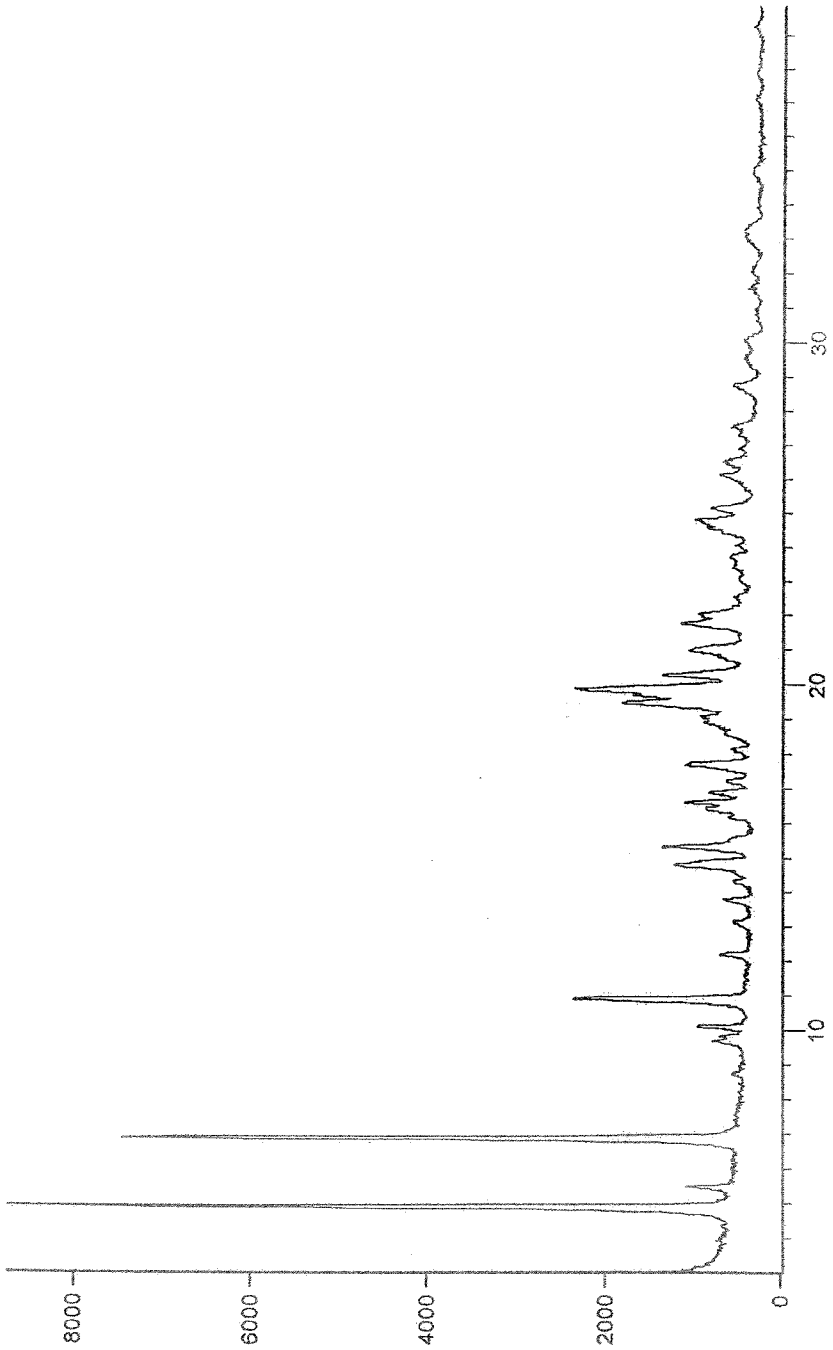


Fig. 8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2012/057752

A. CLASSIFICATION OF SUBJECT MATTER

See extra sheet

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)

C07D215/-, A61K31/-, A61P9/-

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)

EPODOC, WPI, CNABS, CNKI, CA: pitavastatin calcium, crystal+, 147526-32-7

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X A	EP 0520406 A1 (NISSAN CHEMICAL INDUSTRIES LTD.), 30 December 1992 (30.12.1992) example 3	1-23 24-25
X A	CN 102285917 A (HAINAN MEIDA PHARM. CO. LTD.), 21 December 2011 (21.12.2011) examples 1-2	1-23 24-25
X A	WO 2010077062 A2 (HANMI PHARM. CO., LTD.), 08 July 2010 (08.07.2010) examples 10-11	1-23 24-25
X A	WO 2007132482 A2 (SATYANARAYANA REDDY MANNE ET AL), 22 November 2007 (22.11.2007) examples 7-9	1-23 24-25

☒ 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
03 May 2013 (03.05.2013)	**23 May 2013 (23.05.2013)**
Name and mailing address of the ISA/CN The State Intellectual Property Office, the P.R.China 6 Xitucheng Rd., Jimen Bridge, Haidian District, Beijing, China 100088 Facsimile No. 86-10-62019451	Authorized officer LI,Shikun Telephone No. (86-10)82246725

Form PCT/ISA /210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2012/057752

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X A	WO 2004072040 A1 (CIBA SPECIALTY CHEMICALS HOLDING INC.), 26 August 2004 (26.08.2004) pages 8-9, example 7, figure 6, claims 11-12 pages 3-8 , examples 1-6, claims 1-10, figures 1-5	7-8, 15-20 1-6, 9-25
A	CN 101195603 A (CHONGQING PHARM. RES. INST. CO. LTD.), 11 June 2008(11.06.2008) examples 1-3, figure	1-25
A	WO 2005063711 A1 (NISSAN CHEMICAL INDUSTRIES, LTD.), 14 July 2005(14.07.2005) description, page 5 line 9 to page 7 line 10, pages 13-14, figures 1-2	1-25
PX	WO 2012063254 A1 (HETERO RESEARCH FOUNDATION), 18 May 2012(18.05.2012) description, page 5 lines 11-30, page 7 line 18 to page 8 line 29, examples 3-13	1-23

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2012/057752

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

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

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

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

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

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

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

See extra sheet

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

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

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

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

Remark on protest

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

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

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2012/057752

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

This authority considers that there are seven inventions covered by the claims indicated as follows:

I: claims 1-2(completely), 15-20(partially), 24-25(partially);

crystalline form IV of pitavastatin calcium, process for its preparation and the use for preparation of crystalline form V of pitavastatin calcium

II: claims 3-4(completely), 15-20(partially), 21-25(completely);

crystalline form V of pitavastatin calcium and process for its preparation

III: claims 5-6(completely), 15-20(partially), 24-25(partially);

crystalline form VI of pitavastatin calcium, process for its preparation and the use for preparation of crystalline form V of pitavastatin calcium

IV: claims 7-8(completely), 15-20(partially), 24-25(partially);

crystalline form VII of pitavastatin calcium, process for its preparation and the use for preparation of crystalline form V of pitavastatin calcium

V: claims 9-10(completely), 15-20(partially);

crystalline formVIII of pitavastatin calcium and process for its preparation ;

VI: claims 11-12(completely), 15-20(partially);

crystalline form IX of pitavastatin calcium and process for its preparation;

VII: claims 13-14(completely), 15-20(partially);

crystalline form X of pitavastatin calcium and process for its preparation;

The same or corresponding technical feature among the inventions I-VII is pitavastatin calcium. However, several crystalline forms of pitavastatin calcium are already known in the prior art(see D5, claims 1-12). Hence, the same or corresponding technical feature contained in inventions above does not make a contribution over the prior art and can not be regarded as special technical feature within the meaning of Rule 13.2 PCT. Therefore, the application does not meet the requirements of unity of invention as defined in Rule 13.1 PCT.

Continuation of : "A. CLASSIFICATION OF SUBJECT MATTER"

C07D215/14 (2006.01) i
A61K31/47 (2006.01) i
A61P9/00 (2006.01) i

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IB2012/057752

Patent Documents referred in the Report	Publication Date	Patent Family	Publication Date
EP 0520406 A1	30.12.1992	CA 2072162 A	25.12.1992
		JP 5148237 A	15.06.1993
		US 5284953 A	08.02.1994
		US 5473075 A	05.12.1995
		US 5514804 A	07.05.1996
		TW 293007 A	11.12.1996
		EP 0520406 B1	02.09.1998
		DE 69226822 E	08.10.1998
		ES 2120973 T3	16.11.1998
		CA 2072162 C	19.11.2002
		JP 3528186 B2	17.05.2004
		KR 100208867 B1	15.07.1999
CN 102285917 A	21.12.2011	None	
WO 2010077062 A2	08.07.2010	WO 2010077062 A3	04.11.2010
		KR 20100080432 A	08.07.2010
WO 2007132482 A2	22.11.2007	WO 2007132482 A3	10.04.2008
		INCHE 200600867 A	21.12.2007
WO 2004072040 A1	26.08.2004	AU 2004212160 A1	26.08.2004
		EP 1592668 A1	09.11.2005
		TW 200420541 A	16.10.2004
		US 2006142582 A1	29.06.2006
		CN 1747934 A	15.03.2006
		JP 2006518354 A	10.08.2006
		INCHENP 200502219 E	06.04.2007
		DE 202004021379 U1	27.03.2008
		CN 100374422 C	12.03.2008
		CN 101219992 A	16.07.2008
		US 2009182008 A1	16.07.2009
		INCHENP 200900507 E	05.06.2009
		AU 2004212160 B2	14.05.2009
		JP 2011201915 A	13.10.2011

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IB2012/057752

Patent Documents referred in the Report	Publication Date	Patent Family	Publication Date
		CN 101219992 B	31.08.2011
		CN 102285916 A	21.12.2011
		US 2012101126 A1	26.04.2012
		CA 2785954 A1	26.08.2004
		EP 2500339 A1	19.09.2012
CN 101195603 A	11.06.2008	None	
WO 2005063711 A1	14.07.2005	EP 1697326 A1	06.09.2006
		AU 2004309241 A1	14.07.2005
		US 2007112024 A1	17.05.2007
		CN 1898211 A	17.01.2007
		MXPA 06007435 A	01.12.2006
		JP 2007516952 A	28.06.2007
		INKOLNP 200601757 E	11.05.2007
		KR 20070001910 A	04.01.2007
		ZA 200605658 A	28.11.2007
		US 2009176987 A1	09.07.2009
		TW 200530186 A	16.09.2005
		RU 2370489 C2	20.10.2009
		NZ 548041 A	30.04.2010
		KR 20110017936 A	22.02.2011
		US 2011082298 A1	07.04.2011
		EP 1697326 B1	03.08.2011
		AU 2011213742 A1	08.09.2011
		MX 288297 B	11.07.2011
		IL 176470 A	31.10.2011
		TWI 328006 B	01.08.2010
		US 2011319624 A1	29.12.2011
		CN 102321019 A	18.01.2012
		JP 2012072175 A	12.04.2012
		US 2012245200 A1	27.09.2012
WO 2012063254 A1	18.05.2012	INCHE 201003399 A	20.07.2012