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(54) **Title**: NOVEL POLYMORPHS OF SITAGLIPTIN HYDROCHLORIDE, PROCESSES FOR ITS PREPARATION AND PHARMACEUTICAL COMPOSITION THEREOF

(57) **Abstract**: The present invention relates to novel polymorphic forms of sitagliptin hydrochloride, processes for its preparation and pharmaceutical compositions comprising the same.

WO 2015/170340 A2

"NOVEL POLYMORPHS OF SITAGLIPTIN HYDROCHLORIDE, PROCESSES FOR ITS PREPARATION AND PHARMACEUTICAL COMPOSITION THEREOF"

PRIORITY:

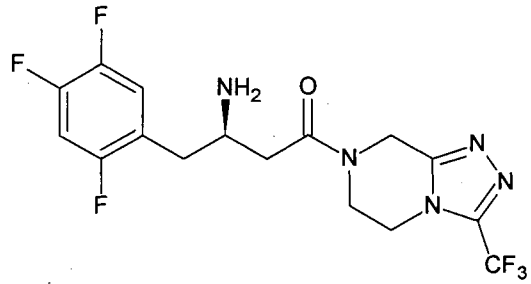
This application claims the benefit under Indian Provisional Application No. 2266/CHE/2014 filed on May 6, 2014 entitled "Novel polymorphs of sitagliptin hydrochloride, processes for its preparation and pharmaceutical composition thereof", the content of which is incorporated by reference herein.

FIELD OF THE INVENTION:

The present invention relates to novel polymorphic forms of sitagliptin hydrochloride, processes for its preparation and pharmaceutical compositions containing the same.

BACKGROUND OF THE INVENTION:

Sitagliptin is an orally-active dipeptidyl peptidase-4 (DPP-IV) enzyme inhibitor that improves glycemic control in patients with Type 2 diabetes mellitus by slowing the inactivation of incretin hormones. Sitagliptin may be used as a monotherapy, as an adjunct to diet and exercise, or in combination with metformin or a PPARγ agonist (e.g., thiazolidinediones). Sitagliptin is chemically designated as (3R)-3-amino-1-[9-(trifluoromethyl)-1,4,7,8-tetrazabicyclo[4.3.0]nona-6,8--dien-4-yl]-4-(2,4,5-trifluorophenyl)butan-1-one, is represented by the following structural Formula I:



Formula I

Sitagliptin is currently marketed in its phosphate salt in the United States under the trade name JANUVIA™ in its monohydrate form. JANUVIA™ is indicated to improve glycemic control in patients with type 2 diabetes mellitus.

U.S. Patent No. 6,699,871 ("the '871 patent") discloses a class of beta-amino-tetrahydrotriazolo[4,3-a]pyrazines such as sitagliptin, processes for their preparation, pharmaceutical compositions and method of use thereof. It also discloses a process for the preparation of hydrochloride salt of sitagliptin.

PCT publication No. WO 2005/072530 discloses crystalline sitagliptin hydrochloride monohydrate, process for its preparation and pharmaceutical composition comprising the

same. The crystalline sitagliptin hydrochloride monohydrate was characterized by its PXRD, IR spectra and DSC thermogram. This publication also discloses crystalline tartaric acid, benzene sulfonic acid, p-toluenesulfonic acid and 10-camphor sulfonic acid salts of sitagliptin and their preparation.

PCT publication No. WO 2010/000469 discloses crystalline forms of sitagliptin monobasic, dibasic and tribasic acid addition salts such as hydrochloric acid (Form I and Form II), sulfuric acid (Form I and Form II), methane sulfonic acid (Form I and Form II), fumaric acid (Form I and Form II), malonic acid, malic acid, succinic acid (Form I, Form II and Form III), lactic acid, glycolic acid, maleic acid (Form I and Form II), citric acid (crystalline and amorphous Form), aspartic acid and mandelic acid and process for the preparation thereof. The crystalline forms reported in this publication were characterized by their PXRD pattern.

US patent No. 8,183,373 (the "373" patent) discloses crystalline forms of sitagliptin hydrochloride designated as Form III, Form IV and Form V. Also discloses characterization details such as PXRD pattern and process for their preparation. This patent further discloses different crystalline forms of sitagliptin sulfate, sitagliptin L-malate and sitagliptin acetate.

PCT publication No. WO 2012/0147092 discloses crystalline form of sitagliptin hydrochloride characterized by its PXRD pattern, as well as process for its preparation. This publication also discloses different polymorphic forms of sitagliptin gentisate, adipate, trifluoro acetic acid and besylate salts.

US patent publication No. 2013/0158265 discloses crystalline forms of sitagliptin hydrochloride designated as Form III, Form IV and Form V. Also discloses characterization details such as PXRD pattern and process for their preparation. This publication also disclosed different crystalline forms of sitagliptin phosphate and sitagliptin esylate.

PCT publication No. WO2008/000418 discloses a process for the preparation of sitagliptin hydrochloride in amorphous form.

KR200011109 discloses novel crystalline form of sitagliptin hydrochloride characterized by its PXRD, IR and DSC. This publication also discloses a process for its preparation.

Polymorphism is the occurrence of different crystalline forms of a single compound and it is a property of some compounds and complexes. Thus, polymorphs are distinct solids sharing the same molecular formula, yet each polymorph may have distinct physical properties. Therefore, a single compound may give rise to a variety of polymorphic forms where each form has different and distinct physical properties, such as different solubility profiles, different melting point temperatures and/or different x-ray diffraction peaks. Since the solubility of each polymorph may vary, identifying the existence of pharmaceutical polymorphs is essential for providing pharmaceuticals with predictable solubility profiles. It is desirable to investigate all solid state forms of a drug, including all polymorphic forms and

solvates, and to determine the stability, dissolution and flow properties of each polymorphic form.

Polymorphic forms and solvates of a compound can be distinguished in a laboratory by X-ray diffraction spectroscopy and by other methods such as, infrared spectrometry. Additionally, polymorphic forms and solvates of the same drug substance or active pharmaceutical ingredient, can be administered by itself or formulated as a drug product (also known as the final or finished dosage form), and are well known in the pharmaceutical art to affect, for example, the solubility, stability, flowability, tractability and compressibility of drug substances and the safety and efficacy of drug products.

The discovery of new polymorphic forms and solvates of a pharmaceutically useful compound, like sitagliptin, may provide a new opportunity to improve the performance characteristics of a pharmaceutical product. It also adds to the material that a formulation scientist has available for designing, for example, a pharmaceutical dosage form of a drug with a targeted release profile or other desired characteristic. New polymorphic forms of the sitagliptin hydrochloride have now been discovered and have been designated as sitagliptin hydrochloride Form-L1, Form-L2, Form-L3, Form-L4, Form-L5, Form-L6, Form-L7, Form-L8, Form-L9, Form-L10, Form-L11, Form-L12, Form-L13, Form-L14 and Form-L15.

SUMMARY OF THE INVENTION:

The present invention provides novel polymorphic forms of sitagliptin hydrochloride, processes for their preparation and pharmaceutical compositions comprising one or more of the novel polymorphic forms of sitagliptin hydrochloride.

The present invention further provides a pharmaceutical composition comprising novel polymorphic forms of sitagliptin hydrochloride prepared by the processes of the present invention and at least one pharmaceutically acceptable excipient.

BRIEF DESCRIPTION OF THE DRAWINGS:

The accompanying drawings, which are incorporated in and constitute a part of this specification, illustrate several embodiments of the invention and together with the description, serve to explain the principles of the invention.

Figure 1 is the characteristic powder X-ray diffraction (XRD) pattern of sitagliptin hydrochloride Form-L1.

Figure 2 is the characteristic powder X-ray diffraction (XRD) pattern of sitagliptin hydrochloride Form-L2.

Figure 3 is the characteristic powder X-ray diffraction (XRD) pattern of sitagliptin hydrochloride Form-L3.

Figure 4 is the characteristic powder X-ray diffraction (XRD) pattern of sitagliptin hydrochloride Form-L4.

Figure 5 is the characteristic powder X-ray diffraction (XRD) pattern of sitagliptin hydrochloride Form-L5.

Figure 6 is the characteristic powder X-ray diffraction (XRD) pattern of sitagliptin hydrochloride Form-L6.

Figure 7 is the characteristic powder X-ray diffraction (XRD) pattern of sitagliptin hydrochloride Form-L7.

Figure 8 is the characteristic powder X-ray diffraction (XRD) pattern of sitagliptin hydrochloride Form-L8.

Figure 9 is the characteristic powder X-ray diffraction (XRD) pattern of sitagliptin hydrochloride Form-L9.

Figure 10 is the characteristic differential scanning calorimetric (DSC) thermogram of sitagliptin hydrochloride Form-L9.

Figure 11 is the characteristic thermo gravimetric analysis (TGA) of sitagliptin hydrochloride Form-L9.

Figure 12 is the characteristic powder X-ray diffraction (XRD) pattern of sitagliptin hydrochloride Form-L10.

Figure 13 is the characteristic powder X-ray diffraction (XRD) pattern of sitagliptin hydrochloride Form-L11.

Figure 14 is the characteristic powder X-ray diffraction (XRD) pattern of sitagliptin hydrochloride Form-L12.

Figure 15 is the characteristic powder X-ray diffraction (XRD) pattern of sitagliptin hydrochloride Form-L13.

Figure 16 is the characteristic powder X-ray diffraction (XRD) pattern of sitagliptin hydrochloride Form-L14.

Figure 17 is the characteristic powder X-ray diffraction (XRD) pattern of sitagliptin hydrochloride Form-L15.

DETAILED DESCRIPTION OF THE INVENTION:

The present invention provides novel polymorphic forms of sitagliptin hydrochloride, processes for their preparation and pharmaceutical compositions comprising one or more of such polymorphic forms.

The polymorphic forms of sitagliptin hydrochloride of the present invention have advantageous properties selected from at least one of: chemical purity, flowability, solubility, morphology or crystal habit, stability - such as storage stability, stability to dehydration, stability to polymorphic conversion, low hygroscopicity, and low content of residual solvents.

The term "solvate," as used herein and unless indicated otherwise, refers to a crystal form that incorporates a solvent in the crystal structure. When the solvent is water, the solvate is often referred to as a "hydrate." The solvent in a solvate may be present in either a stoichiometric or in a non-stoichiometric amount.

The polymorphic forms of sitagliptin hydrochloride of the present invention are characterized by one or more analytical methods such as X-ray Powder Diffraction (XRPD) Patterns, Differential Scanning Calorimetry (DSC) and Thermo Gravimetric Analysis (TGA).

The X-Ray powder diffraction can be measured by an X-ray powder Diffractometer equipped with a Cu-anode ([λ] = 1.54 Angstrom), X-ray source operated at 30kV, 10 mA and a Ni filter is used to strip K-beta radiation. Two-theta calibration is performed using a Bruker Corundum plate standard (A26-B26-S). The sample was analyzed using the following instrument parameters: measuring range = 3-40°2θ; step width = 0.012°; and scan speed = 1.45°/minute.

All DSC data reported herein were analyzed in hermitically sealed aluminium pan, with a blank hermitically sealed aluminium pan as the reference and were obtained using DSC (DSC Q200, TA instrumentation, Waters) at a scan rate of 10°C per minute with an Indium standard.

All TGA data reported herein were analyzed using TGA Q500 V 20.2 build 27 in platinum pan with a temperature rise of about 10°C/min in the range of about 30°C to about 250°C.

In one embodiment, the present invention provides novel polymorphic forms of sitagliptin hydrochloride; which are designated as sitagliptin hydrochloride Form-L1, sitagliptin hydrochloride Form-L2, sitagliptin hydrochloride Form-L3, sitagliptin hydrochloride Form-L4, sitagliptin hydrochloride Form-L5, sitagliptin hydrochloride Form-L6, sitagliptin hydrochloride Form-L7, sitagliptin hydrochloride Form-L8, sitagliptin hydrochloride Form-L9, sitagliptin hydrochloride Form-L10, sitagliptin hydrochloride Form-L11, sitagliptin hydrochloride Form-L12, sitagliptin hydrochloride Form-L13, sitagliptin hydrochloride Form-L14 and sitagliptin hydrochloride Form-L15.

In another embodiment, the present invention provides sitagliptin hydrochloride Form-L1.

In another embodiment, the sitagliptin hydrochloride Form-L1 of the present invention is an acetonitrile solvate.

In another embodiment, the present invention provides sitagliptin hydrochloride Form-L1 characterized by a powder X-Ray diffraction pattern substantially in accordance with Figure 1.

In another embodiment, the present invention provides sitagliptin hydrochloride Form-L1 characterized by a powder X-Ray diffraction pattern having one or more peaks at about 6.60, 8.50, 8.71, 9.71, 12.22, 15.54, 16.56, 17.13, 18.09, 18.77, 19.24, 20.67, 21.67, 22.89, 23.68, 24.32, 24.66, 25.80, 27.47, 27.71, 28.05, 31.43, 32.70 and 35.81 ± 0.2° 2θ.

In another embodiment, the present invention provides a process for preparation of sitagliptin hydrochloride Form-L1, comprising:

a) slurrying sitagliptin hydrochloride in acetonitrile; and
b) isolating the sitagliptin hydrochloride Form-L1.

The slurrying of sitagliptin hydrochloride in acetonitrile can be done for the sufficient period of time, preferably for about 6 hours at suitable temperature, preferably at about room temperature to form sitagliptin hydrochloride Form-L1. Then the sitagliptin hydrochloride Form-L1 can be isolated by the methods known in the art, for example filtration.

In another embodiment, the present invention provides sitagliptin hydrochloride Form-L2.

In another embodiment, the sitagliptin hydrochloride Form-L2 of the present invention is an ethyl acetate solvate.

In another embodiment, the present invention provides sitagliptin hydrochloride Form-L2 characterized by a powder X-Ray diffraction pattern substantially in accordance with Figure 2.

In another embodiment, the present invention provides sitagliptin hydrochloride Form-L2 characterized by a powder X-Ray diffraction pattern having one or more peaks at about 5.92, 7.14, 9.52, 10.17, 11.93, 14.39, 14.78, 15.15, 16.97, 17.98, 18.68, 19.17, 20.40, 22.07, 23.16, 24.10, 24.33, 26.48, 29.15 and 29.60 ± 0.2° 2θ.

In another embodiment, the present invention provides a process for preparation of sitagliptin hydrochloride Form-L2, comprising:

a) slurrying sitagliptin hydrochloride in ethyl acetate, and
b) isolating the sitagliptin hydrochloride Form-L2.

The slurrying of sitagliptin hydrochloride, preferably any form of sitagliptin hydrochloride, more preferably amorphous form of sitagliptin hydrochloride in ethyl acetate may be carried out at a suitable temperature ranging from about 20°C to about 60°C, preferably at about 25°C to about 35°C for a sufficient period of time, preferably for about 24 hrs to form sitagliptin hydrochloride Form-L2. Then the sitagliptin hydrochloride Form-L2 can be isolated by methods known in the art, for example filtration.

In another embodiment, the present invention provides sitagliptin hydrochloride Form-L3.

In another embodiment, the present invention provides sitagliptin hydrochloride Form-L3 characterized by a powder X-Ray diffraction pattern substantially in accordance with Figure 3.

In another embodiment, the present invention provides sitagliptin hydrochloride Form-L3 characterized by a powder X-Ray diffraction pattern having one or more peaks at about 6.03, 6.19, 8.11, 13.73, 15.91, 17.90, 18.44, 19.63, 20.38, 22.58, 23.45, 25.47, 26.89, 31.04 and 32.05 ± 0.2° 2θ.

In another embodiment, the present invention provides a process for preparation of sitagliptin hydrochloride Form-L3, comprising:

a) providing a solution of sitagliptin in 1,4-dioxane,
b) adding hydrochloric acid to the step a) solution, and
c) isolating the sitagliptin hydrochloride Form-L3.

Sitagliptin hydrochloride Form-L3 can be obtained by adding hydrochloric acid to the solution of sitagliptin in 1,4-dioxane at a suitable temperature, preferably at about room temperature to reflux, more preferably at about 25°C to about 35°C, followed by stirring the reaction mass for a sufficient period of time to precipitate, preferably about one hour, and then isolating the sitagliptin hydrochloride Form-L3 by methods known in the art, for example filtration.

In another embodiment, the present invention provides sitagliptin hydrochloride Form-L4.

In another embodiment, the sitagliptin hydrochloride Form-L4 of the present invention is an ethanol solvate.

In another embodiment, the present invention provides sitagliptin hydrochloride Form-L4 characterized by a powder X-Ray diffraction pattern substantially in accordance with Figure 4.

In another embodiment, the present invention provides sitagliptin hydrochloride Form-L4 characterized by a powder X-Ray diffraction pattern having one or more peaks at about 5.71,

6.29, 6.52, 8.00, 10.67, 12.60, 13.16, 13.73, 15.90, 17.85, 18.25, 18.73, 18.94, 19.80, 22.50, 25.35, 26.61 and 30.57 ± 0.2° 2θ.

In another embodiment, the present invention provides a process for preparation of sitagliptin hydrochloride Form-L4, comprising:

a) providing a solution of sitagliptin hydrochloride in ethanol,
b) combining the step a) solution and a suitable hydrocarbon solvent, and
c) isolating the sitagliptin hydrochloride Form-L4.

Providing a solution of sitagliptin hydrochloride in ethanol includes, dissolving sitagliptin hydrochloride in ethanol at a suitable temperature. The suitable temperature includes at about 25°C to about reflux, preferably at about 25°C to about 35°C. Then, combining the step a) solution and a suitable hydrocarbon solvent at a temperature of about 25°C to about 45°C followed by stirring the reaction mass for sufficient period of time, preferably for about 2 to 3 hrs to precipitating out the sitagliptin hydrochloride Form-L4. The suitable hydrocarbon solvent includes, but is not limited to hexane, heptane, cyclohexane and the like and mixtures thereof; preferably heptane. The precipitated sitagliptin hydrochloride Form-L4 can be isolated by conventional techniques known in the art, for example filtration.

In another embodiment, the present invention provides sitagliptin hydrochloride Form-L5.

In another embodiment, the sitagliptin hydrochloride Form-L5 of the present invention is a methyl acetate solvate.

In another embodiment, the present invention provides sitagliptin hydrochloride Form-L5 characterized by a powder X-Ray diffraction pattern substantially in accordance with Figure 5.

In another embodiment, the present invention provides sitagliptin hydrochloride Form-L5 characterized by a powder X-Ray diffraction pattern having one or more peaks at about 5.71, 6.61, 7.67, 13.32, 14.68, 15.49, 15.49, 16.30, 17.64, 18.43, 19.44, 20.12, 20.74, 21.45, 23.32, 22.91, 23.45, 23.94, 24.72, 26.71, 27.99, 28.64, 29.96 and 31.95 ± 0.2° 2θ.

In another embodiment, the present invention provides a process for preparation of sitagliptin hydrochloride Form-L5, comprising:

a) providing a solution of sitagliptin hydrochloride in dimethylacetamide,
b) combining the step a) solution and methyl acetate, and
c) isolating the sitagliptin hydrochloride Form-L5.

Providing a solution of sitagliptin hydrochloride in dimethylacetamide includes, first heating to about 25°C to about reflux temperature, preferably at about 50°C to about 70°C. Then combining the step a) solution and methyl acetate at about 25°C to about 45°C, preferably methyl acetate is added in to step a) solution, followed by stirring the reaction mass for

sufficient period of time, preferably for about 30 minutes to about 3 hrs. Sitagliptin hydrochloride Form-L5 can be isolated by conventional techniques known in the art, for example filtration.

In another embodiment, the present invention provides sitagliptin hydrochloride Form-L6.

In another embodiment, the sitagliptin hydrochloride Form-L6 of the present invention is a formic acid solvate.

In another embodiment, the present invention provides sitagliptin hydrochloride Form-L6 characterized by a powder X-Ray diffraction pattern substantially in accordance with Figure 6.

In another embodiment, the present invention provides sitagliptin hydrochloride Form-L6 characterized by a powder X-Ray diffraction pattern having one or more peaks at about 6.08, 8.62, 9.65, 12.22, 16.32, 16.89, 17.38, 17.88, 18.50, 19.01, 20.46, 20.92, 21.38, 21.74, 22.20, 22.68, 23.44, 23.92, 24.32, 24.67, 25.48, 26.17, 27.32, 27.67, 27.95, 30.37, 30.99, 31.32, 31.90, 33.40, 35.77 ± 0.2° 2θ.

In another embodiment, the present invention provides a process for preparation of sitagliptin hydrochloride Form-L6, comprising:

a) providing a solution of sitagliptin hydrochloride in formic acid,
b) combining the step a) solution and tertiary butyl methyl ether, and
c) isolating the sitagliptin hydrochloride Form-L6.

Providing a solution of sitagliptin hydrochloride in formic acid includes dissolving sitagliptin hydrochloride in formic acid at a suitable temperature, preferably at about 25°C to about reflux; more preferably at about 25°C to about 35°C. Then, combining the step a) solution and tertiary butyl methyl ether at same temperature, preferably by adding tertiary butyl methyl ether to the step a) solution followed by stirring for a sufficient period of time, preferably for about 6 hrs to about 60 hrs at a temperature of about 25°C to about 45°C. Sitagliptin hydrochloride Form-L6 can be isolated by any conventional techniques known in the art, for example filtration.

In another embodiment, the present invention provides sitagliptin hydrochloride Form-L7.

In another embodiment, the sitagliptin hydrochloride Form-L7 of the present invention is a 1-butanol solvate.

In another embodiment, the present invention provides sitagliptin hydrochloride Form-L7 characterized by a powder X-Ray diffraction pattern substantially in accordance with Figure 7.

In another embodiment, the present invention provides sitagliptin hydrochloride Form-L7 characterized by a powder X-Ray diffraction pattern having one or more peaks at about 5.58, 6.10, 6.87, 8.01, 10.25, 12.23, 13.69, 16.05, 17.97, 18.40, 19.63, 20.22, 21.46, 22.55, 23.42, 25.24, 25.49, 26.13, 26.61 and 29.99 ± 0.2° 2θ.

In another embodiment, the present invention provides a process for preparation of sitagliptin hydrochloride Form-L7, comprising:

a) providing a solution of sitagliptin in 1-butanol,
b) adding hydrochloric acid to the step a) solution, and
c) isolating the sitagliptin hydrochloride Form-L7.

Providing a solution of sitagliptin in 1-butanol includes dissolving sitagliptin in 1-butanol at a suitable temperature, preferably at about 25°C to about reflux, more preferably at about 25°C to about 35°C. Then adding hydrochloric acid to the step a) solution and stirring for sufficient period of time, preferably for about 2 hrs at same temperature and then isolating the sitagliptin hydrochloride Form-L7 by methods known in the art, for example filtration.

In another embodiment, the present invention provides sitagliptin hydrochloride Form-L8.

In another embodiment, the present invention provides sitagliptin hydrochloride Form-L8 characterized by a powder X-Ray diffraction pattern substantially in accordance with Figure 8.

In another embodiment, the present invention provides sitagliptin hydrochloride Form-L8 characterized by a powder X-Ray diffraction pattern having one or more peaks at about 6.67, 7.71, 8.17, 13.88, 16.13, 16.81, 18.17, 18.75, 19.80, 20.46, 22.77, 23.61, 23.83, 24.32, 25.68 and 27.15 ± 0.2° 2θ.

In another embodiment, the present invention provides a process for preparation of sitagliptin hydrochloride Form-L8, comprising:

a) providing a solution of sitagliptin hydrochloride in dimethylformamide,
b) combining the step a) solution and aromatic hydrocarbon solvent, and
c) isolating the sitagliptin hydrochloride Form-L8.

Providing a solution of sitagliptin hydrochloride in dimethylformamide includes first heating to about 25°C to about reflux temperature, preferably at about 50°C to about 70°C. Then, adding aromatic hydrocarbon solvent to step a) solution to precipitate the sitagliptin hydrochloride Form-L8. The aromatic hydrocarbon solvent includes, but is not limited to toluene, xylene, benzene and the like and mixtures thereof; preferably benzene. Then the reaction mass may be stirred for sufficient period of time, preferably for about 2 hrs at a temperature of about 25°C to about 35°C and the sitagliptin hydrochloride Form-L8 can be isolated by any conventional techniques known in the art, for example filtration.

In another embodiment, the present invention provides sitagliptin hydrochloride Form-L9.

In another embodiment, the present invention provides sitagliptin hydrochloride Form-L9 characterized by a powder X-Ray diffraction pattern substantially in accordance with Figure 9.

In another embodiment, the present invention provides sitagliptin hydrochloride Form-L9 characterized by a powder X-Ray diffraction pattern having one or more peaks at about 7.51, 8.59, 11.32, 13.45, 14.79, 15.82, 16.21, 17.07, 17.32, 18.31, 19.74, 20.13, 20.68, 20.89, 21.97, 22.38, 22.83, 24.82, 25.48, 26.18, 27.06, 27.54, 29.41, 30.62, 32.04, 32.70, 33.10, 33.82 ± 0.2° 2θ.

In another embodiment, the present invention provides sitagliptin hydrochloride Form-L9 characterized by its differential scanning calorimetry (DSC) substantially in accordance with Figure 10.

In another embodiment, the present invention provides sitagliptin hydrochloride Form-L9 characterized by its differential scanning calorimetry (DSC) having endothermic at about 118.28°C and 172.04°C.

In another embodiment, the present invention provides sitagliptin hydrochloride Form-L9 characterized by its thermo gravimetric analysis (TGA) substantially in accordance with Figure 11.

In another embodiment, the present invention provides a process for preparation of sitagliptin hydrochloride Form-L9, comprising:

i) providing a solution of sitagliptin hydrochloride in dipolar aprotic solvent,
ii) combining the step i) solution and ester solvent,
iii) optionally seeding the reaction mass with sitagliptin hydrochloride Form-L9, and
iv) isolating the sitagliptin hydrochloride Form-L9.

The step i) of providing a solution of sitagliptin hydrochloride in dipolar aprotic solvent includes first heating to about 25°C to reflux temperature. Preferably the reaction mass heated to about 50°C to about 65°C to provide a solution. The suitable dipolar aprotic solvent used herein is selected from the group consisting of dimethylacetamide, dimethylformamide, dimethyl sulfoxide, N-methyl pyrrolidone and the like and mixtures thereof; preferably dimethylacetamide.

The step ii) of the forgoing process involves combining the solution of step i) with a suitable ester solvent. The step ii) may be carried out by either adding ester solvent to the solution of reaction step i) or adding step i) solution to an ester solvent at a suitable temperature ranging from about 10°C to about 65°C; preferably at about 25°C to about 35°C. The suitable ester solvent used herein is selected from the group consisting of ethyl acetate, methyl acetate,

n-propyl acetate, isopropyl acetate, n-butyl acetate, isobutyl acetate and the like and mixtures thereof; preferably n-butyl acetate.

The step iii) of the forgoing process optionally involves seeding the reaction mass with sitagliptin hydrochloride form-L9 to initiate the crystallization.

The step iv) of the forgoing process involves isolation of sitagliptin hydrochloride Form L9, which can be done by any conventional techniques known in the art, for example filtration. Typically, if stirring is involved, the temperature during stirring can range from about 0°C to about 35°C. The resultant product may optionally be further dried at suitable temperatures i.e., about 30°C to about 80°C.

In another embodiment, the present invention provides a process for preparation of sitagliptin hydrochloride Form-L9, comprise of slurrying sitagliptin hydrochloride in a suitable ester solvent at a temperature of about 25°C to about 45°C for a sufficient period of time, preferably for about 65 hrs to about 80 hrs to provide sitagliptin hydrochloride Form-L9. The suitable ester solvent is selected from the group consisting of ethyl acetate, methyl acetate, n-propyl acetate, isopropyl acetate, n-butyl acetate, isobutyl acetate and the like and mixtures thereof; preferably ethyl acetate.

In another embodiment, the present invention provides a process for preparation of sitagliptin hydrochloride Form-L9, comprise of storing sitagliptin hydrochloride Form-L8 of the present invention at a temperature of about 25°C to about 35°C under ambient conditions such as under packed condition (closed) for sufficient period of time to provide sitagliptin hydrochloride Form-L9.

In another embodiment, the present invention provides a process for the preparation of sitagliptin hydrochloride Form-L9, comprises

a) providing a solution of sitagliptin in a suitable dipolar aprotic solvent,
b) adding hydrochloric acid to the step a) solution,
c) adding suitable ester solvent to the solution of step b),
d) optionally seeding the reaction mass with sitagliptin hydrochloride Form-L9,
e) stirring the reaction mass for sufficient period of time, and
f) isolating the sitagliptin hydrochloride Form-L9.

The suitable dipolar aprotic solvent of step a) includes, but is not limited to dimethylacetamide, dimethylformamide, dimethyl sulfoxide, N-methyl pyrrolidone and the like and mixtures thereof; preferably dimethylacetamide.

The step a) of providing a solution of sitagliptin in a suitable dipolar aprotic solvent may be carried out at a temperature of about 25°C to about reflux, preferably at about 25°C to about 35°C. Then, adding hydrochloric acid to the solution of step a) and adding a suitable ester solvent to precipitating out the sitagliptin hydrochloride Form-L9. The suitable ester solvent

used herein include, but is not limited to ethyl acetate, methyl acetate, n-propyl acetate, isopropyl acetate, n-butyl acetate, isobutyl acetate and the like and mixtures thereof; preferably n-butyl acetate.

Optionally, sitagliptin hydrochloride Form-L9 seed crystals may be added to initiate the precipitation.

The isolation of sitagliptin hydrochloride Form L9 can be carried out by any conventional techniques known in the art, for example filtration. Typically, if stirring is involved, the temperature during stirring can range from about 0°C to about 35°C. The resultant product may optionally be further dried at suitable temperatures i.e. about 30°C to about 80°C; preferably at about 60°C.

In another embodiment, the present invention provides sitagliptin hydrochloride Form-L10.

In another embodiment, the present invention provides sitagliptin hydrochloride Form-L10 characterized by a powder X-Ray diffraction pattern substantially in accordance with Figure 12.

In another embodiment, the present invention provides sitagliptin hydrochloride Form-L10 characterized by a powder X-Ray diffraction pattern having one or more peaks at about 6.57, 7.60, 7.81, 9.52, 10.37, 12.31, 12.76, 13.22, 13.74, 16.04, 16.41, 16.66, 17.71, 18.07, 18.57, 19.31, 19.51, 20.03, 20.21, 20.41, 20.73, 21.64, 22.10, 22.64, 23.62, 24.40, 24.75, 24.97, 25.47, 25.55, 25.81, 26.57, 28.38, 28.96, 29.48, 30.61 and 32.59 ± 0.2° 2θ.

In another embodiment, the present invention provides a process for preparation of sitagliptin hydrochloride Form-L10, which comprises drying sitagliptin hydrochloride Form-L9 at a suitable temperature of about 70°C to about 100°C for sufficient period of time, preferably for about 4 hrs in hot air oven to provide sitagliptin hydrochloride Form-L10.

In another embodiment, the present invention provides sitagliptin hydrochloride Form-L11.

In another embodiment, the present invention provides sitagliptin hydrochloride Form-L11 characterized by a powder X-Ray diffraction pattern substantially in accordance with Figure 13.

In another embodiment, the present invention provides sitagliptin hydrochloride Form-L11 characterized by a powder X-Ray diffraction pattern having one or more peaks at about 6.21, 8.74, 9.76, 12.31, 16.59, 17.39, 17.92, 18.73, 19.26, 20.66, 21.73, 22.18, 22.86, 23.43, 24.56, 25.60, 26.16, 27.45, 27.88, 31.84, 33.35 and 35.81 ± 0.2° 2θ.

In another embodiment, the present invention provides a process for preparation of sitagliptin hydrochloride Form-L11, comprising;

a) providing a solution of sitagliptin in dimethylformamide,
b) adding hydrochloric acid to the step a) solution,
c) optionally evaporating the solvent from the solution of step b), and
d) isolating the sitagliptin hydrochloride Form-L11.

Providing a solution of sitagliptin in dimethylformamide includes, first heating to about 25°C to about reflux temperature, preferably at about 50°C to about 70°C. Then adding hydrochloric acid to the step a) solution and evaporating the solvent from the solution of step b) by the methods known in the art, preferably by keeping the step b) solution in an open vessel for sufficient period of time, preferably for about 10 hrs to 48 hrs at a suitable temperature ranging from about 25°C to about 35°C. Finally isolation of sitagliptin hydrochloride Form-L11 can be carried out by any conventional techniques known in the art, for example filtration.

In another embodiment, the present invention provides sitagliptin hydrochloride Form-L12.

In another embodiment, the present invention provides sitagliptin hydrochloride Form-L12 characterized by a powder X-Ray diffraction pattern substantially in accordance with Figure 14.

In another embodiment, the present invention provides sitagliptin hydrochloride Form-L12 characterized by a powder X-Ray diffraction pattern having one or more peaks at about 8.39, 8.71, 11.77, 12.30, 13.05, 14.98, 16.78, 17.28, 17.76, 18.74, 19.18, 20.89, 21.29, 22.55, 22.77, 23.88, 25.17, 26.15 and 26.73 ± 0.2° 2θ.

In another embodiment, the present invention provides a process for preparation of sitagliptin hydrochloride Form-L12, which comprises drying sitagliptin hydrochloride Form-L11 at a suitable temperature, preferably at about 50°C to about 60°C for sufficient period of time, preferably for about 4 hrs in hot air oven to provide sitagliptin hydrochloride Form-L12.

In another embodiment, the present invention provides sitagliptin hydrochloride Form-L13.

In another embodiment, the sitagliptin hydrochloride Form-L13 of the present invention is an isobutyl methyl ketone solvate.

In another embodiment, the present invention provides sitagliptin hydrochloride Form-L13 characterized by a powder X-Ray diffraction pattern substantially in accordance with Figure 15.

In another embodiment, the present invention provides sitagliptin hydrochloride Form-L13 characterized by a powder X-Ray diffraction pattern having one or more peaks at about 5.90, 6.45, 6.80, 8.06, 13.69, 15.86, 17.79, 18.39, 19.59, 20.30, 21.72, 22.51, 22.82, 23.47, 24.65, 25.25, 25.59, 26.49, 26.93 and 27.90 ± 0.2° 2θ.

In another embodiment, the present invention provides a process for preparation of sitagliptin hydrochloride Form-L13, comprising;

a) providing a solution of sitagliptin hydrochloride in dimethylacetamide,
b) combining the step a) solution and isobutyl methyl ketone at a suitable temperature, and
c) isolating the sitagliptin hydrochloride Form-L13.

Providing a solution of sitagliptin hydrochloride in dimethylacetamide includes first heating to about 25°C to about reflux temperature, preferably at about 50°C to about 70°C. Then the resultant solution may be combined with isobutyl methyl ketone to precipitating out the sitagliptin hydrochloride Form-L13, preferably isobutyl methyl ketone added in to a solution of step a). The reaction mass may be stirred for sufficient period of time, preferably for about 3 hrs and recovered the product. Sitagliptin hydrochloride Form-L13 can be recovered by any conventional techniques known in the art, for example filtration.

In another embodiment, the present invention provides sitagliptin hydrochloride Form-L14.

In another embodiment, the present invention provides sitagliptin hydrochloride Form-L14 characterized by a powder X-Ray diffraction pattern substantially in accordance with Figure 16.

In another embodiment, the present invention provides sitagliptin hydrochloride Form-L14 characterized by a powder X-Ray diffraction pattern having one or more peaks at about 6.08, 6.63, 8.24, 12.13, 12.85, 13.25, 13.66, 14.71, 15.44, 16.14, 17.00, 18.50, 19.33, 19.88, 20.36, 20.65, 21.59, 22.92, 24.25, 24.80, 26.23, 26.96, 27.21, 28.19, 29.59 and $31.56 \pm 0.2° 2\theta$.

In another embodiment, the present invention provides a process for preparation of sitagliptin hydrochloride Form-L14, comprising;

a) providing a solution of sitagliptin hydrochloride in acetone at a temperature of about 25°C to reflux,
b) cooling the reaction mass to 5°C, and
c) isolating the sitagliptin hydrochloride Form-L14.

Providing a solution of sitagliptin hydrochloride in acetone includes first heating to about 25°C to about reflux temperature. Preferably, the reaction mass heated to about 50°C to about reflux and then the resultant reaction solution may be cooled to about 5°C and maintained for sufficient period to time, preferably for overnight. The sitagliptin hydrochloride Form-L14 can be isolated by methods known in the art, for example filtration.

In another embodiment, the present invention provides sitagliptin hydrochloride Form-L15.

In another embodiment, the present invention provides sitagliptin hydrochloride Form-L15 characterized by a powder X-Ray diffraction pattern substantially in accordance with Figure 17.

In another embodiment, the present invention provides sitagliptin hydrochloride Form-L15 characterized by a powder X-Ray diffraction pattern having one or more peaks at about 5.35, 7.67, 8.98, 11.65, 13.13, 14.70, 15.45, 16.22, 16.81, 17.89, 18.07, 19.11, 19.95, 20.90, 21.72, 22.31, 23.05, 23.84, 25.66, 25.90, 26.91, 27.53 and 27.96 ± 0.2° 2θ.

In another embodiment, the present invention provides a process for preparation of sitagliptin hydrochloride Form-L15, comprising;

a) providing a solution of sitagliptin hydrochloride in dimethylacetamide,
b) combining the step a) solution and butyl acetate at a suitable temperature, and
c) isolating the sitagliptin hydrochloride Form-L15.

Providing a solution of sitagliptin hydrochloride in dimethylacetamide includes first heating to about 25°C to about reflux temperature, preferably at about 50°C to about 70°C and then adding butyl acetate to the above reaction solution, stirring the solution for a sufficient period of time, preferably for 4 hrs at room temperature. Further the sitagliptin hydrochloride Form-L15 can be isolated by any conventional techniques known in the art, for example filtration.

As used herein above, sitagliptin or sitagliptin hydrochloride which is used as a starting material is known in the art and can be prepared by any known method. The starting sitagliptin or sitagliptin hydrochloride may be in any form such as crude obtained directly from the reaction mass, crystalline, amorphous or other form of sitagliptin or its hydrochloride salt, including various solvates and hydrates known in the art.

In another embodiment, the present invention provides novel polymorphic forms of sitagliptin hydrochloride, having a chemical purity of 96% or more as measured by HPLC, preferably 99% or more, more preferably 99.5% or more.

The novel polymorphs of sitagliptin hydrochloride and solvates thereof described above are stable under ambient conditions; further novel polymorphs of sitagliptin hydrochloride and solvates thereof described above having higher dissolution rate compared to known solid forms of sitagliptin and its salts.

Other embodiments of the invention include composition containing one or more polymorphic forms of sitagliptin hydrochloride described above, such as pharmaceutical dosage forms. Such pharmaceutical dosage forms may include one or more excipients, including, without limitation, binders, fillers, lubricants, emulsifiers, suspending agents, sweeteners, flavorings, preservatives, buffers, wetting agents, disintegrants, effervescent agents, and other conventional excipients and additives. The compositions of the invention can thus include any one or a combination of the following: a pharmaceutically acceptable carrier or excipient; other medicinal agent(s); pharmaceutical agent(s); adjuvants; buffers; preservatives; diluents; and various other pharmaceutical additives and agents known to those skilled in the art. These additional formulation additives and agents will often be biologically

inactive and can be administered to humans without causing deleterious side effects or interactions.

Sitagliptin hydrochloride Form L9 of the present invention is thermodynamically stable over the known crystalline forms of sitagliptin hydrochloride. This can be evidenced by making phase mixture (50% & 50%) of the sitagliptin hydrochloride Form L9 with other known crystalline forms of sitagliptin hydrochloride and slurried in ethyl acetate for 2-4 days. The resulting product was tested and observed that substantially pure sitagliptin hydrochloride Form L9 was formed. The thermodynamic stability of sitagliptin hydrochloride Form L9 of the present invention results are tabulated in Table I.

EXAMPLES:

The following non limiting examples illustrate specific embodiments of the present invention. They are not intended to be limiting the scope of the present invention in any way.

EXAMPLE 1: Preparation of sitagliptin hydrochloride Form-L1:

Acetonitrile (20 mL) was added to sitagliptin hydrochloride (1.5 g) and slurried for 6 hours at 30±5°C. The obtained solid was filtered to get sitagliptin hydrochloride Form-L1.
The XRPD is set forth in Figure-1

EXAMPLE 2: Preparation of sitagliptin hydrochloride Form-L2:

Ethyl acetate (3 mL) was added to amorphous sitagliptin hydrochloride (250 mg) and slurried for 24 hours at 30±5°C. The obtained solid was filtered to get sitagliptin hydrochloride Form-L2.
The XRPD is set forth in Figure-2

EXAMPLE 3: Preparation of sitagliptin hydrochloride Form-L3:

Sitagliptin (330 mg) was dissolved in 1,4-dioxane (3 mL) at 30±5°C. 12N hydrochloric acid (0.1 mL) was added to the reaction mass and stirred for an hour. The obtained solid was filtered to get sitagliptin hydrochloride Form-L3.
The XRPD is set forth in Figure-3

EXAMPLE 4: Preparation of sitagliptin hydrochloride Form-L4:

Sitagliptin hydrochloride (300 mg) was dissolved in ethanol (30 mL) at 30±5°C. Heptane (300 mL) was added to the reaction mass and stirred for about 2 hrs. The obtained solid was filtered to get sitagliptin hydrochloride Form-L4.
The XRPD is set forth in Figure-4

EXAMPLE 5: Preparation of sitagliptin hydrochloride Form-L5:

Sitagliptin hydrochloride (500 mg) was dissolved in dimethylacetamide (1.5 mL) at 60°C. Methyl acetate (60 ml) was added to the reaction mass. The reaction mass was then cooled to 30±5°C and stirred for another 2 hrs at the same temperature. The obtained solid was filtered to get sitagliptin hydrochloride Form-L5.
The XRPD is set forth in Figure-5

EXAMPLE 6: Preparation of sitagliptin hydrochloride Form-L6:

Sitagliptin hydrochloride (1 g) was dissolved in formic acid (4 mL) at 30±5°C. Tertiary butyl methyl ether (80 mL) was added to the reaction mass and stirred for about 48 hrs. The obtained solid was filtered to get sitagliptin hydrochloride Form-L6.
Purity by HPLC: 98.80%
MC: 5.715%;
DSC showing endothermic peak at 103.81°C;
The XRPD is set forth in Figure-6

EXAMPLE 7: Preparation of sitagliptin hydrochloride Form-L7:

Sitagliptin (2 g) was dissolved in 1-butanol (50 mL) at 30±5°C. 12N hydrochloric acid (0.6 mL) was added to the reaction mass and stirred for about 2 hrs. The obtained solid was filtered to get sitagliptin hydrochloride Form-L7.
The XRPD is set forth in Figure-7

EXAMPLE 8: Preparation of sitagliptin hydrochloride Form-L8:

Sitagliptin hydrochloride (1 g) was dissolved in dimethylformamide (2 mL) at 60°C. Benzene (40 mL) was added to the reaction mass and precipitated solid was stirred for about 2 hrs at 30±5°C. The obtained solid was filtered to get sitagliptin hydrochloride Form-L8.
The XRPD is set forth in Figure-8

EXAMPLE 9: Preparation of sitagliptin hydrochloride Form-L9:

Sitagliptin hydrochloride (2 g) in ethyl acetate (30 ml) was stirred for 3 days at 30±5°C. The obtained solid was filtered to get sitagliptin hydrochloride Form-L9.
The XRPD is set forth in Figure-9

EXAMPLE 10: Preparation of sitagliptin hydrochloride Form-L9:

Sitagliptin hydrochloride (10 g) was dissolved in dimethylacetamide (20 mL) at 60°C and the obtained solution was filtered. The reaction mass was allowed to cool to room temperature and stirred for 10 mins. Butyl acetate (250 ml) was added to the reaction mass at 30±5°C and

seeded with sitagliptin hydrochloride Form-L9 (1g). The reaction mass was stirred for about 5 hrs at 30±5°C. The solid obtained was filtered and dried at 60°C in hot air oven for 6 hrs to get sitagliptin hydrochloride Form-L9.
Purity by HPLC: 99.73%
Moisture content: 4.33%
The XRPD is set forth in Figure-9

EXAMPLE 11: Preparation of sitagliptin hydrochloride Form-L9:

Sitagliptin hydrochloride Form L8 was packed in to a vial and stored at 30±5°C for 9 days yielded sitagliptin hydrochloride Form-L9.
The XRPD is set forth in Figure-9

EXAMPLE 12: Preparation of sitagliptin hydrochloride Form-L9:

Sitagliptin (5 g) was dissolved in dimethylacetamide (10 mL) at 30±5°C. Concentrated hydrochloric acid (1.05 mol eq) was added to the reaction mass. n-butyl acetate (125 mL) was added to the reaction mass and seeded with sitagliptin hydrochloride Form-L9. Then the reaction mass was stirred for 6 hrs at 30±5°C. The solid obtained was filtered and dried to get sitagliptin hydrochloride Form-L9.
The XRPD is set forth in Figure-9

EXAMPLE 13: Preparation of sitagliptin hydrochloride Form-L10:

Sitagliptin hydrochloride Form-L9 was dried at about 90°C in hot air oven for 4 hrs to get sitagliptin hydrochloride Form-L10.
The XRPD is set forth in Figure-12

EXAMPLE 14: Preparation of sitagliptin hydrochloride Form-L11:

Sitagliptin (333 mg) was dissolved in dimethylformamide (0.6 mL) at 60°C. 12N hydrochloric acid (0.1 mL) was added to the reaction mass. The reaction mass was allowed to cool to 30±5°C and the solution was left in an open vessel for a couple of days to recrystallize. The obtained solid was filtered to get sitagliptin hydrochloride Form-L11.
The XRPD is set forth in Figure-13

EXAMPLE 15: Preparation of sitagliptin hydrochloride Form-L12:

Sitagliptin hydrochloride Form-L11 was dried at 60°C in hot air oven for 4 hrs to get sitagliptin hydrochloride Form-L12.
The XRPD is set forth in Figure-14

EXAMPLE 16: Preparation of sitagliptin hydrochloride Form-L13:

Sitagliptin hydrochloride (500 mg) was dissolved in dimethylacetamide (1 mL) at 60°C. Isobutyl methyl ketone (20 mL) was added to the reaction mass and was allowed to cool to 30±5°C. The precipitated solid was stirred for 3 hrs and filtered to get sitagliptin hydrochloride Form-L13.
The XRPD is set forth in Figure-15

EXAMPLE 17: Preparation of sitagliptin hydrochloride Form-L14:

Sitagliptin hydrochloride (100 mg) was dissolved in acetone (1 mL) at 60°C. The reaction mass was allowed to cool to 0-5°C and maintained overnight at the same temperature. The obtained solid was filtered to get sitagliptin hydrochloride Form-L14.
The XRPD is set forth in Figure-16

EXAMPLE 18: Preparation of sitagliptin hydrochloride Form-L15:

Sitagliptin hydrochloride (1 g) was dissolved in dimethylacetamide (2 mL) at 60°C. Butyl acetate (15 mL) was added to the above reaction mass and was allowed to cool to 30±5°C. The precipitated solid was stirred for 4 hrs and filtered to get sitagliptin hydrochloride Form-L15.
The XRPD is set forth in Figure-17

Example-19: Thermodynamic stability of sitagliptin hydrochloride Form-L9:

Phase mixture of sitagliptin hydrochloride Form-L9 with crystalline sitagliptin hydrochloride reported in literature such as WO 2005/072530, WO 20120147092 and form IV of US 20130158265 was prepared in 50:50 ratios and subjected to slurrying in presence of ethyl acetate shows that the sitagliptin hydrochloride Form-L9 of the present invention is thermodynamically stable over these reported forms. The results are tabulated as follows:

Table-1:

Phase mixture (50 % & 50 %)	**solvent**	**Slurry time**	**Resulted form**
Form L9 & Crystalline form of WO 2005/072530	Ethyl acetate	2 days	Form L9
Form L9 & Crystalline form of WO 20120147092	Ethyl acetate	4 days	Form L9
Form L9 & Crystalline form-IV of US 20130158265	Ethyl acetate	4 days	Form L9

WE CLAIM

Claim 1: Sitagliptin hydrochloride Form-L9 characterized by a powder X-Ray diffraction pattern having one or more peaks at about 7.51, 8.59, 11.32, 13.45, 14.79, 15.82, 16.21, 17.07, 17.32, 18.31, 19.74, 20.13, 20.68, 20.89, 21.97, 22.38, 22.83, 24.82, 25.48, 26.18, 27.06, 27.54, 29.41, 30.62, 32.04, 32.70, 33.10, 33.82 ± 0.2° 2θ.

Claim 2: Sitagliptin hydrochloride Form-L9 of claim 1 is further characterized by a powder X-Ray diffraction pattern substantially in accordance with Figure 9.

Claim 3: Sitagliptin hydrochloride Form-L9 of claim 1 is further characterized by its differential scanning calorimetry (DSC) substantially in accordance with Figure 10.

Claim 4: A process for preparation of sitagliptin hydrochloride Form-L9, comprising:
i) providing a solution of sitagliptin hydrochloride in dipolar aprotic solvent,
ii) combining the step i) solution and ester solvent,
iii) optionally seeding the reaction mass with sitagliptin hydrochloride Form-L9, and
iv) isolating the sitagliptin hydrochloride Form-L9.

Claim 5: The process of claim 4, wherein the dipolar aprotic solvent is selected from the group consisting of dimethylacetamide, dimethylformamide, dimethylsulfoxide, N-methylpyrrolidone and mixtures thereof.

Claim 6: The process of claim 4, wherein the dipolar aprotic solvent is dimethyl acetamide.

Claim 7: The process of claim 4, wherein the suitable ester solvent is selected from the group consisting of ethyl acetate, methyl acetate, n-propyl acetate, isopropyl acetate, n-butyl acetate, isobutyl acetate and mixtures thereof.

Claim 8: The process of claim 4, wherein the suitable ester solvent is n-butyl acetate.

Claim 9: A process for preparation of sitagliptin hydrochloride Form-L9, comprise of slurrying sitagliptin hydrochloride in a suitable ester solvent at a temperature of about 25°C to about 45°C for a sufficient period of time to provide sitagliptin hydrochloride Form-L9, wherein the suitable ester solvent is selected from the group consisting of ethyl acetate, methyl acetate, n-propyl acetate, isopropyl acetate, n-butyl acetate, isobutyl acetate and mixtures thereof.

Claim 10: A process for preparation of sitagliptin hydrochloride Form-L9, comprise of storing sitagliptin hydrochloride Form-L8 at a temperature of about 25°C to about 35°C under ambient conditions such as under packed condition (closed) for sufficient period of time to provide sitagliptin hydrochloride Form-L9.

Claim 11: A process for the preparation of sitagliptin hydrochloride Form-L9, comprises
a) providing a solution of sitagliptin in a suitable dipolar aprotic solvent,
b) adding hydrochloric acid to the step a) solution,
c) adding suitable ester solvent to the solution of step b),
d) optionally seeding the reaction mass with sitagliptin hydrochloride Form-L9,
e) stirring the reaction mass for sufficient period of time, and
f) isolating the sitagliptin hydrochloride Form-L9.

Claim 12: The process of claim 11, wherein the dipolar aprotic solvent is selected from dimethylacetamide, dimethylformamide, dimethylsulfoxide, N-methylpyrrolidone and mixtures thereof; and the ester solvent is selected from ethyl acetate, methyl acetate, n-propyl acetate, isopropyl acetate, n-butyl acetate, isobutyl acetate and mixtures thereof.

Claim 13: Sitagliptin hydrochloride Form-L1 characterized by a powder X-Ray diffraction pattern having one or more peaks at about 6.60, 8.50, 8.71, 9.71, 12.22, 15.54, 16.56, 17.13, 18.09, 18.77, 19.24, 20.67, 21.67, 22.89, 23.68, 24.32, 24.66, 25.80, 27.47, 27.71, 28.05, 31.43, 32.70 and 35.81 ± 0.2° 2θ.

Claim 14: Sitagliptin hydrochloride Form-L1 of claim 13 is further characterized by a powder X-Ray diffraction pattern substantially in accordance with Figure 1.

Claim 15: A process for preparation of sitagliptin hydrochloride Form-L1, comprising:
a) slurrying sitagliptin hydrochloride in acetonitrile; and
b) isolating the sitagliptin hydrochloride Form-L1.

Claim 16: Sitagliptin hydrochloride Form-L2 characterized by a powder X-Ray diffraction pattern having one or more peaks at about 5.92, 7.14, 9.52, 10.17, 11.93, 14.39, 14.78, 15.15, 16.97, 17.98, 18.68, 19.17, 20.40, 22.07, 23.16, 24.10, 24.33, 26.48, 29.15 and 29.60 ± 0.2° 2θ.

Claim 17: Sitagliptin hydrochloride Form-L2 of claim 16 is further characterized by a powder X-Ray diffraction pattern substantially in accordance with Figure 2.

Claim 18: A process for preparation of sitagliptin hydrochloride Form-L2, comprising:
a) slurrying sitagliptin hydrochloride in ethyl acetate, and
b) isolating the sitagliptin hydrochloride Form-L2.

Claim 19: Sitagliptin hydrochloride Form-L3 characterized by a powder X-Ray diffraction pattern having one or more peaks at about 6.03, 6.19, 8.11, 13.73, 15.91, 17.90, 18.44, 19.63, 20.38, 22.58, 23.45, 25.47, 26.89, 31.04 and 32.05 ± 0.2° 2θ.

Claim 20: Sitagliptin hydrochloride Form-L3 of claim 19 is further characterized by a powder X-Ray diffraction pattern substantially in accordance with Figure 3.

Claim 21: A process for preparation of sitagliptin hydrochloride Form-L3, comprising:
a) providing a solution of sitagliptin in 1,4-dioxane,
b) adding hydrochloric acid to the step a) solution, and
c) isolating the sitagliptin hydrochloride Form-L3.

Claim 22: Sitagliptin hydrochloride Form-L4 characterized by a powder X-Ray diffraction pattern having one or more peaks at about 5.71, 6.29, 6.52, 8.00, 10.67, 12.60, 13.16, 13.73, 15.90, 17.85, 18.25, 18.73, 18.94, 19.80, 22.50, 25.35, 26.61 and 30.57 ± 0.2° 2θ.

Claim 23: Sitagliptin hydrochloride Form-L4 of claim 22 is further characterized by a powder X-Ray diffraction pattern substantially in accordance with Figure 4.

Claim 24: A process for preparation of sitagliptin hydrochloride Form-L4, comprising:
a) providing a solution of sitagliptin hydrochloride in ethanol,
b) combining the step a) solution and a suitable hydrocarbon solvent, and
c) isolating the sitagliptin hydrochloride Form-L4.

Claim 25: The process of claim 24, wherein the hydrocarbon solvent is selected from hexane, heptane and cyclohexane and mixtures thereof.

Claim 26: Sitagliptin hydrochloride Form-L5 characterized by a powder X-Ray diffraction pattern having one or more peaks at about 5.71, 6.61, 7.67, 13.32, 14.68, 15.49, 15.49, 16.30, 17.64, 18.43, 19.44, 20.12, 20.74, 21.45, 23.32, 22.91, 23.45, 23.94, 24.72, 26.71, 27.99, 28.64, 29.96 and 31.95 ± 0.2° 2θ.

Claim 27: Sitagliptin hydrochloride Form-L5 of claim 26 is further characterized by a powder X-Ray diffraction pattern substantially in accordance with Figure 5.

Claim 28: A process for preparation of sitagliptin hydrochloride Form-L5, comprising:
a) providing a solution of sitagliptin hydrochloride in dimethylacetamide,
b) combining the step a) solution and methyl acetate, and
c) isolating the sitagliptin hydrochloride Form-L5.

Claim 29: Sitagliptin hydrochloride Form-L6 characterized by a powder X-Ray diffraction pattern having one or more peaks at about 6.08, 8.62, 9.65, 12.22, 16.32, 16.89, 17.38, 17.88, 18.50, 19.01, 20.46, 20.92, 21.38, 21.74, 22.20, 22.68, 23.44, 23.92, 24.32, 24.67, 25.48, 26.17, 27.32, 27.67, 27.95, 30.37, 30.99, 31.32, 31.90, 33.40, 35.77 ± 0.2° 2θ.

Claim 30: Sitagliptin hydrochloride Form-L6 of claim 29 is further characterized by a powder X-Ray diffraction pattern substantially in accordance with Figure 6.

Claim 31: A process for preparation of sitagliptin hydrochloride Form-L6, comprising:
a) providing a solution of sitagliptin hydrochloride in formic acid,
b) combining the step a) solution and tertiary butyl methyl ether, and
c) isolating the sitagliptin hydrochloride Form-L6.

Claim 32: Sitagliptin hydrochloride Form-L7 characterized by a powder X-Ray diffraction pattern having one or more peaks at about 5.58, 6.10, 6.87, 8.01, 10.25, 12.23, 13.69, 16.05, 17.97, 18.40, 19.63, 20.22, 21.46, 22.55; 23.42, 25.24, 25.49, 26.13, 26.61 and 29.99 ± 0.2° 2θ.

Claim 33: Sitagliptin hydrochloride Form-L7 of claim 32 is further characterized by a powder X-Ray diffraction pattern substantially in accordance with Figure 7.

Claim 34: A process for preparation of sitagliptin hydrochloride Form-L7, comprising:
a) providing a solution of sitagliptin in 1-butanol,
b) adding hydrochloric acid to the step a) solution, and
c) isolating the sitagliptin hydrochloride Form-L7.

Claim 35: Sitagliptin hydrochloride Form-L8 characterized by a powder X-Ray diffraction pattern having one or more peaks at about 6.67, 7.71, 8.17, 13.88, 16.13, 16.81, 18.17, 18.75, 19.80, 20.46, 22.77, 23.61, 23.83, 24.32, 25.68 and 27.15 ± 0.2° 2θ.

Claim 36: Sitagliptin hydrochloride Form-L8 of claim 35 is further characterized by a powder X-Ray diffraction pattern substantially in accordance with Figure 8.

Claim 37: A process for preparation of sitagliptin hydrochloride Form-L8, comprising:
a) providing a solution of sitagliptin hydrochloride in dimethylformamide,
b) combining the step a) solution and aromatic hydrocarbon solvent, and
c) isolating the sitagliptin hydrochloride Form-L8.

Claim 38: The process of claim 37, wherein the aromatic hydrocarbon solvent is selected from toluene, xylene, benzene and mixtures thereof.

Claim 39: Sitagliptin hydrochloride Form-L10 characterized by a powder X-Ray diffraction pattern having one or more peaks at about 6.57, 7.60, 7.81, 9.52, 10.37, 12.31, 12.76, 13.22, 13.74, 16.04, 16.41, 16.66, 17.71, 18.07, 18.57, 19.31, 19.51, 20.03, 20.21, 20.41, 20.73, 21.64, 22.10, 22.64, 23.62, 24.40, 24.75, 24.97, 25.47, 25.55, 25.81, 26.57, 28.38, 28.96, 29.48, 30.61 and 32.59 ± 0.2° 2θ.

Claim 40: Sitagliptin hydrochloride Form-L10 of claim 39 is further characterized by a powder X-Ray diffraction pattern substantially in accordance with Figure 12.

Claim 41: A process for preparation of sitagliptin hydrochloride Form-L10, which comprises drying sitagliptin hydrochloride Form-L9 at a suitable temperature of about 70°C to about 100°C for sufficient period of time, in hot air oven to provide sitagliptin hydrochloride Form-L10.

Claim 42: Sitagliptin hydrochloride Form-L11 characterized by a powder X-Ray diffraction pattern having one or more peaks at about 6.21, 8.74, 9.76, 12.31, 16.59, 17.39, 17.92, 18.73, 19.26, 20.66, 21.73, 22.18, 22.86, 23.43, 24.56, 25.60, 26.16, 27.45, 27.88, 31.84, 33.35 and 35.81 ± 0.2° 2θ.

Claim 43: Sitagliptin hydrochloride Form-L11 of claim 42 is further characterized by a powder X-Ray diffraction pattern substantially in accordance with Figure 13.

Claim 44: A process for preparation of sitagliptin hydrochloride Form-L11, comprising;

a) providing a solution of sitagliptin in dimethylformamide,
b) adding hydrochloric acid to the step a) solution,
c) optionally evaporating the solvent from the solution of step b), and
d) isolating the sitagliptin hydrochloride Form-L11.

Claim 45: Sitagliptin hydrochloride Form-L12 characterized by a powder X-Ray diffraction pattern having one or more peaks at about 8.39, 8.71, 11.77, 12.30, 13.05, 14.98, 16.78, 17.28, 17.76, 18.74, 19.18, 20.89, 21.29, 22.55, 22.77, 23.88, 25.17, 26.15 and 26.73 ± 0.2° 2θ.

Claim 46: Sitagliptin hydrochloride Form-L12 of claim 45 is further characterized by its powder X-Ray diffraction pattern substantially in accordance with Figure 14.

Claim 47: A process for preparation of sitagliptin hydrochloride Form-L12, which comprises drying sitagliptin hydrochloride Form-L11 at a suitable temperature for sufficient period of time in hot air oven to provide sitagliptin hydrochloride Form-L12.

Claim 48: Sitagliptin hydrochloride Form-L13 characterized by a powder X-Ray diffraction pattern having one or more peaks at about 5.90, 6.45, 6.80, 8.06, 13.69, 15.86, 17.79, 18.39, 19.59, 20.30, 21.72, 22.51, 22.82, 23.47, 24.65, 25.25, 25.59, 26.49, 26.93 and 27.90 ± 0.2° 2θ.

Claim 49: Sitagliptin hydrochloride Form-L13 of claim 48 is further characterized by its powder X-Ray diffraction pattern substantially in accordance with Figure 15.

Claim 50: A process for preparation of sitagliptin hydrochloride Form-L13, comprising;

a) providing a solution of sitagliptin hydrochloride in dimethylacetamide,
b) combining the step a) solution and isobutyl methyl ketone at a suitable temperature, and
c) isolating the sitagliptin hydrochloride Form-L13.

Claim 51: Sitagliptin hydrochloride Form-L14 characterized by a powder X-Ray diffraction pattern having one or more peaks at about 6.08, 6.63, 8.24, 12.13, 12.85, 13.25, 13.66, 14.71, 15.44, 16.14, 17.00, 18.50, 19.33, 19.88, 20.36, 20.65, 21.59, 22.92, 24.25, 24.80, 26.23, 26.96, 27.21, 28.19, 29.59 and 31.56 ± 0.2° 2θ.

Claim 52: Sitagliptin hydrochloride Form-L14 of claim 51 is further characterized by its powder X-Ray diffraction pattern substantially in accordance with Figure 16.

Claim 53: A process for preparation of sitagliptin hydrochloride Form-L14, comprising;

a) providing a solution of sitagliptin hydrochloride in acetone at a temperature of about 25°C to reflux,
b) cooling the reaction mass to 5°C, and
c) isolating the sitagliptin hydrochloride Form-L14.

Claim 54: Sitagliptin hydrochloride Form-L15 characterized by a powder X-Ray diffraction pattern having one or more peaks at about 5.35, 7.67, 8.98, 11.65, 13.13, 14.70, 15.45, 16.22, 16.81, 17.89, 18.07, 19.11, 19.95, 20.90, 21.72, 22.31, 23.05, 23.84, 25.66, 25.90, 26.91, 27.53 and 27.96 ± 0.2° 2θ.

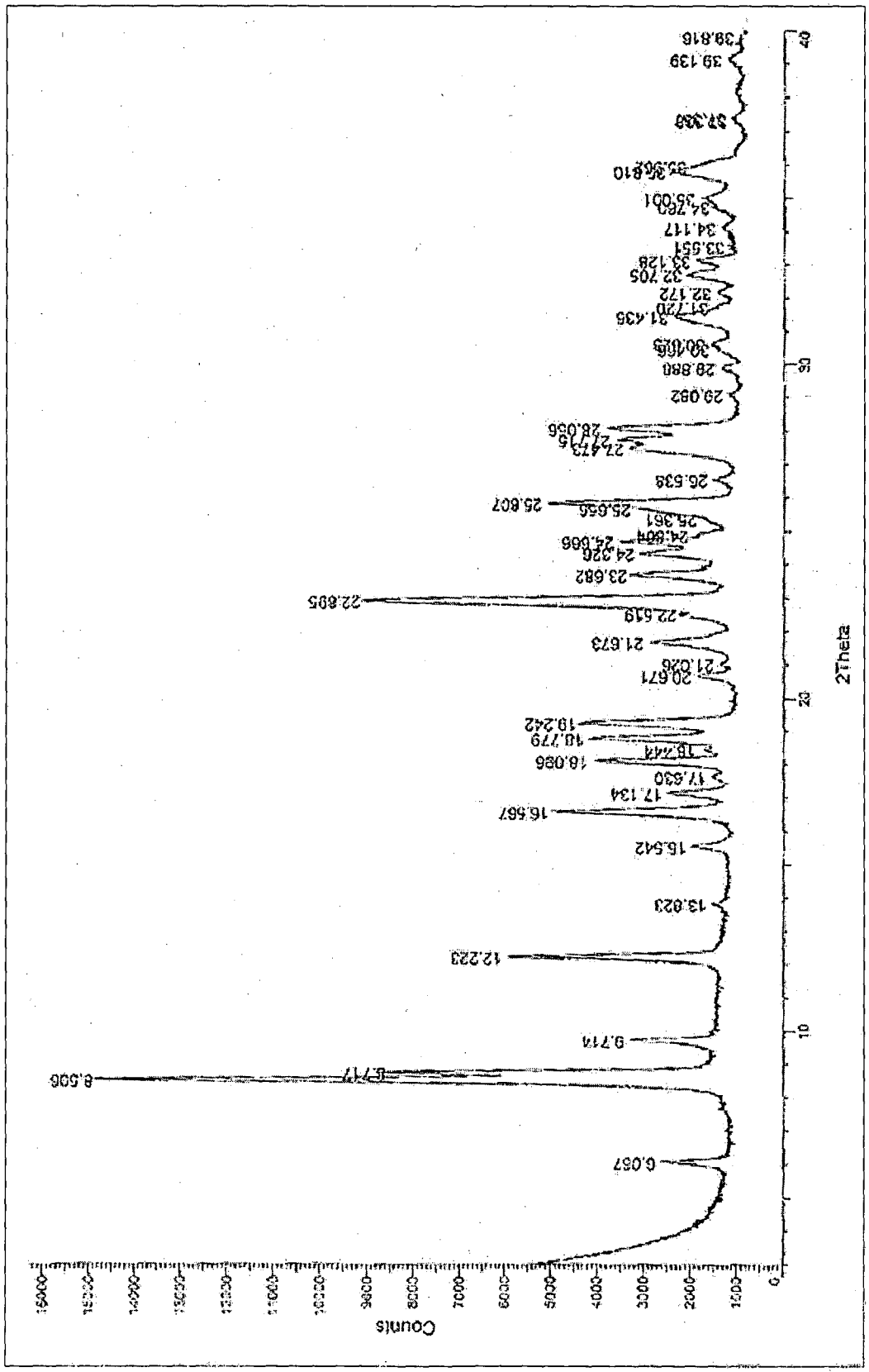
Claim 55: Sitagliptin hydrochloride Form-L15 of claim 54 is further characterized by its powder X-Ray diffraction pattern substantially in accordance with Figure 17.

Claim 56: A process for preparation of sitagliptin hydrochloride Form-L15, comprising;

a) providing a solution of sitagliptin hydrochloride in dimethylacetamide,
b) combining the step a) solution and butyl acetate at a suitable temperature, and
c) isolating the sitagliptin hydrochloride Form-L15.

Claim 57: A pharmaceutical composition comprising one or more polymorphic forms of sitagliptin hydrochloride according to claim 1 to 56, and at least one pharmaceutically acceptable excipient.

Figure 1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21.026
21.673
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Figure 2

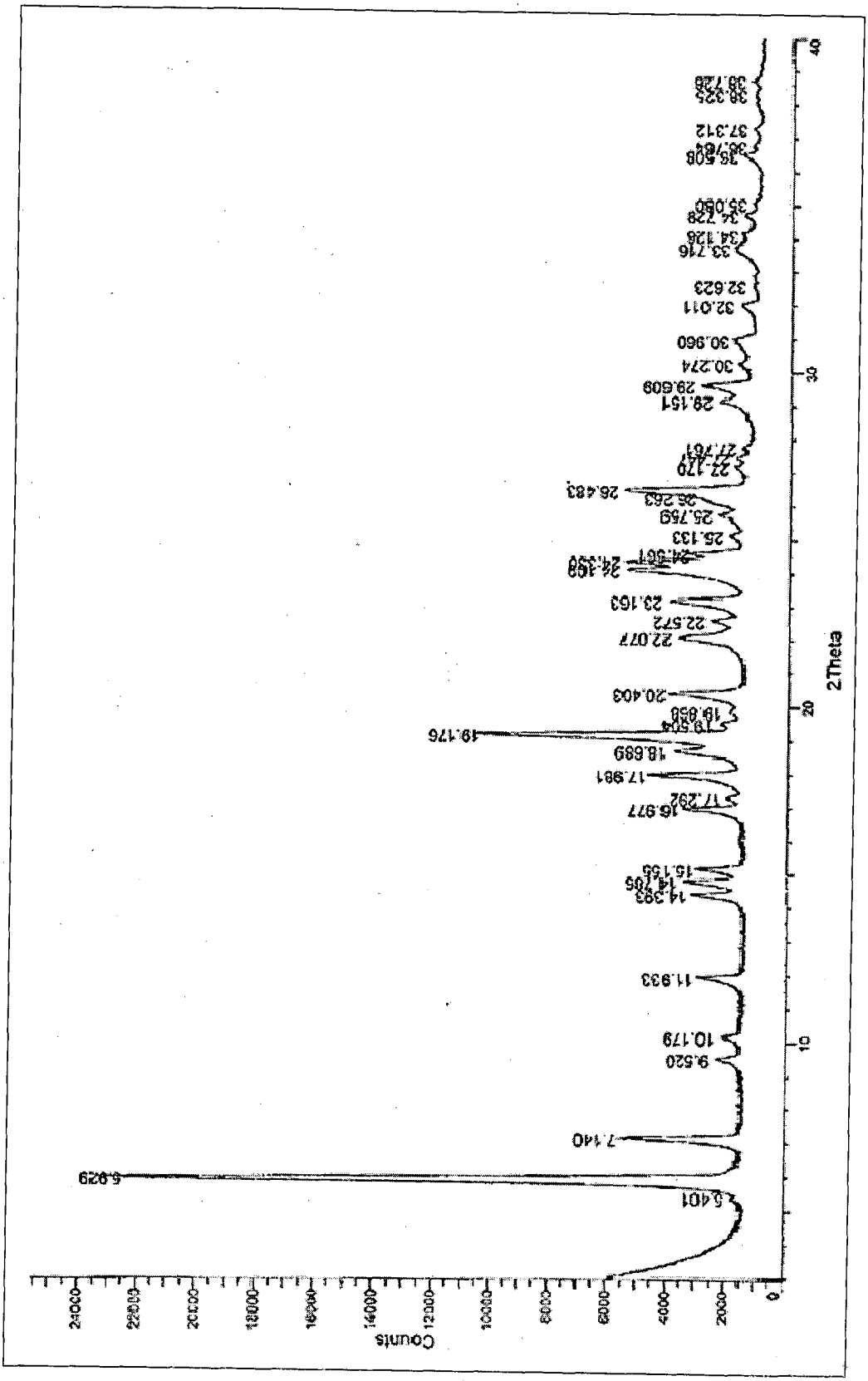
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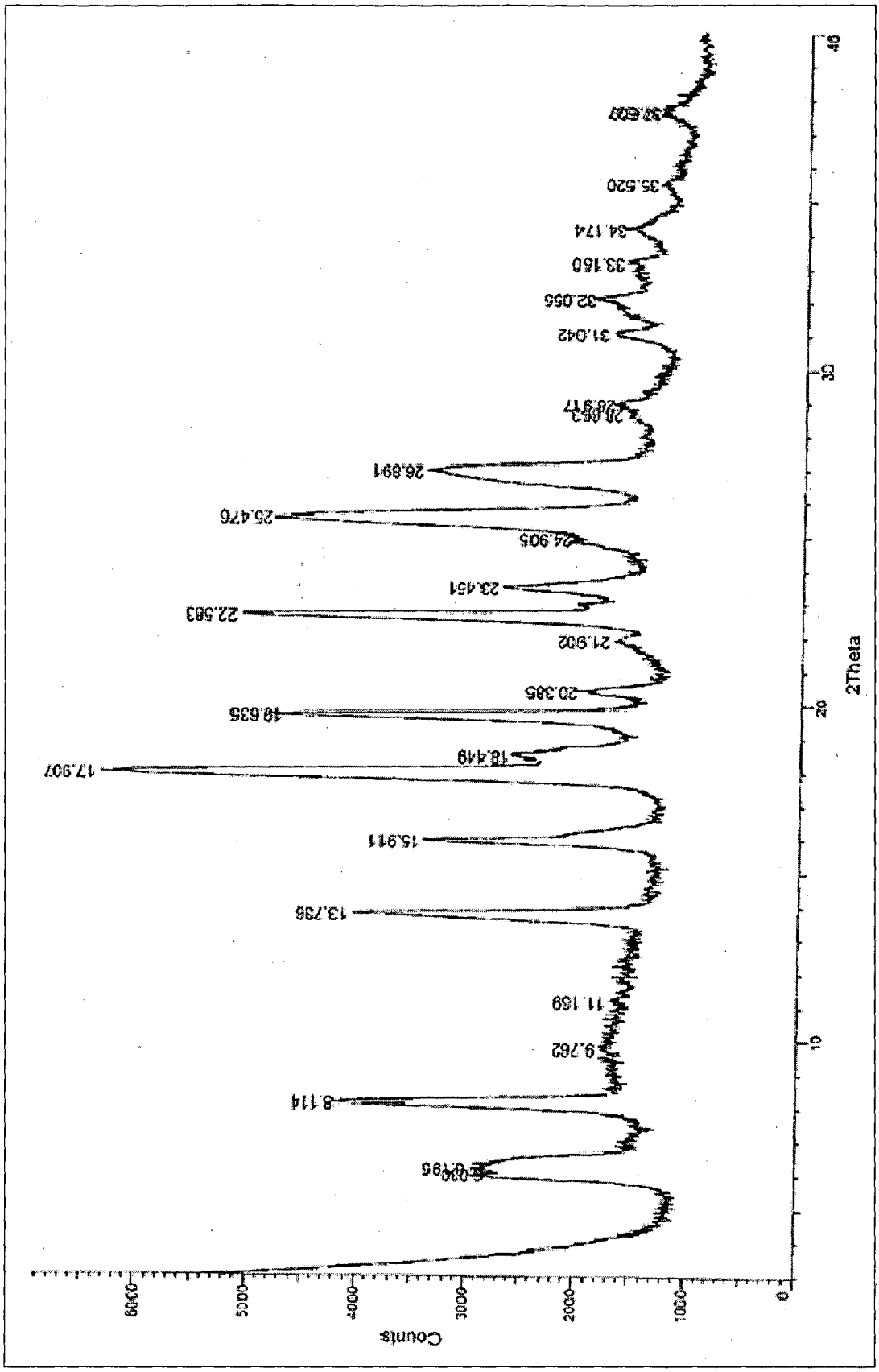
Figure 3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8.114
6.095

Figure 4

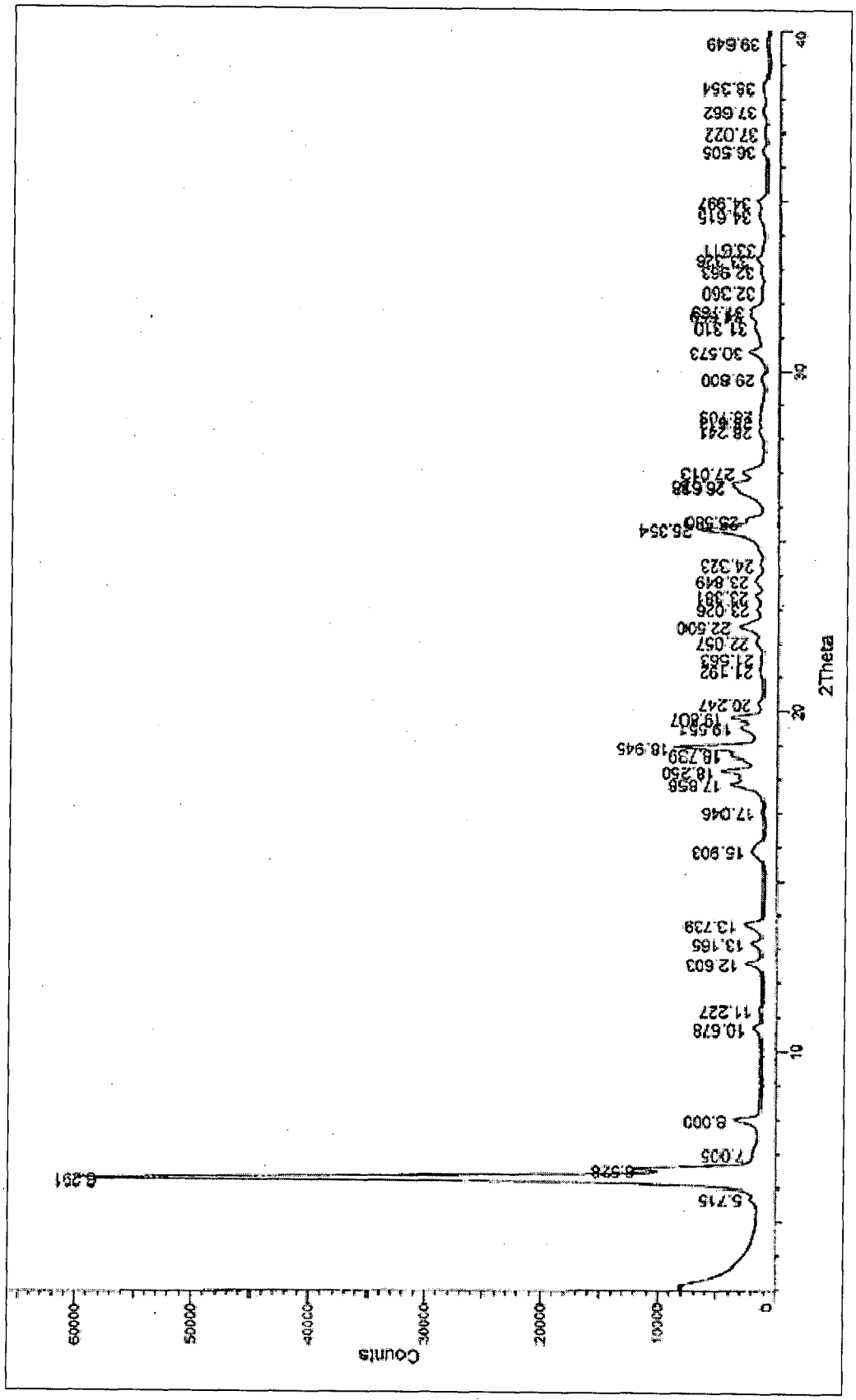
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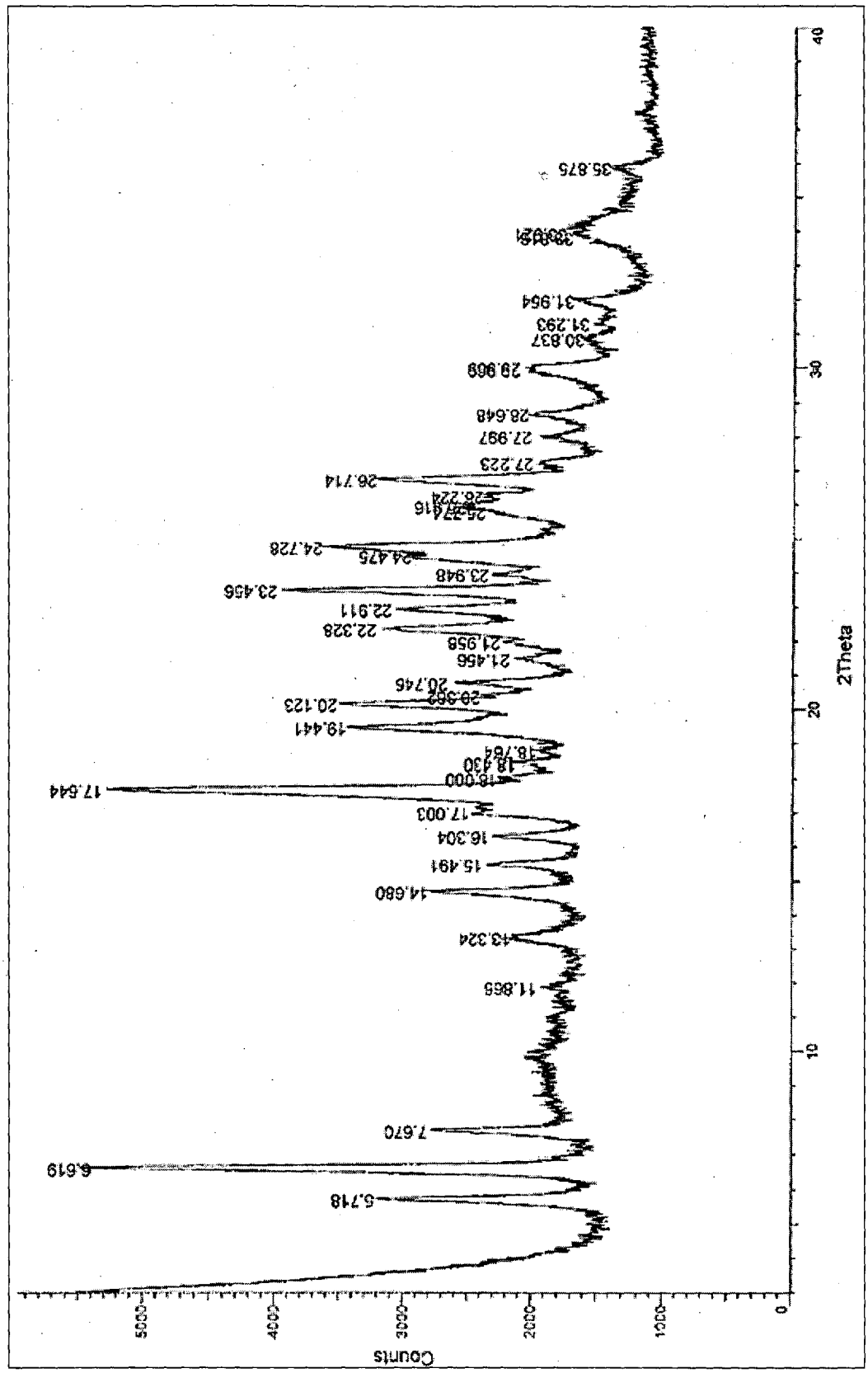
Figure 5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23.948
24.475
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Figure 6

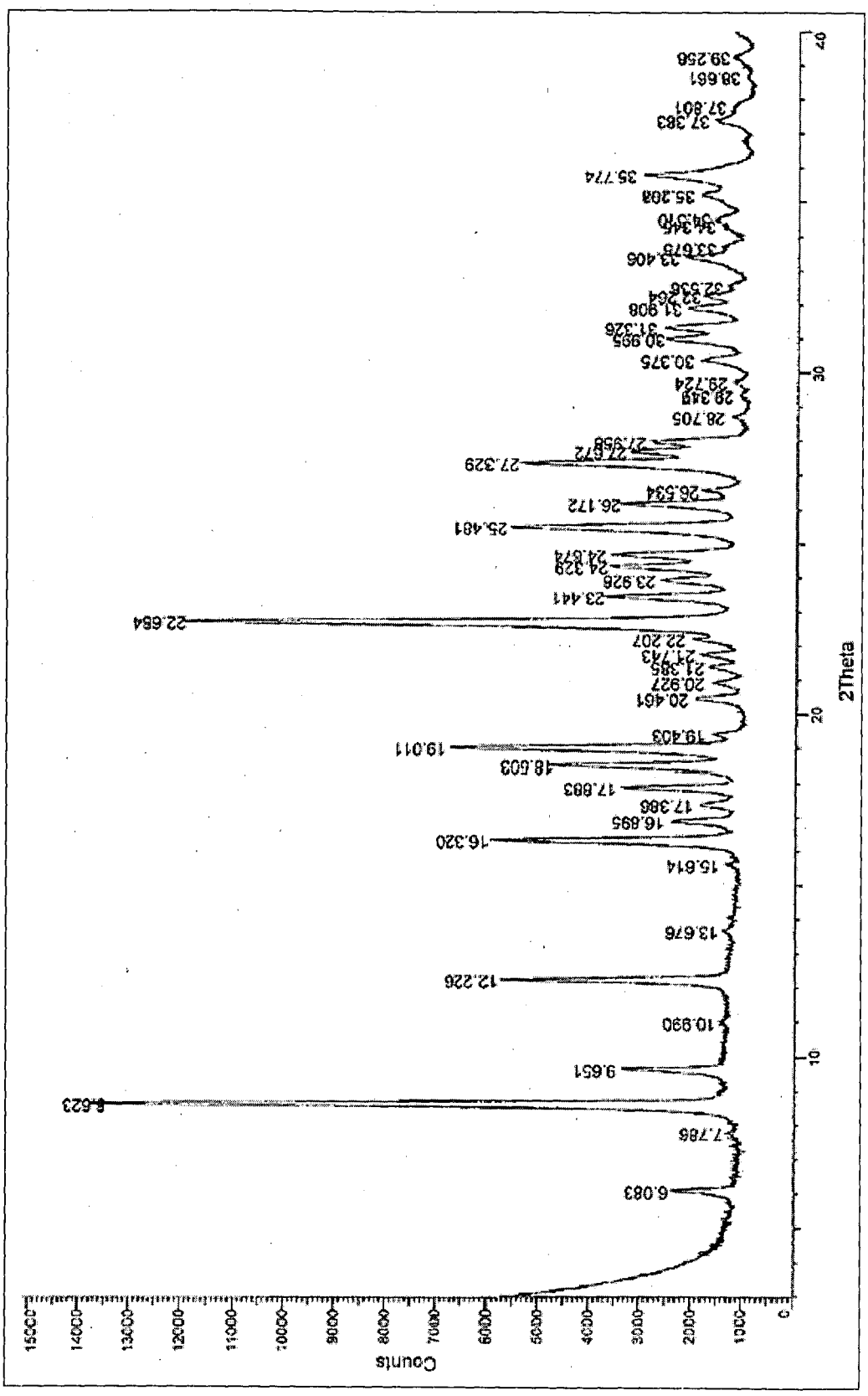
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Figure 7

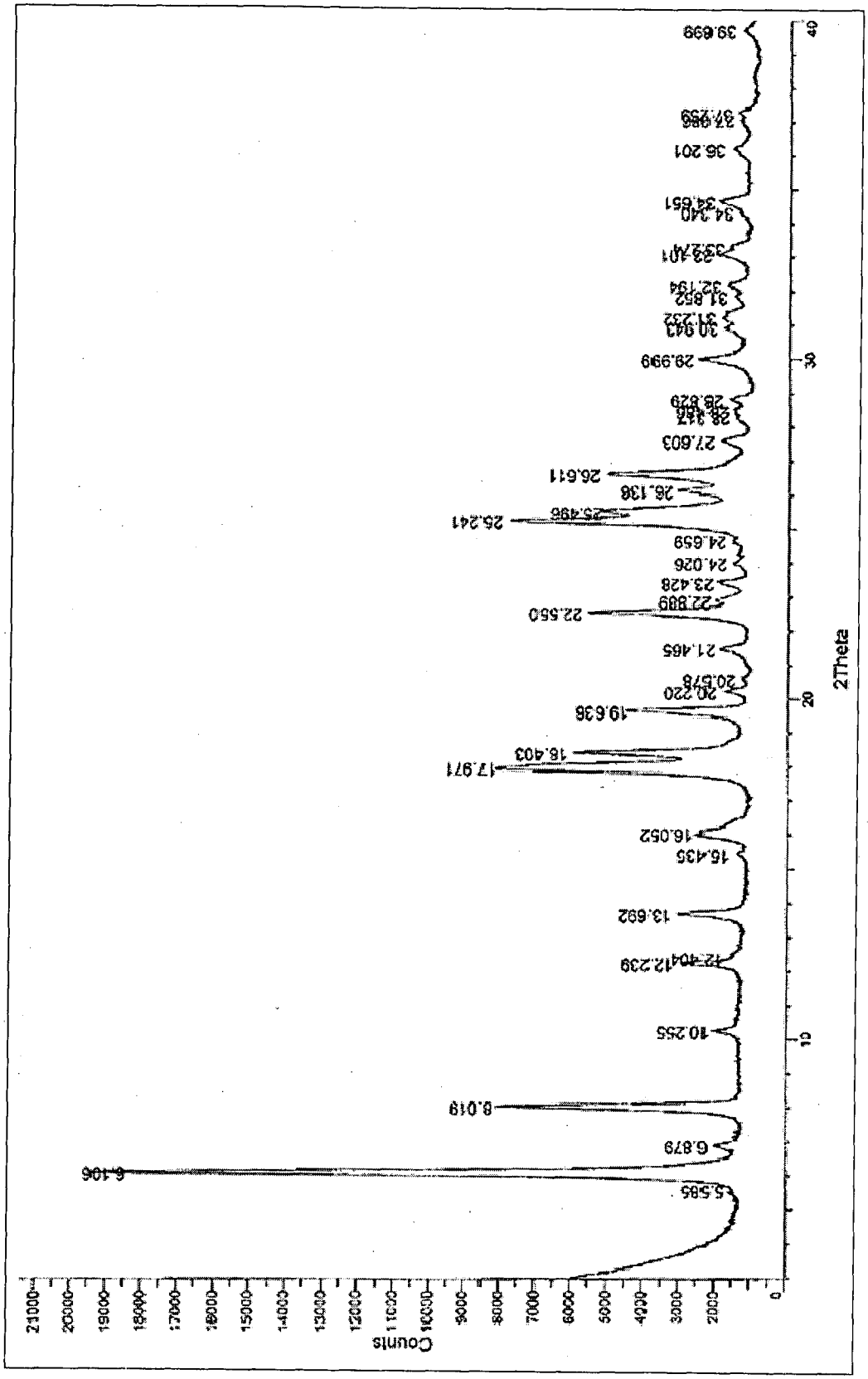
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Figure 8

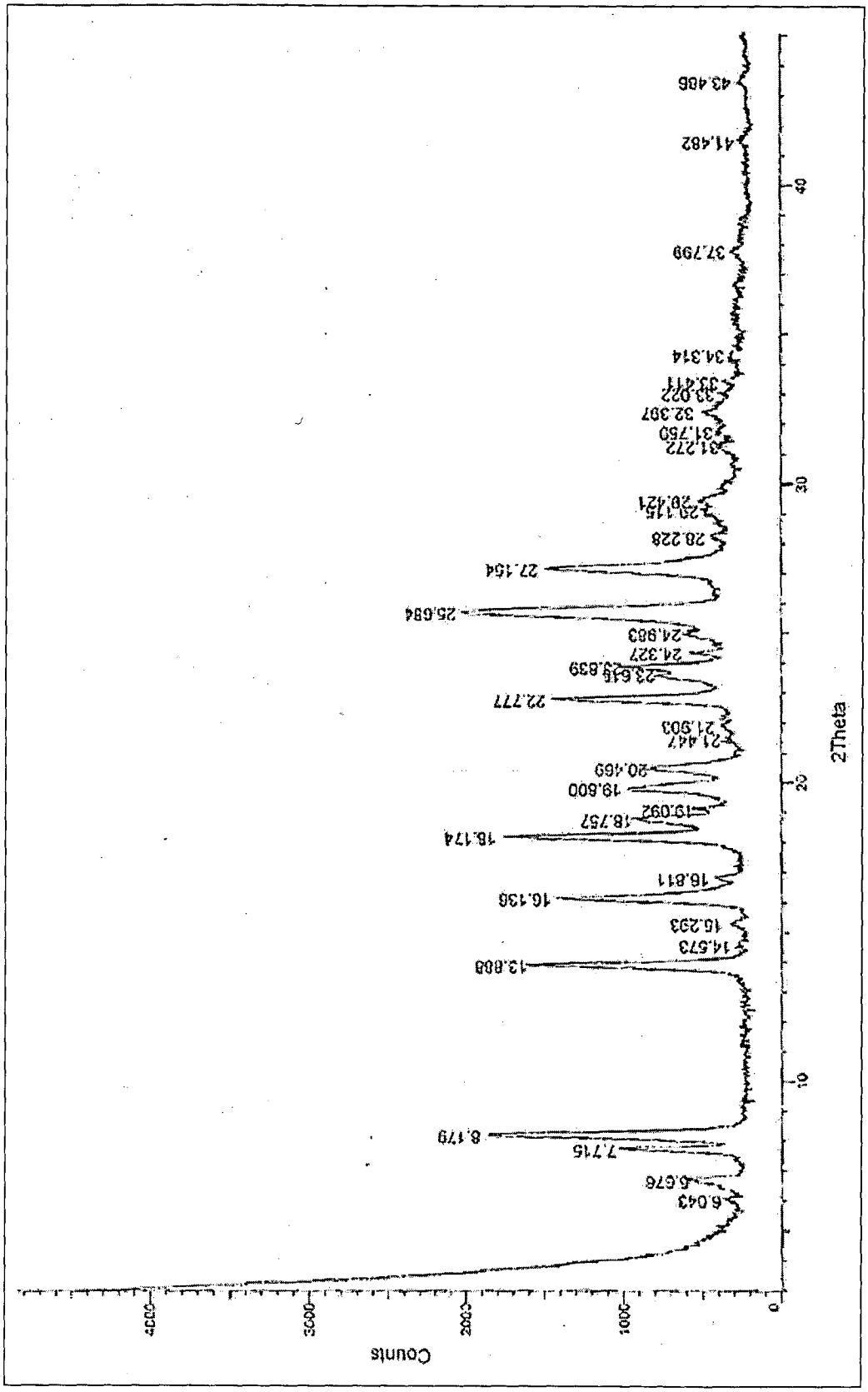
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Figure 9

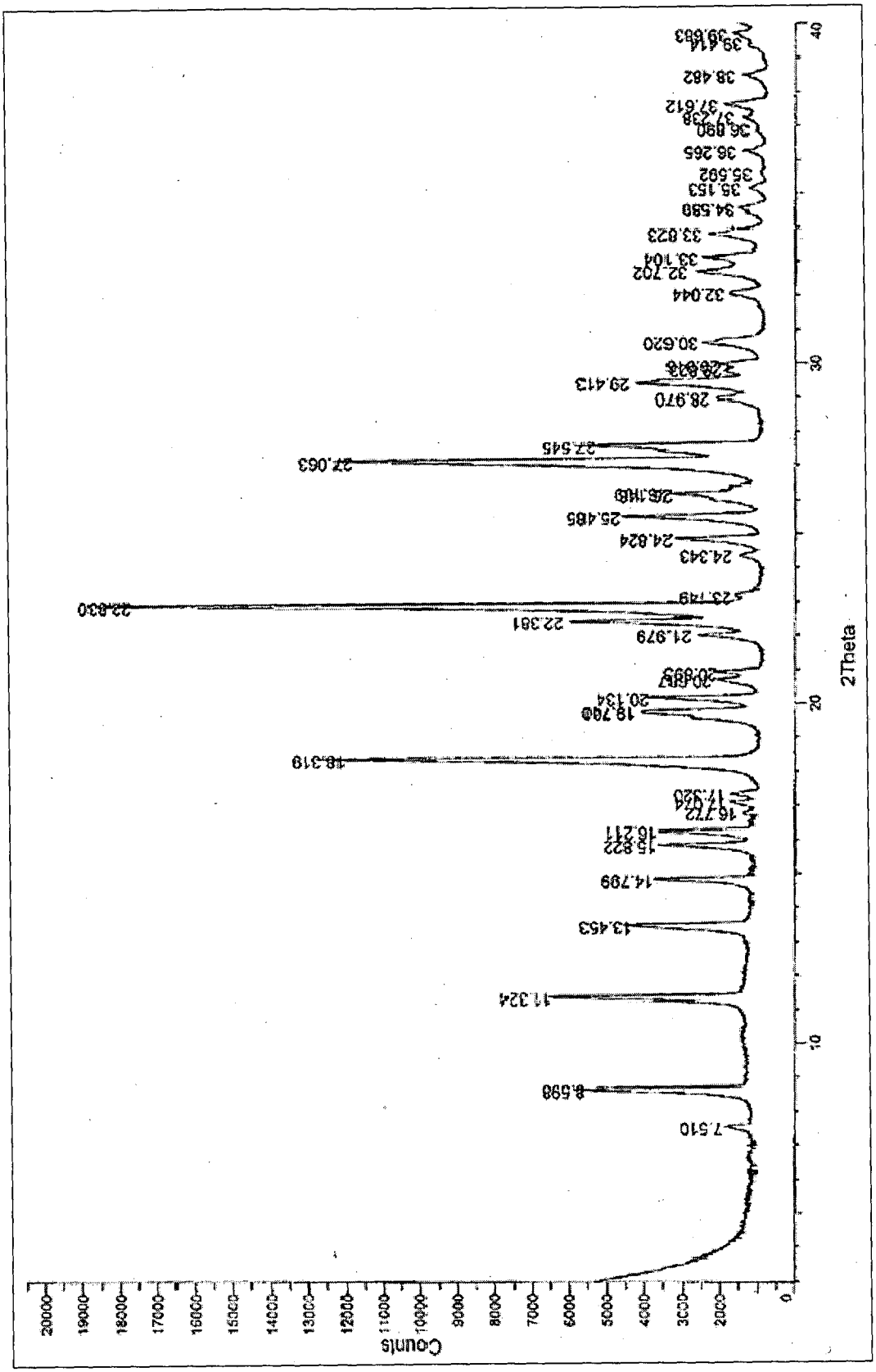
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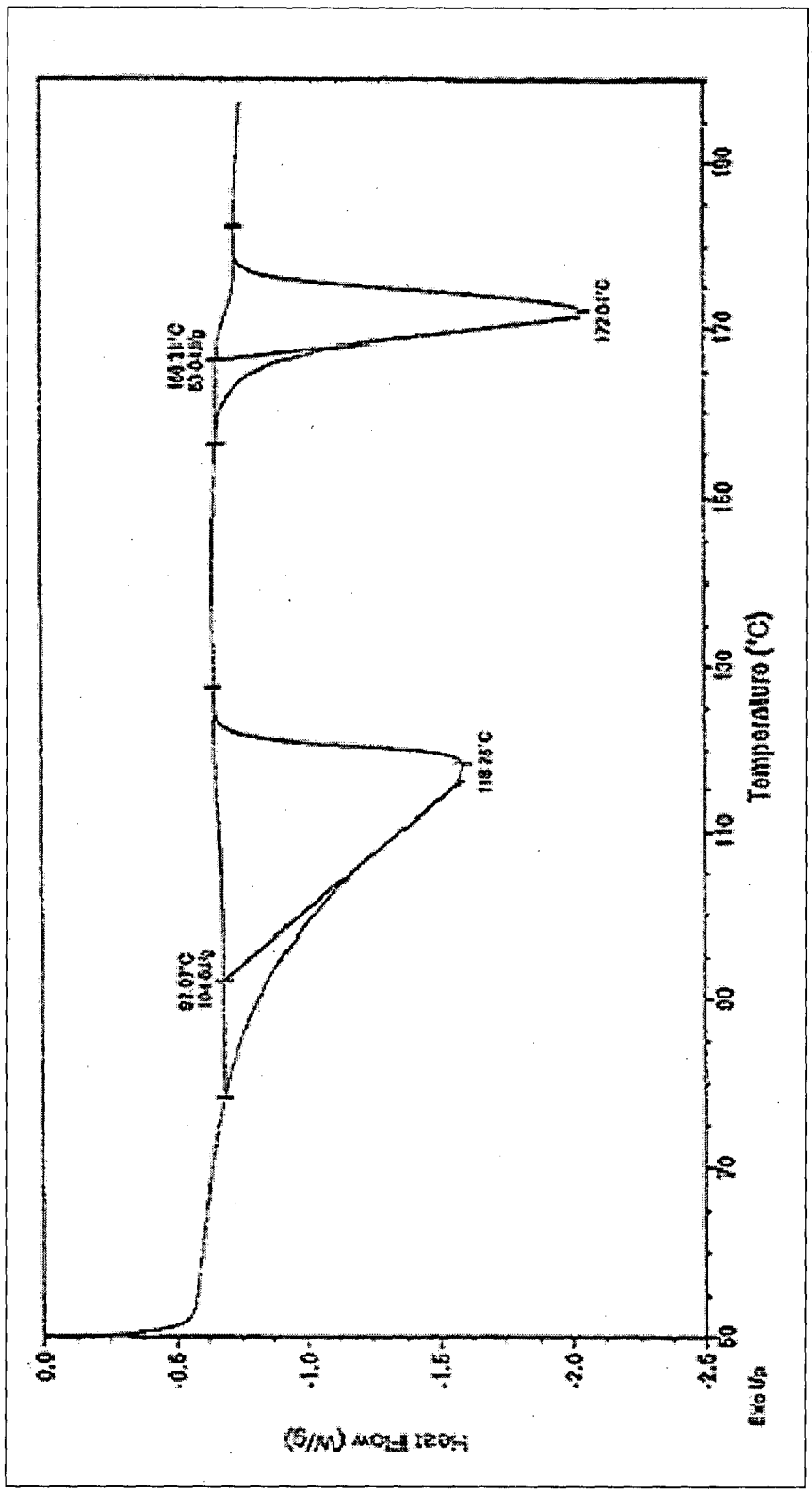
Figure 10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104.63J/g

Figure 11

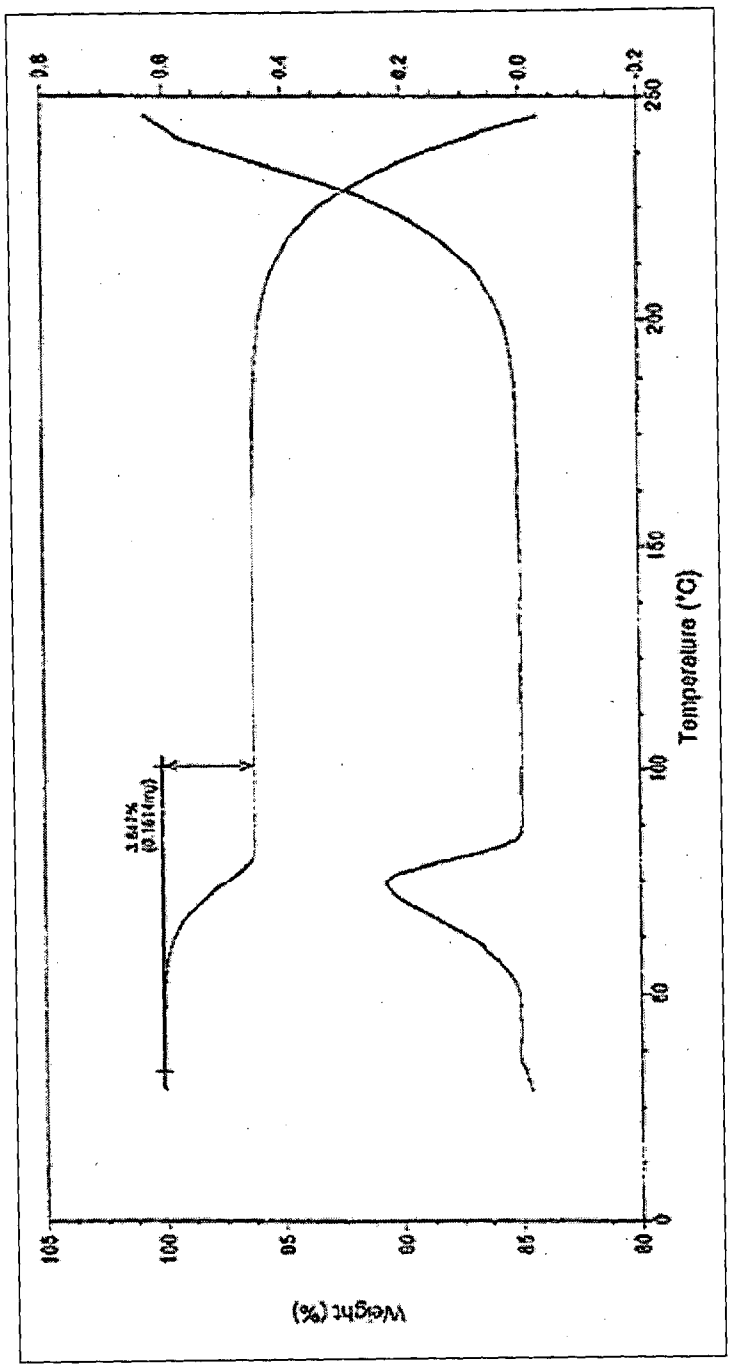

Figure 12

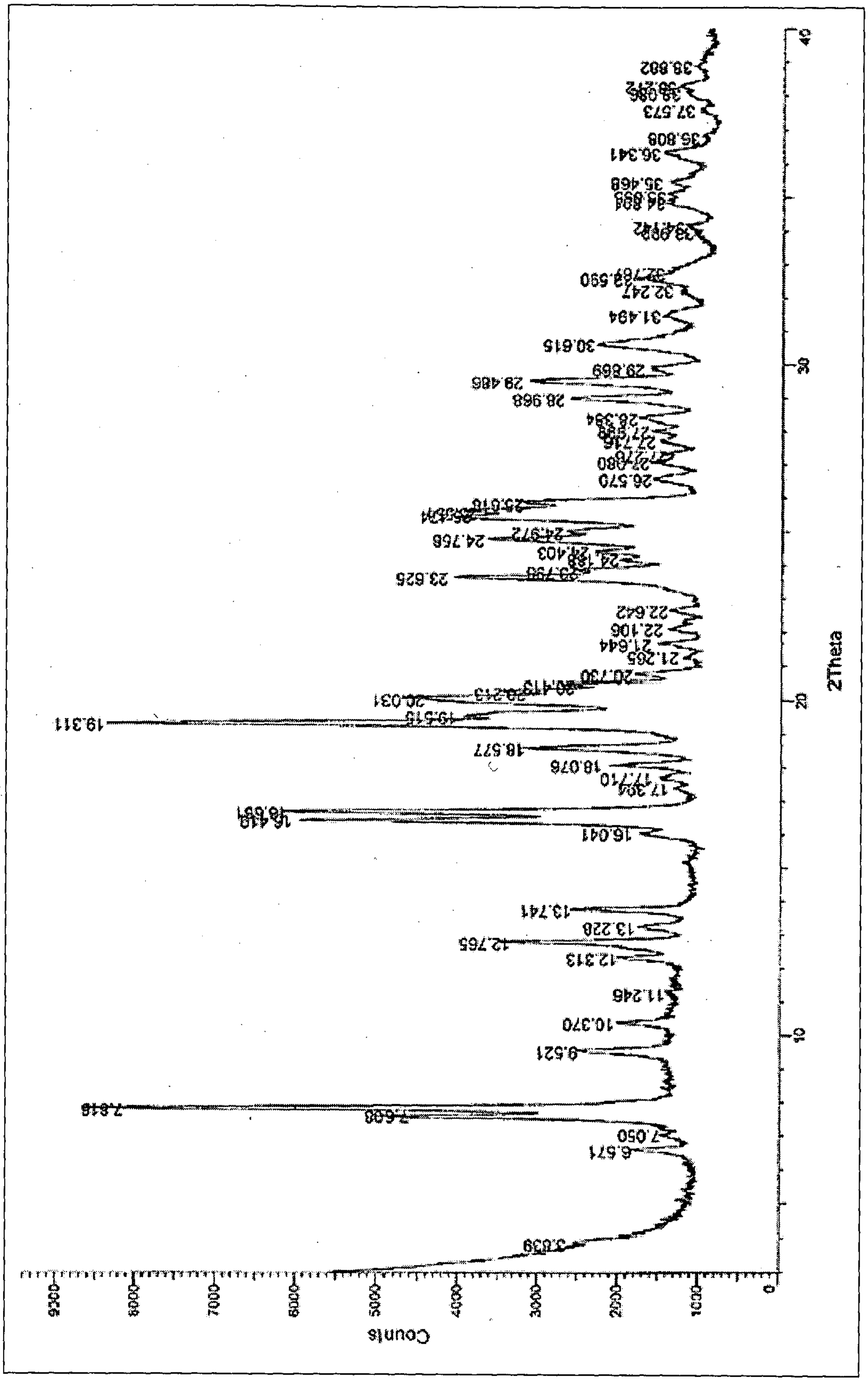
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Figure 13

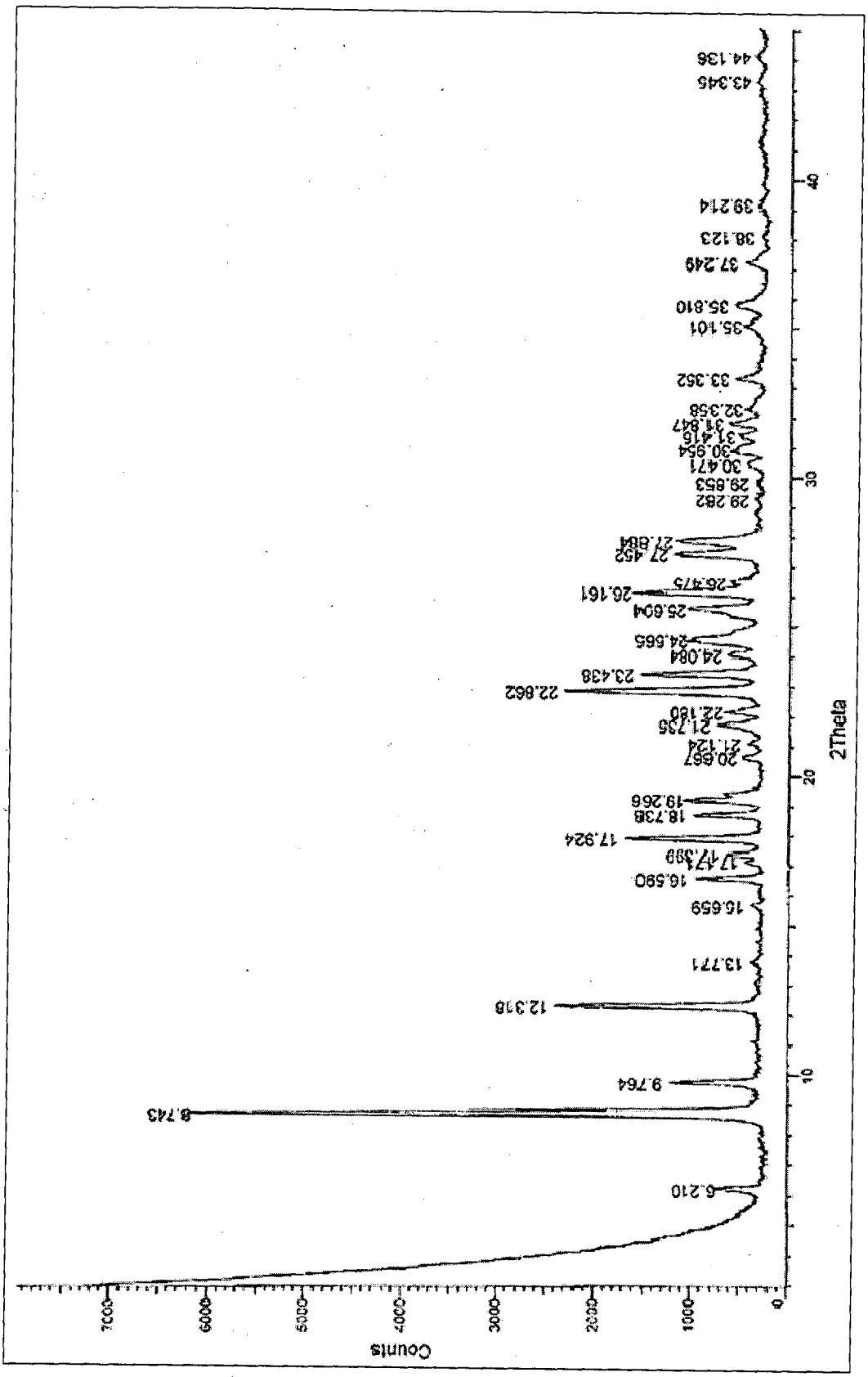
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Figure 14

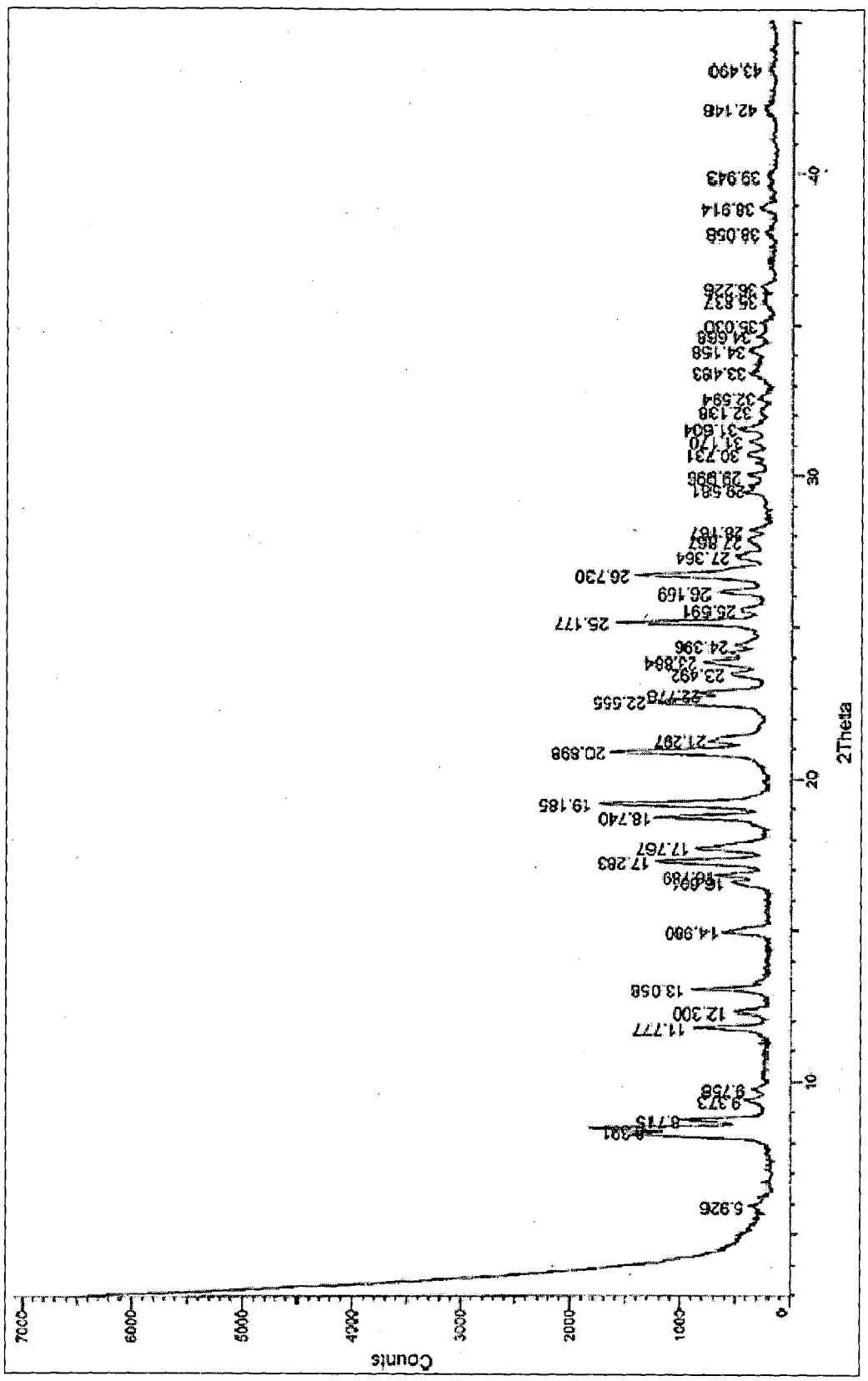
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Figure 15

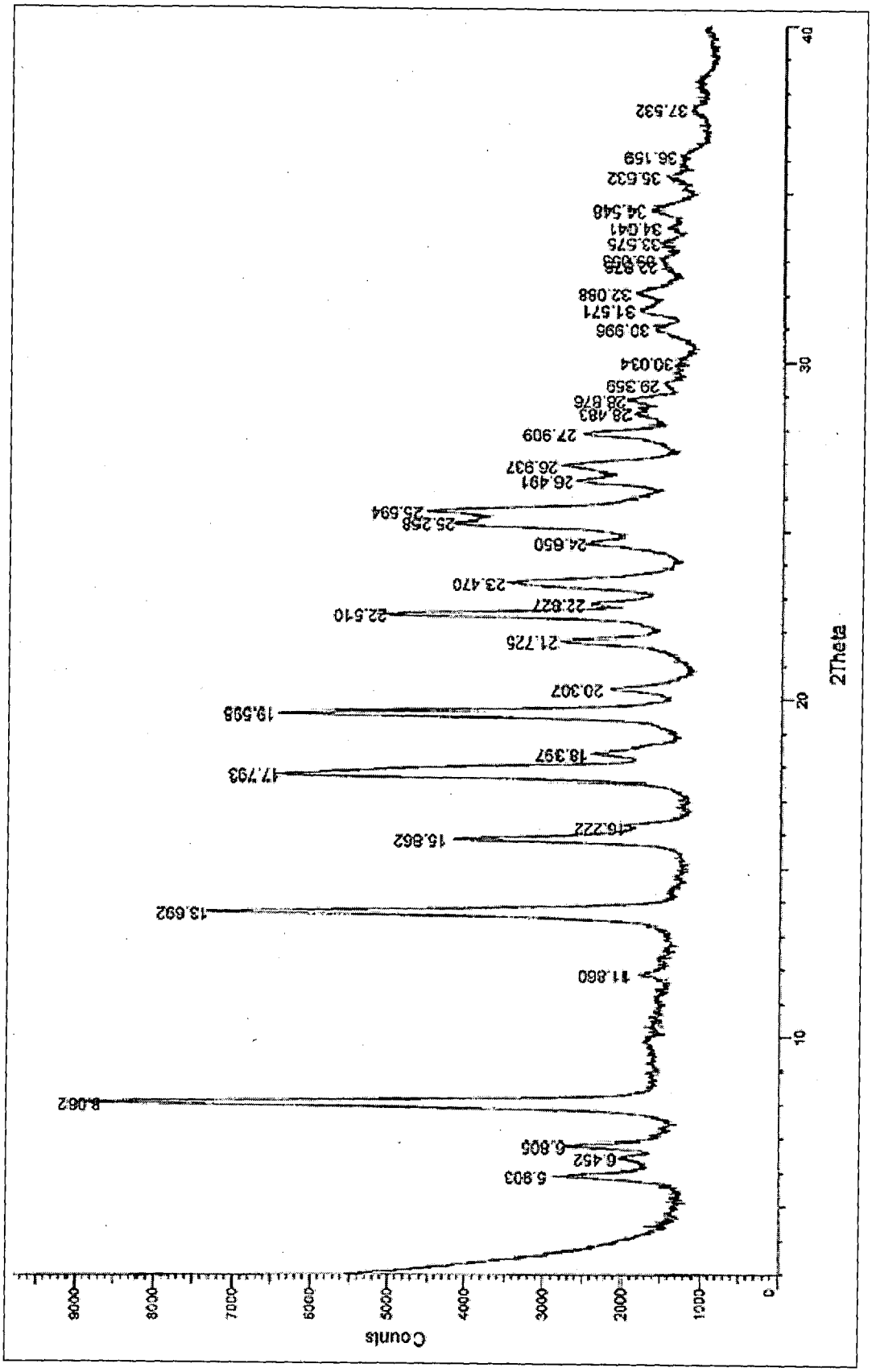
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Figure 16

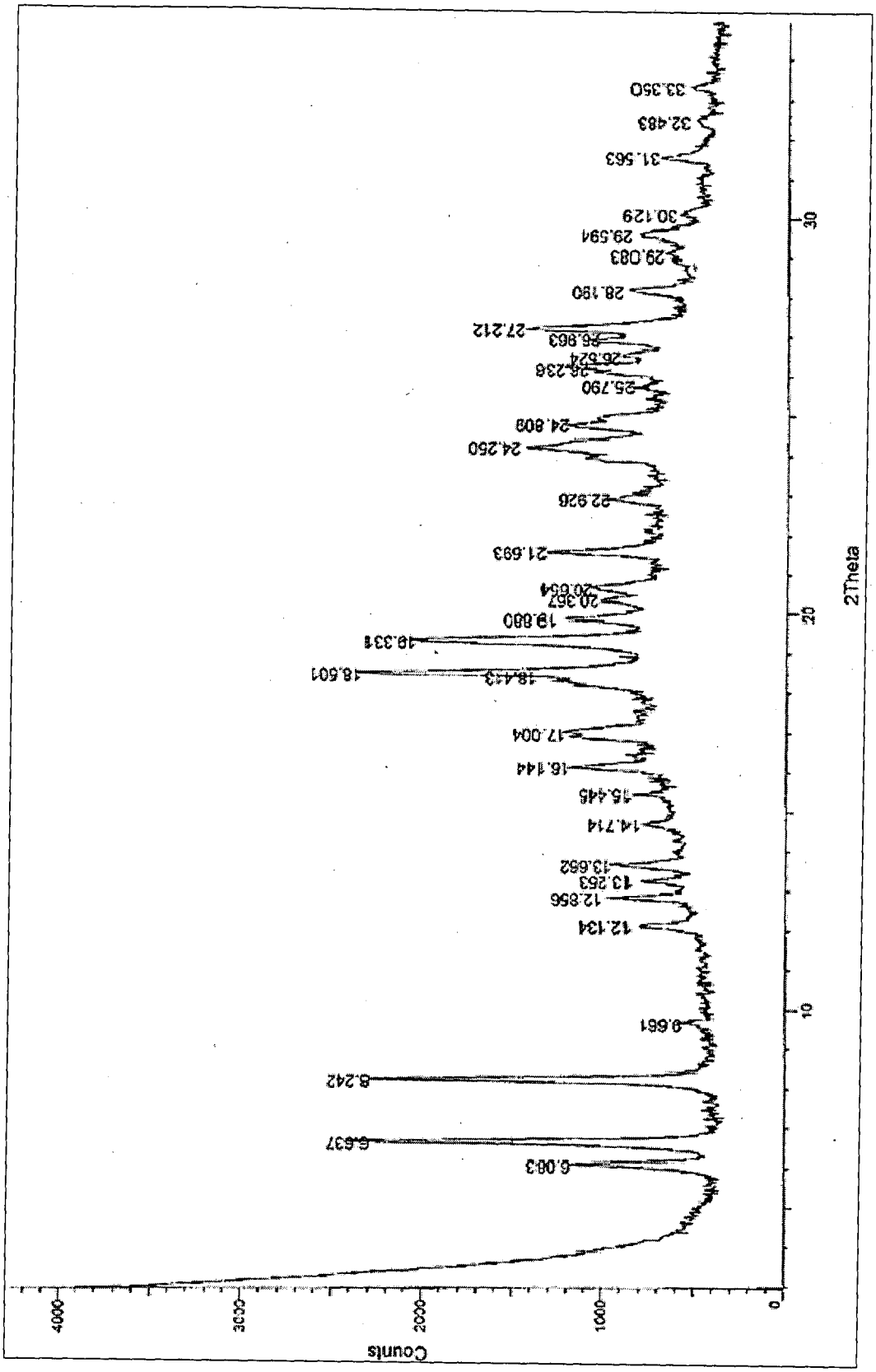
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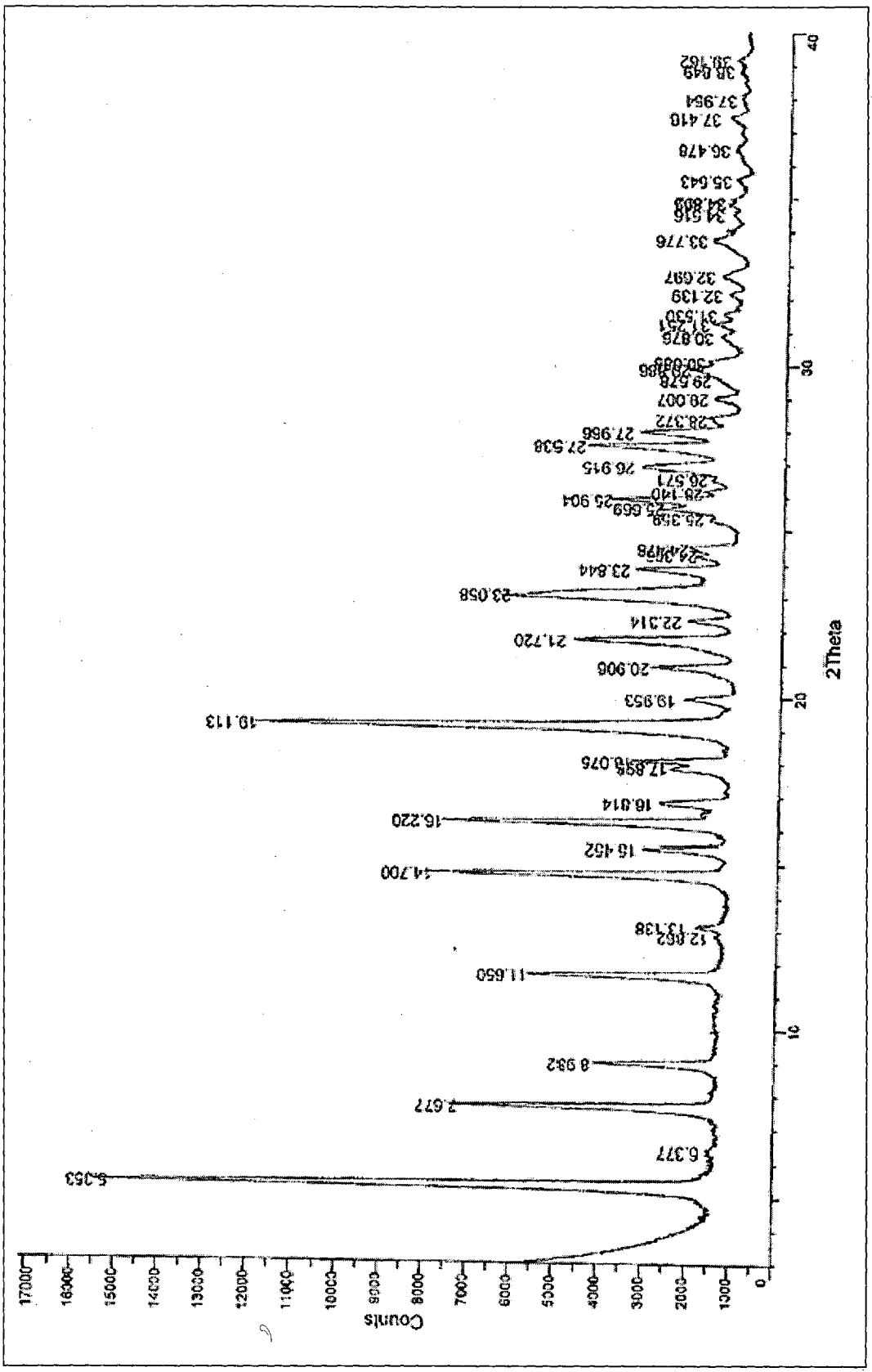
Figure 17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