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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 January 2012 (19.01.2012)

PCT

(10) International Publication Number
WO 2012/007555 A2

(51) International Patent Classification:
C07D 417/12 (2006.01)

(21) International Application Number:
PCT/EP2011/062080

(22) International Filing Date:
14 July 2011 (14.07.2011)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
P391810 14 July 2010 (14.07.2010) PL

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(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, 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, PE, PG, PH, PL, PT, RO, RS, RU, 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, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, 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).

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

WO 2012/007555 A2

(54) **Title**: NEW ZIPRASIDONE SALTS AND METHODS OF THEIR FORMATION

(57) **Abstract**: New salts of ziprasidone and their solvates were disclosed, in particular in crystalline form. More specifically, the present invention relates to a ziprasidone salt selected from a group comprising ziprasidone succinate and ziprasidone ascorbate, a process for the manufactured of the ziprasidone salt and a pharmaceutical composition comprises said salt.

New ziprasidone salts and methods of their formation

The invention concerns new ziprasidone salts and their crystalline forms, a pharmaceutical composition containing these salts, and their uses.

Background art

Described in patent PL157897, 5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2H-indol-2-one, also known as ziprasidone, is used to manufacture a medicine for the treatment of mental illnesses, especially schizophrenia. Commercially available drugs (Geodon, Zeldox) contain ziprasidone hydrochloride, mostly monohydrate. United States Patent description US 4 831 031 discloses 5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2H-indol-2-one hydrochloride in the form of hemihydrate, which is however hygroscopically unstable, which may cause problems with the weight of active ingredient during the process of tabletting or encapsulation.

Patent descriptions EP0584903, EP00586191, EP0706524, EP0790236 and EP01029861 present various methods of ziprasidone synthesis, especially its hydrochloride monohydrate form, which due to its better hygroscopic stability is currently the most often used hydrochloride form, both amorphous and crystalline.

There is still demand, however, for alternative forms of ziprasidone, especially crystalline forms, which would be suitable for use in the pharmaceutical industry and in particular allow easy production of ziprasidone preparations in solid form, such as tablets, capsules, chewable tablets, powders etc. for oral administration. There is also demand for a ziprasidone salt in a pure and crystalline form which would allow the manufacture of preparations meeting strict pharmaceutical standards.

In addition, the method of synthesising new ziprasidone forms must be suitable for large-scale production. The product form should also be easy to filter and dry.

Lastly, for reasons of economy and product/process efficiency, the product should be stable for long periods of time without the need for special storage conditions, as well as readily soluble in aqueous solutions and not excessively hygroscopic. Such salts could provide for better storage stability and/or handling. It would further be desirable to form ziprasidone compositions from such salts. Such formulations may avoid some of the limitation of the present the tablets known in the art.

Summary of the invention

The present invention relates to the discovery of moderately water-soluble salts of ziprasidone. The salts of the herein disclosed have excellent properties to be used in industrial scale, and specially to be used in the formulation of solid oral form comprising such salts of ziprasidone. Firstly, they can be isolated in a solid form, even in a crystalline form, which is highly desirable for drugs which are to be formulated in a solid oral form. Furthermore, the salts provided by herein disclosed show an excellent stability *per se* for long periods of time without the need for special storage conditions. This good stability is also shown after after being formulated, for example, in oral dosage form. In addition to their good stability, the salts provided by herein disclosed show a good dissolution profile, but without showing a excessively hygroscopic. The salts herein disclosed are easy to filter and dry and they can be in a substantially pure form and/or isolated form. Another advantage of the salts herein disclosed is the fact that they can be obtained in process suitable for large-scale production.

Therefore, the present invention is defined according the following clauses:

1. A ziprasidone salt selected from a group comprising ziprasidone succinate and ziprasidone ascorbate.

2. A ziprasidone salt according to clause 1, characterized in that it is ziprasidone succinate.

3. A ziprasidone salt according to any one of the preceding clauses, characterized in that it is ziprasidone succinate in a solid form.

4. A ziprasidone salt according to any one of the preceding clauses, characterized in that it is ziprasidone succinate in crystalline form.

5. A ziprasidone salt according to any one of the preceding clauses, characterized in that it is ziprasidone succinate in crystalline form with an X-ray powdered-crystal pattern comprising the following 2θ (±0.2) values measured using CuKα radiation: 8.3400, 12.5200, 16.7063, 21.4300, 22.6379, 23.4339 and 25.1807.

6. A ziprasidone salt according to any one of the preceding clauses, characterized in that it is ziprasidone succinate in crystalline form with an X-ray powdered-crystal pattern comprising the following 2θ (±0.2) values measured using CuKα radiation: 8.3400, 12.5200, 16.3644, 16.7063, 19.3528, 21.4300, 22.6379, 23.3682, 23.4339, 24.6158, 25.1807, 25.368, 26.1065, 26.5365, 27.3895, 27.7657, 28.92 and 39.8769.

7. A ziprasidone salt according to any one of the preceding clauses, characterized in that it is ziprasidone has a particle size from 5 to 350 microns.

8. A ziprasidone salt according to any one of the preceding clauses, characterized in that it is ziprasidone salt has a mean particle size from 10 to 90 microns.

9. A ziprasidone salt according to clause 1, characterized in that it is ziprasidone ascorbate.

10. A ziprasidone salt according to the preceding clause, characterized in that it is ziprasidone ascorbate in a solid form.

11. A ziprasidone salt according to any one of the two preceding clauses, characterized in that it is ziprasidone ascorbate in crystalline form.

12. A ziprasidone salt according to any one of the three preceding clauses, characterized in that it is crystalline form I with an X-ray powdered-crystal pattern comprising the following 2θ (±0.2) values measured using CuKα radiation: 12.6428, 15.9127, 19.7082, 20.3825, 20.9116 and 25.6078.

13. A ziprasidone salt according to the preceding clause, characterized in that it is crystalline form I with an X-ray powdered-crystal pattern comprising the following 2θ (±0.2) values measured using CuKα radiation: 7.2806, 12.6428, 12.7479, 15.9127, 19.1654, 19.7082, 20.3825, 20.9116, 21.6101, 23.9734, 25.6078, 26.1883; 26.2496, 28.7584 and 31.739.

14. A ziprasidone salt according to clauses 9 to 11, characterized in that it is crystalline form II with an X-ray powdered-crystal pattern comprising the following 2θ (±0.2) values measured using CuKα radiation: 18.0934, 20.2581, 21.6581, 22.7161 and 25.2264.

15. A ziprasidone salt according to the preceding clause, characterized in that it is crystalline form II with an X-ray powdered-crystal pattern comprising the following 2θ (±0.2) values measured using CuKα radiation: 14.8648, 17.719, 17.9232, 18.0934, 18.9212, 20.2581, 21.6581, 22.7161, 23.9379, 25.2264, 25.4468, 26.8346, 28.7283, 29.2495 and 29.862.

16. A process for the manufactured of the ziprasidone salt according to clauses one, characterised in that the process comprises at least the following steps: contacting a solution of ziprasidone free base in a solvent system with more than 1.5 equivalents of the acid; isolation of the salt formed; wherein the temperature of the solution of ziprasidone free base in the solvent system is between 20ºC and reflux temperature of the solvent system.

17. A process according to the preceding clause, characterised in that more than 2.5 equivalent of acid are contacted with a solution of ziprasidone free base in a solvent system.

18. A process according to any one of the two preceding clauses, characterised in that between more 3.5 and 20 equivalents of acid are contacted with a solution of ziprasidone free base in a solvent system.

19. A process according to any one of the three preceding clauses, characterised in that the solvent system comprises one or more polar solvents.

20. A process according to any one of the three preceding clauses, characterised in that the solvent system consists essentially in one or more polar solvents.

21. A process according to any one of the four preceding clauses, characterised in that the polar solvent is selected from water, an C_1-C_6 alcohol, and C_1-C_6 ether and a C_1-C_9 ketone.

22. A process according to any one of the four preceding clauses, characterised in that the polar solvent is selected from water, ethanol, THF or any mixture thereof.

23. A pharmaceutical composition comprising an active substance and at least a pharmaceutically acceptable carrier, characterised in that the active substance is a ziprasidone salt of any one clauses 1 to 15, in particular in its crystalline form specified in clauses 4 and 11.

24. A pharmaceutical composition according to the preceding clause, characterised in that it is in oral dosage form.

25. A pharmaceutical composition according to the preceding clause, characterised in that the oral dosage form are tablets or capsules.

26. A process for the manufacture of a pharmaceutical composition of any one of the two preceding clauses clauses, characterised in that simple admixture or dry granulation techniques are used.

27. The process according to clause 8, comprising at least the steps of: i) Mixing all the ingredients; optionally ii) Compressing the mixture and grinding the product obtained; iii) and recompressing it to form tablets or filling the capsules.

28. The method for the manufacture of a pharmaceutical composition according to any one of the clauses 24 or 25 comprising at least the steps of: a) Preparation of binder solution, preferably with an aqueous solvent, preferably water; b) Spraying the binder solution onto the mixture to form a granulate; c) Drying the granulate at inlet temperature equal to or below 70ºC, preferably below 60ºC; d) Sizing the dried granules, preferably through a 1 mm mesh screen; e) Mixing the granules with the rest of the pharmaceutical acceptable excipients; and f) either compressing the granulate to form a tablet, and optionally coating, or filling the capsules with the granulate.

29. Use of the ziprasidone salt specified in clause 1 to 15, in particular in its crystalline form specified in clauses 4 and 11, or the pharmaceutical composition of clauses 23 to 25, to manufacture a medicament to treat or prevent mental illnesses, in particular schizophrenia, and their accompanying symptoms.

Therefore, the subject of the invention is a ziprasidone salt selected from a group comprising ziprasidone succinate and ziprasidone ascorbate. Salts according to the invention may occur in any form, especially amorphous or various crystalline forms and/or solvates. Preferably, a ziprasidone salt according to the invention is ziprasidone succinate in crystalline form. Especially preferably, it is ziprasidone succinate in crystalline form with an X-ray powdered-crystal pattern comprising the following 2θ (±0.2) values measured using CuKα radiation: 8.3400, 12.5200, 16.3644, 16.7063, 19.3528, 21.4300, 22.6379, 23.3682, 23.4339, 24.6158, 25.1807, 25.368, 26.1065, 26.5365, 27.3895, 27.7657, 28.92 and 39.8769.

Equally preferably, a ziprasidone salt according to the invention is a crystalline form containing ziprasidone ascorbate, and preferably it is crystalline form I with an X-ray powdered-crystal pattern comprising the following 2θ (±0.2) values measured using CuKα radiation: 7.2806, 12.6428, 12.7479, 15.9127, 19.1654, 19.7082,

20.3825, 20.9116, 21.6101, 23.9734, 25.6078, 26.1883; 26.2496, 28.7584 and 31.739, or crystalline form II with an X-ray powdered-crystal pattern comprising the following 2θ (±0.2) values measured using CuKα radiation: 14.8648, 17.719, 17.9232, 18.0934, 18.9212, 20.2581, 21.6581, 22.7161, 23.9379, 25.2264, 25.4468, 26.8346, 28.7283, 29.2495 and 29.862. Unexpectedly, as a result of works leading up to obtaining the invention under consideration, it was discovered that ziprasidone may be synthesised in the form of new salts according to the invention, in particular in crystalline form. Unexpectedly, it was established that new ziprasidone salts according to the invention may be easily obtained in crystalline form and are better soluble than both ziprasidone in base form and its hydrochloride.

Another subject of the invention is a pharmaceutical composition containing an active substance and a pharmaceutically acceptable carrier, where the active substance is a ziprasidone salt according to the invention as described above, in particular in crystalline form as described above.

Another subject of the invention is the use of a ziprasidone salt according to the invention as described above, in particular in crystalline form as described above, to manufacture a pharmaceutical composition to treat or prevent mental illnesses, in particular schizophrenia, and their accompanying symptoms.

Therefore, this invention provides two new ziprasidone salts which may be obtained in preferred crystalline forms. The new salts are better soluble than the previously known forms of ziprasidone and its salts, and can be easily obtained in crystalline form using the disclosed methods which are suitable for use in the pharmaceutical industry.

The ziprasidone salts thus obtained may be administered as a pharmaceutical, especially for the treatment of schizophrenia. It may be administered to humans either as the compound itself or preferably admixed with pharmaceutically acceptable carriers or excipients in a pharmaceutical composition, in accordance with standard pharmaceutical practice. The salts may be administered orally or

parenterally, which includes, but is not limited to, intravenous and intramuscular administration. Relevant pharmaceutical carriers include solid excipients and/or fillers as well as sterile aqueous solutions and various organic solvents.

Pharmaceutically acceptable carriers for the manufacture of pharmaceutical compositions containing compounds according to herein disclosed may be either liquids or solids. Solid preparations include powders, tablets, pills, capsules, cachets, suppositories and dispersed granules. Solid carriers may include one or more substances, which may also act as diluents, flavouring agents, solubilising agents, lubricating agents, digesting agents, binders, preservatives, or agents for disintegrating the tablet or capsule material. A solid oral form comprising that salts of the herein disclosed has a good dissolution profile without the need of reducing the particle size and/or adding additional excipients, as for instance surfactants.

In the case of powders, a carrier in the form of finely ground solid is mixed with a finely ground active ingredient. In the case of tablets, the active ingredients is admixed with a carrier having the required binding properties, in appropriate proportion, and then pressed into the required size and shape.

Preferably, powders and tablets contain between 2 or 10 to circa 70 percent active compound. Appropriate carriers include: magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatine, tragacanth gum, methylcellulose, sodium carboxymethylcellulose, low-melting waxes, cocoa butter etc. The term “manufacture” includes an active compound preparation with the encapsulating material as a carrier, which constitutes a capsule in which the active ingredient, with or without other carriers, is surrounded with a carrier, which is thus bound to the active ingredient. This also pertains to cachets and chewable tablets. Tablets, powders, pills, capsules, cachets and chewable tablets may be used in the form of solid dosages appropriate for oral administration.

In order to manufacture suppositories, first a low-melting wax is melted, such as a mixture of fatty acid or cocoa butter glycerides, and then the active ingredient is

homogenously dispersed into the wax on mixing. Next, the melted homogenous mixture is poured into forms of appropriate size and left to cool and thus solidify.

Liquid preparations include solutions, suspensions, intermittent infusions and emulsions, e.g. aqueous solutions or aqueous propylene glycol solutions. For parenteral administration, liquid preparations may be prepared in the form of aqueous solutions of propylene glycol. Aqueous solutions suitable for oral administration may be prepared by dissolving the active ingredient in water and adding, if necessary, appropriate dyes, flavouring, stabilizers and thickeners.

Aqueous suspensions suitable for oral administration may be prepared by dispersing a finely ground active ingredient in water with a viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose or other well-known agents for suspension formation.

Solid preparations intended to be transformed, shortly before use, into liquid preparations for oral administration. Such liquid forms include solutions, suspensions and emulsions. Other than the active ingredient, such preparations may also contain dyes, flavouring agents, stabilizers, buffers, natural and artificial sweeteners, dispersing agents, thickeners, solubilising agents etc.

Preferably a pharmaceutical preparation occurs in a form suitable for combined dosage. In such a form the preparation is divided into unit doses containing an appropriate amount of the active ingredient. The form intended for combined dosage may be a packaged preparation containing separated amounts of the preparation, such as packaged tablets or capsules, or powders in vials or ampoules. A unit dose may also consist of a single capsule, tablet, cachet or chewable tablet, or a suitable number of any of such packaged forms.

The amount of the active ingredient in a unit dose of a preparation may vary or may be adjusted between 0.5-100 mg, preferably, 2.5-80 mg, depending on the type of use and the active ingredient strength. The more preferably dosage form unit is

from 10 to 80 mg per unit, specially for oral dosage forms. If required, the composition may also contain other compatible therapeutic agents.

In therapeutic uses as psychiatric medication, new ziprasidone salts, especially in crystalline form, used in the pharmaceutical method, are administered at an initial dose of between 2.5 mg and ca. 80 mg daily. The preferred daily dose varies between ca. 2.5 mg and ca. 20 mg. However, dosage may vary depending on patient's needs, stadium of the illness treated and the type of compound used. Establishing the appropriate dosage in a given case depends on the doctor. Usually, treatment begins with a lower dosage which is below the optimum dosage for the compound. Then the dosage is increased in small increments until the optimum effect in the given circumstances is achieved. It may be useful to divide the total daily dose and administer it in portions throughout the day, if appropriate.

Brief description of the drawings

For the purpose of better presentation of the invention described above, the description contains the following illustrations:

Fig. 1 X-ray pattern of ziprasidone (free amine),
Fig. 2. X-ray pattern of ziprasidone ascorbate, form I,
Fig. 3. X-ray pattern of ziprasidone ascorbate, form II,
Fig. 4. X-ray pattern of ziprasidone succinate,
Fig. 5. Comparison of X-ray patterns for ziprasidone and two forms of ascorbate,
Fig. 6. Comparison of X-ray patterns for ziprasidone and succinate,
Fig. 7. IR spectrum of ziprasidone ascorbate, form I,
Fig. 8. IR spectrum of ziprasidone ascorbate, form II,
Fig. 9. Comparison of IR spectra for forms I and II of ziprasidone ascorbate,
Fig. 10. IR spectrum of ziprasidone succinate,
Fig. 11. DSC curve for ziprasidone ascorbate, form I,
Fig. 12. DSC curve for ziprasidone ascorbate, form II,
Fig. 13. DSC curve for ziprasidone succinate.
Fig. 14. diffractogram of ziprasidone succinate.

Examples

The following non-limiting examples illustrate the preferred methods of synthesizing compounds according to herein disclosed.

Example 1. Synthesis of ziprasidone ascorbate

Ziprasidone and THF were added to a round-bottomed flask and maintained at a temperature of 60°C while stirring the solution with a magnetic stirrer for 1 hour. Upon complete dissolution of ziprasidone into a clear solution, five-time excess of ascorbic acid (in relation to ziprasidone) was added. The reaction mixture was kept at a temperature of 60°C for one and a half hours, then activated carbon was added and the entire mixture was stirred for another half an hour. The hot solution was filtered through celite. The clear solution obtained was left overnight at room temperature in order to crystallize. In a preferred realization, in order to achieve better crystallization effectiveness, the solution was inoculated with ziprasidone ascorbate crystals. Excess solvent was then evaporated. The precipitate was filtered off under vacuum, and excess ascorbic acid used for synthesis was washed out with water. The reaction product was dried at 40°C. The reaction yield was *ca.* 78%.

Examples of amounts used for synthesis:
1 g Ziprasidone (2.4 mmol)
2.11 g ascorbic acid (12 mmol)
100 ml THF,
0.2 g activated carbon.
NMR for ziprasidone ascorbate

Base: Acid = 1:1
1H NMR (250 MHz, DMSO-d6): δ= 2.68-2.75 (m, 2H, CH2), 2.83-2.94 (m, 6H, 3xCH2), 3.40-3.45 (m, 2H, CH2), 3.47 (s, 2H, CH2), 3.51-3.56 (m, 2H, CH2), 3.74 (td, 1H, 3JHH= 6.9 Hz, 3JHH = 1.7 Hz, CH), 4.70 (d, 1H, 3JHH = 1.7 Hz, CH), 6.84

(s, 1H, CHAr), 7.23 (s, 1H, CHAr), 7.43 (t, 1H, 3JHH = 7.9 Hz, CHAr), 7.55 (t, 1H, 3JHH = 7.9 Hz, CHAr), 8.00-8.07 (m, 2H, 2xCHAr), 10.29 (s, 1H,NH).

13C NMR (62.9 MHz, DMSO-d6): δ= 29.41, 35.32, 49.01, 52.05, 57.56, 62.15, 68.67, 74.73, 109.63, 118.13, 120.88, 124.03, 124.31, 125.15, 126.70, 127.30, 127.77, 129.20, 131.36, 143.34, 152.07, 152.63, 163.16, 176.10.

Unexpectedly it was established that various conditions of synthesis and crystallization lead to various crystalline forms of ziprasidone ascorbate. It was established that the optimum temperature for ziprasidone ascorbate synthesis is between 64-66ºC (the yield was better by around 2% compared to 60ºC). The presence of water in the reaction environment promotes the formation of form I (A1) of ziprasidone ascorbate. It was also noted that nucleation of the crystallization process with crystals of the desired form produces pure form I or II of ziprasidone ascorbate regardless of the presence of water.

Procedure of ziprasidone ascorbate synthesis – using nucleation.

Two samples of ziprasidone were weighed (1.0 g, 2.4 mmol each) and added to two round-bottomed flasks, to which a solvent was then added (THF, 100 ml each). The solutions thus prepared were stirred with a magnetic stirrer for an hour at a temperature of 64-66°C. After an hour a five-time excess of ascorbic acid (2.11g 12 mmol) was added, and the solution was stirred for another hour at a constant temperature. 10 minutes before the end of the set time activated carbon was added (20% by weight ZP), upon the lapse of said time the hot mixture was filtrated through celite and then the following were added to the filtrates, respectively:

a) form I nuclei

b) form II nuclei

and left for ca. 12 hours at a temperature of 20°C.

The precipitate obtained was filtered off on a vacuum filter and washed with water to remove excess ascorbic acid used for synthesis. Wet product was dried at a temperature of 40°C for two hours.

a) after drying the yellow sample was tested on a powdered-crystal diffractometer. The X-ray pattern obtained confirmed that form I had been synthesized.

b) after drying the pale yellow sample was tested on a powdered-crystal diffractometer. The X-ray pattern obtained confirmed that form II had been synthesized.

Example 2. Synthesis of ziprasidone succinate

Ziprasidone and THF were added to a round-bottomed flask and maintained at a temperature of 60°C while stirring the solution with a magnetic stirrer for 1 hour. Upon complete dissolution of ziprasidone into a solution, ten-time excess of succinic acid (in relation to ziprasidone) was added and the mixture was stirred for another 10 minutes. Then activated carbon was added and the entire mixture was stirred for half an hour at temperature of 60°C. The hot solution was filtered through celite. The clear solution obtained was left overnight at room temperature. The precipitate was filtered off on a vacuum filter, and washed with water to remove excess succinic acid used for synthesis. The reaction product was dried at 40°C. The reaction yield was ca. 90%.

Examples of amounts used for synthesis:

1 g Ziprasidone (2.4 mmol)

2.83 g succinic acid (24.0 mmol),

100 ml THF,

0.2 g activated carbon.

NMR for succinate

Base: Acid = 1:1.7

1H NMR (700 MHz, DMSO-d6): δ= 2.42 (s, 4H, 2x CH2COOH), 2.56-2.59 (m, 2H, CH2), 2.70-2.73 (m, 4H, 2xCH2), 2.84-2.87 (m, 2H, CH2), 3.46 (s, 2H, CH2), 3.46-3.48 (m, 2H, CH2), 6.81 (s, 1H, CHAr), 7.23 (s, 1H, CHAr), 7.34 (t, 1H, 3JHH= 7.9 Hz, CHAr), 7.56 (t, 1H, 3JHH= 7.9 Hz, CHAr), 8.05 (d, 1H, 3JHH= 7.9 Hz, CHAr), 8.06 (d, 1H, 3JHH= 7.9 Hz, CHAr), 10.41 (s, 1H, NH), 12.16 (bs, 2H, COOH).

13C NMR (176 MHz, DMSO-d6): δ= 28.81, 28.78, 35.32, 49.52, 52.30, 58.09, 66.98, 109.50, 121.03, 124.12, 124.37, 125.21, 126.82, 127.30, 127.83, 131.22, 143.22, 151.95, 163.46, 173.56, 176.23.

Example 3. Physico-chemical properties of the salts obtained

The above described synthesis using succinic acid or ascorbic acid led to the formation of new salts i.e. ziprasidone succinate (B) and ascorbate (A). In the case of ascorbate two forms of salt were obtained (A1 and A2). This example presents the physico-chemical properties of the salts using the following analytical techniques XRD, IR, thermal analysis (DSC, TGA) and NMR (1H, 13C).

Melting point

The melting point was determined using the following apparatus: MELT TEMP2

Ziprasidone ascorbate – melting point = 225°C

Ziprasidone succinate - melting point = 190°C

Diffractometry (XRD)

Sample preparation

The sample was ground in an agate mortar and then about 300 mg of the substance was placed in a sample holder of 16 mm in diameter and 2.4 mm in thickness. The sample was gently pressed from the back to produce a flat surface. The sample thus prepared was placed in an automatic (15-position) sample feeder. The measurement was taken at a temperature of 22°C.

Measurement parameters

The measurement was made using a PANanalytical X'Pert PRO MPD multi-task polycrystalline diffractometer. CuKα radiation was used, obtained by monochromatization of X-rays using a nickel filter. Continuous scan was used (step 0.0084º), measurement time for each step was 30 seconds. Measurements were made at 2θ (±0.2) from 3.5 to 55º.

Optics of the apparatus during measurements

a) On the primary beam the following were used: constant slit (0.5º), Soller slits (0.04 rad.), anti-scatter slit (1.52 mm).

b) On the reflected beam the following were used: anti-scatter slit (5 mm), Soller slits (0.04 rad), nickel filter and an X`Celerator semiconductor strip detector.

Computation procedures used

X'Pert Viewer software was used for graphic representation of results.

Presentation of XRD results

Figures 1, 2, 3 and 4 present X-ray patterns obtained during measurements for, respectively, free ziprasidone base, ziprasidone ascorbate form I, ascorbate form II and succinate. Figures 5 and 6 are superimposed X-ray patterns of free amine and salt. The patterns show significant differences which confirm the formation of ziprasidone salt. Tables 1, 2 and 3 present structural data for the salts obtained.

Table 1 Structural data for ziprasidone succinate

No.	Pos. [°2Th.]	d-spacing [A]	FWHM [°2Th.]	Rel. Int. [%]
1	8.3131	10.63626	0.0945	2.15
2	11.2685	7.85246	0.0866	12.72
3	11.8423	7.47321	0.0551	10.65
4	11.9514	7.40524	0.0472	5.44
5	12.5137	7.07375	0.0708	8.28
6	12.7244	6.95709	0.0945	9.03
7	13.5932	6.51431	0.063	10.69
8	15.0124	5.90152	0.0945	0.74
9	16.076	5.51339	0.0394	11.39
10	16.3644	5.41688	0.1181	46.21
11	16.7063	5.30679	0.0866	28.56
12	16.8402	5.26489	0.0472	7.77
13	18.0052	4.92676	0.063	6.58
14	18.7102	4.74269	0.0551	8.9
15	19.3528	4.58664	0.1023	15.72
16	19.6448	4.51912	0.0945	6.89
17	19.9975	4.44019	0.063	13.71
18	21.4059	4.15113	0.063	9.62
19	21.9757	4.04478	0.0787	7.02
20	22.2572	3.99425	0.0787	12.92
21	22.6379	3.92794	0.0866	47.24
22	22.8753	3.8877	0.063	5.13

23	23.3682	3.80366	0.1152	100
24	23.4339	3.80256	0.0384	25.84
25	23.8092	3.7342	0.192	13.21
26	24.1979	3.67508	0.1536	8.63
27	24.6158	3.61362	0.1536	20.46
28	25.1807	3.53382	0.0672	30.66
29	25.368	3.50815	0.0768	22.97
30	26.1065	3.41056	0.1344	99.51
31	26.5365	3.35627	0.1344	27.14
32	27.0835	3.28971	0.1344	12.69
33	27.3895	3.25365	0.1344	15.14
34	27.7657	3.21042	0.096	17.61
35	28.5891	3.1198	0.1152	6.23
36	28.92	3.08485	0.192	19.6
37	29.5634	3.01916	0.2304	12.45
38	30.6671	2.91296	0.4608	6.34
39	31.4993	2.83788	0.0672	10.97
40	32.38	2.76267	0.192	9.29
41	33.2361	2.69344	0.1344	9.5
42	33.8913	2.64286	0.192	3.07
43	34.6216	2.58876	0.2304	8.65
44	35.0633	2.55716	0.2304	4.94
45	36.0639	2.48847	0.1536	3.05
46	36.9309	2.43202	0.1344	7.72
47	37.5344	2.39429	0.1536	5.73
48	37.9814	2.36713	0.0768	5.78
49	38.4626	2.33862	0.096	9.28
50	39.2384	2.29415	0.2304	2.81
51	39.8769	2.25887	0.384	24.36
52	40.6543	2.21745	0.192	3.49
53	41.1635	2.19119	0.384	6.98
54	42.0071	2.14912	0.0768	4.15
55	43.8667	2.06223	0.384	7.48

56	45.5366	1.99041	0.1344	6.52
57	46.2625	1.96085	0.2304	4.83
58	47.0241	1.93085	0.2688	12.02
59	47.3898	1.9168	0.1152	3.74
60	47.8745	1.89852	0.3072	7.61
61	49.1354	1.85271	0.4608	9.48
62	49.9354	1.82489	0.3072	6.63
63	50.6099	1.80214	0.1536	4.77
64	51.5105	1.77273	0.6144	3.83
65	53.2273	1.71952	0.6144	6.09

Table 2. Structural data for ziprasidone ascorbate form I

No.	Pos. [°2Th.]	d-spacing [A]	FWHM [°2Th.]	Rel. Int. [%]
1	5.4205	16.30408	0.0945	14.68
2	6.5682	13.45756	0.0394	19.32
3	7.2806	12.14221	0.063	42.3
4	9.5028	9.30719	0.2519	7.79
5	10.8324	8.16758	0.1574	7.14
6	12.2135	7.24692	0.063	6.89
7	12.6428	7.00183	0.0472	30.82
8	12.7479	6.94428	0.0551	76.52
9	13.1009	6.75798	0.0787	7.96
10	13.5053	6.55651	0.1574	4.33
11	14.1529	6.25792	0.126	9.57
12	14.558	6.08469	0.0708	12.22
13	14.7952	5.98767	0.126	10.65
14	15.248	5.81087	0.126	1.57
15	15.9127	5.56959	0.1417	39.96
16	16.3124	5.43402	0.126	14.23
17	17.0704	5.1944	0.0945	4.66
18	17.401	5.09645	0.0787	9.72
19	17.9713	4.93598	0.0787	21.22

20	19.1654	4.63106	0.1574	100
21	19.7082	4.50472	0.0472	38.71
22	20.3825	4.35718	0.2519	53.34
23	20.9116	4.24814	0.0945	35.2
24	21.6101	4.11237	0.0236	26.08
25	21.9064	4.05406	0.0288	18.18
26	22.825	3.89616	0.126	21.58
27	23.9734	3.71206	0.1102	26.3
28	25.213	3.53229	0.063	16.16
29	25.6078	3.47872	0.1574	45.83
30	26.1883	3.4001	0.096	72.41
31	26.2496	3.3951	0.1102	66.45
32	27.0292	3.29893	0.0315	10.02
33	27.2845	3.26864	0.0945	11.54
34	28.0453	3.18168	0.0945	12.75
35	28.7584	3.10438	0.2834	54.12
36	31.739	2.81933	0.1574	23.96
37	33.0501	2.71042	0.1889	7.5
38	34.0082	2.63622	0.3779	15.87
39	38.834	2.31902	0.2519	8.08
40	40.1797	2.2444	0.5038	6.49
41	41.1887	2.19172	0.3779	6.31
42	43.2606	2.09144	0.2519	7.25
43	44.0245	2.0569	0.1574	9.76
44	52.5873	1.73893	0.768	19.84

Table 3. Structural data for ziprasidone ascorbate form II

No.	Pos. [°2Th.]	d-spacing [A]	FWHM [°2Th.]	Rel. Int. [%]
1	7.2154	12.25177	0.1312	6.12
2	9.4399	9.36905	0.0547	12.07
3	9.6725	9.14423	0.0875	12.57
4	10.8402	8.16174	0.0875	3.57

5	12.2179	7.24432	0.0547	6.95
6	12.9889	6.81601	0.0656	9.46
7	13.8035	6.41554	0.0765	8.43
8	14.4856	6.11493	0.0492	13.07
9	14.8648	5.95978	0.0711	16.04
10	15.2732	5.80134	0.0437	1.64
11	16.3467	5.4227	0.0875	10.75
12	17.1476	5.1712	0.0765	12.32
13	17.719	5.00569	0.0601	21.84
14	17.9232	4.94912	0.0492	18.76
15	18.0934	4.90295	0.0547	23.83
16	18.9212	4.69027	0.0437	15.97
17	20.2581	4.38367	0.0601	57.69
18	20.5717	4.31754	0.0656	5.5
19	21.6581	4.10336	0.0984	16.5
20	22.1317	4.01661	0.0984	13.4
21	22.7161	3.91134	0.12	74.97
22	23.2565	3.82167	0.08	10.41
23	23.9379	3.71441	0.08	100
24	24.4123	3.64329	0.1067	14.2
25	25.2264	3.52753	0.0933	20.88
26	25.4468	3.49747	0.0533	18.59
27	25.9764	3.42735	0.0333	14.43
28	26.8346	3.31966	0.1067	19.29
29	27.299	3.26423	0.1333	10.29
30	27.6603	3.22241	0.1067	6.26
31	28.0491	3.17861	0.0533	4.04
32	28.7283	3.105	0.06	23.86
33	29.2495	3.05085	0.16	15.97
34	29.862	2.98964	0.0933	14.07
35	30.5513	2.92374	0.1067	1.96
36	31.3004	2.85546	0.1067	3.69
37	31.4623	2.84113	0.1067	4.13

38	32.024	2.79257	0.08	4.73
39	32.7378	2.73329	0.1333	2.47
40	33.5233	2.67102	0.1067	2.07
41	33.9047	2.64184	0.1333	5.57
42	34.2555	2.61559	0.1333	6.5
43	34.8401	2.57303	0.0667	3.84
44	36.0347	2.49042	0.1067	3.58
45	36.656	2.44962	0.1333	6.84
46	37.4411	2.40004	0.2133	1.98
47	38.4012	2.34221	0.16	2.9
48	38.829	2.31739	0.1867	5.81
49	39.6229	2.27277	0.1067	2.59
50	40.5626	2.22225	0.1867	6.95
51	41.4386	2.17728	0.1867	4.43
52	43.1964	2.09266	0.1867	13.73
53	43.6308	2.07283	0.0933	8.93
54	44.2091	2.04705	0.2133	11.54
55	45.2436	2.00261	0.2133	2.25
56	46.6124	1.94694	0.2133	7.43
57	47.6552	1.90675	0.1333	6.43
58	48.5716	1.87289	0.24	9.65
59	50.1092	1.81897	0.16	4.42
60	50.9541	1.79077	0.1067	3.93
61	52.628	1.73768	0.2133	2.93

IR spectroscopy

IR spectra of the tested samples were measured using Nicolett 6700 apparatus with a liquid-nitrogen cooled MCT detector. The samples were diluted with KBr (1:100) and pressed at a pressure of 7 tons. Transmittance measurements of the tested samples were taken between 4000-400 cm-1. The resulting IR spectra are presented in fig. 7, 8, 9 and 10.

Thermal analysis

Analysis was made using TA Instruments apparatus. For samples A1, A2, and B thermogravimetry analysis was conducted using TGA 2950 HR V5.4A apparatus in the following conditions: Al crucible, analytical sample 14.765 ÷ 17.953 mg; temperature range between 25ºC and 900ºC, heating rate 10 K/min, N2 atmosphere (100 cm3/min). The same samples were also subjected to DSC analysis using 2920 MDSC V2.6A apparatus, for determining characteristic temperatures. The following conditions were used: Al crucible, analytical sample 4.460 ÷ 6.136 mg, temperature range between 25 and 250ºC, heating rate 10 K/min, N2 atmosphere (50 cm3/min). The DSC curves obtained are given in figures 11, 12 and 13.

NMR spectroscopy

1H and 13C NMR spectra in liquid phase (using DMSO) for ziprasidone succinate and ascorbate were taken using NMR Bruker Avance II 700 MHz spectrometer. The results are given in examples 1 and 2.

Example 4. Solubility analysis of the salts obtained

Below are the solubility results for ziprasidone succinate, ziprasidone base and ziprasidone hydrochloride, obtained in different solutions.

Unexpectedly, it was established that succinate is about 10 times more soluble than the base and about 2 times more soluble than the hydrochloride. A similar rise in solubility was also observed for the ascorbate.

	ρ [µg/ml]		
	ZPR succinate	ZPR base	ZPR HCl
0.1 M HCl / 37°C	9	6	3
acetate buffer pH 4.5 / 37°C	368	156	42
phosphate buffer pH 4.5 / 37°C	35	6	4
phosphate buffer pH 6.8 / 37°C	267	< 0.5	< 0.5
phosphate buffer pH 7.5 / 37°C	< 0.5	< 0.5	< 0.5
water / 37°C	651	0.5	243
	ρ [µg/ml] as per ZPR		
0.1 M HCl / 37°C	7	6	3
acetate buffer pH 4.5 / 37°C	286	156	37
phosphate buffer pH 4.5 / 37°C	27	6	4
phosphate buffer pH 6.8 / 37°C	208	< 0.5	< 0.5
phosphate buffer pH 7.5 / 37°C	< 0.5	< 0.5	< 0.5
water / 37°C	506	0.5	214

Claims

1. A ziprasidone salt selected from a group comprising ziprasidone succinate and ziprasidone ascorbate.

2. A ziprasidone salt according to claim 1, characterized in that it is ziprasidone succinate.

3. A ziprasidone salt according to any one of the preceding claims, characterized in that it is ziprasidone succinate in a solid form.

4. A ziprasidone salt according to any one of the preceding claims, characterized in that it is ziprasidone succinate in crystalline form.

5. A ziprasidone salt according to any one of the preceding claims, characterized in that it is ziprasidone succinate in crystalline form with an X-ray powdered-crystal pattern comprising the following 2θ (±0.2) values measured using CuKα radiation: 8.3400, 12.5200, 16.7063, 21.4300, 22.6379, 23.4339 and 25.1807.

6. A ziprasidone salt according to any one of the preceding claims, characterized in that it is ziprasidone succinate in crystalline form with an X-ray powdered-crystal pattern comprising the following 2θ (±0.2) values measured using CuKα radiation: 8.3400, 12.5200, 16.3644, 16.7063, 19.3528, 21.4300, 22.6379, 23.3682, 23.4339, 24.6158, 25.1807, 25.368, 26.1065, 26.5365, 27.3895, 27.7657, 28.92 and 39.8769.

7. A ziprasidone salt according to any one of the preceding claims, characterized in that it is ziprasidone has a particle size from 5 to 350 microns.

8. A ziprasidone salt according to any one of the preceding claims, characterized in that it is ziprasidone salt has a mean particle size from 10 to 90 microns.

9. A ziprasidone salt according to claim 1, characterized in that it is ziprasidone ascorbate.

10. A ziprasidone salt according to the preceding claim, characterized in that it is ziprasidone ascorbate in a solid form.

11. A ziprasidone salt according to any one of the two preceding claims, characterized in that it is ziprasidone ascorbate in crystalline form.

12. A ziprasidone salt according to any one of the three preceding claims, characterized in that it is crystalline form I with an X-ray powdered-crystal pattern comprising the following 2θ (±0.2) values measured using CuKα radiation: 12.6428, 15.9127, 19.7082, 20.3825, 20.9116 and 25.6078.

13. A ziprasidone salt according to the preceding claim, characterized in that it is crystalline form I with an X-ray powdered-crystal pattern comprising the following 2θ (±0.2) values measured using CuKα radiation: 7.2806, 12.6428, 12.7479, 15.9127, 19.1654, 19.7082, 20.3825, 20.9116, 21.6101, 23.9734, 25.6078, 26.1883; 26.2496, 28.7584 and 31.739.

14. A ziprasidone salt according to claims 9 to 11, characterized in that it is crystalline form II with an X-ray powdered-crystal pattern comprising the following 2θ (±0.2) values measured using CuKα radiation: 18.0934, 20.2581, 21.6581, 22.7161 and 25.2264.

15. A ziprasidone salt according to the preceding claim, characterized in that it is crystalline form II with an X-ray powdered-crystal pattern comprising the following 2θ (±0.2) values measured using CuKα radiation: 14.8648, 17.719, 17.9232, 18.0934, 18.9212, 20.2581, 21.6581, 22.7161, 23.9379, 25.2264, 25.4468, 26.8346, 28.7283, 29.2495 and 29.862.

16. A process for the manufactured of the ziprasidone salt according to claims one, characterised in that the process comprises at least the following steps: contacting

a solution of ziprasidone free base in a solvent system with more than 1.5 equivalents of the acid; isolation of the salt formed; wherein the temperature of the solution of ziprasidone free base in the solvent system is between 20ºC and reflux temperature of the solvent system.

17. A process according to the preceding claim, characterised in that more than 2.5 equivalent of acid are contacted with a solution of ziprasidone free base in a solvent system.

18. A process according to any one of the two preceding claims, characterised in that between more 3.5 and 20 equivalents of acid are contacted with a solution of ziprasidone free base in a solvent system.

19. A process according to any one of the three preceding claims, characterised in that the solvent system comprises one or more polar solvents.

20. A process according to any one of the three preceding claims, characterised in that the solvent system consists essentially in one or more polar solvents.

21. A process according to any one of the four preceding claims, characterised in that the polar solvent is selected from water, an C_1-C_6 alcohol, and C_1-C_6 ether and a C_1-C_9 ketone.

22. A process according to any one of the four preceding claims, characterised in that the polar solvent is selected from water, ethanol, THF or any mixture thereof.

23. A pharmaceutical composition comprising an active substance and at least a pharmaceutically acceptable carrier, characterised in that the active substance is a ziprasidone salt of any one claims 1 to 15, in particular in its crystalline form specified in claims 4 and 11.

24. A pharmaceutical composition according to the preceding claim, characterised in that it is in oral dosage form.

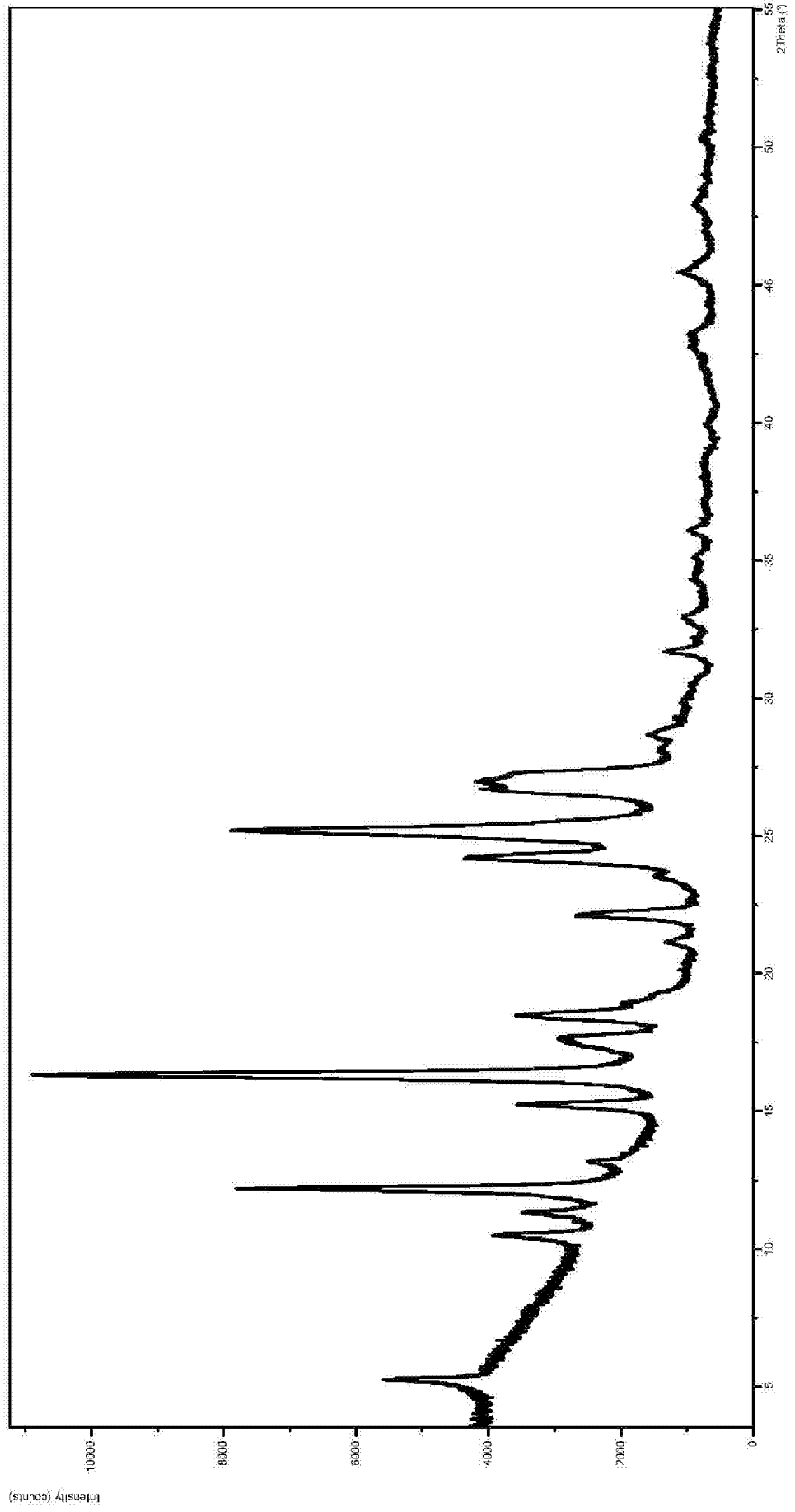
25. A pharmaceutical composition according to the preceding claim, characterised in that the oral dosage form are tablets or capsules.

26. A process for the manufacture of a pharmaceutical composition of any one of the two preceding clauses claims, characterised in that simple admixture or dry granulation techniques are used.

27. The process according to clause 8, comprising at least the steps of: i) Mixing all the ingredients; optionally ii) Compressing the mixture and grinding the product obtained; iii) and recompressing it to form tablets or filling the capsules.

28. The method for the manufacture of the pharmaceutical composition according to any one of the clauses 24 or 25 comprising at least the steps of: a) Preparation of binder solution, preferably with an aqueous solvent, preferably water; b) Spraying the binder solution onto the mixture to form a granulate; c) Drying the granulate at inlet temperature equal to or below 70ºC, preferably below 60ºC; d) Sizing the dried granules, preferably through a 1 mm mesh screen; e) Mixing the granules with the rest of the pharmaceutical acceptable excipients; and f) either compressing the granulate to form a tablet, and optionally coating, or filling the capsules with the granulate.

29. Use of the ziprasidone salt specified in claim 1 to 15, in particular in its crystalline form specified in claims 4 and 11, or the pharmaceutical composition of claims 23 to 25, to manufacture a medicament to treat or prevent mental illnesses, in particular schizophrenia, and their accompanying symptoms.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8000
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4000
2000
0
5
10
15
20
25
30
35
40
45
50
55
2Theta (°)

FIG. 1

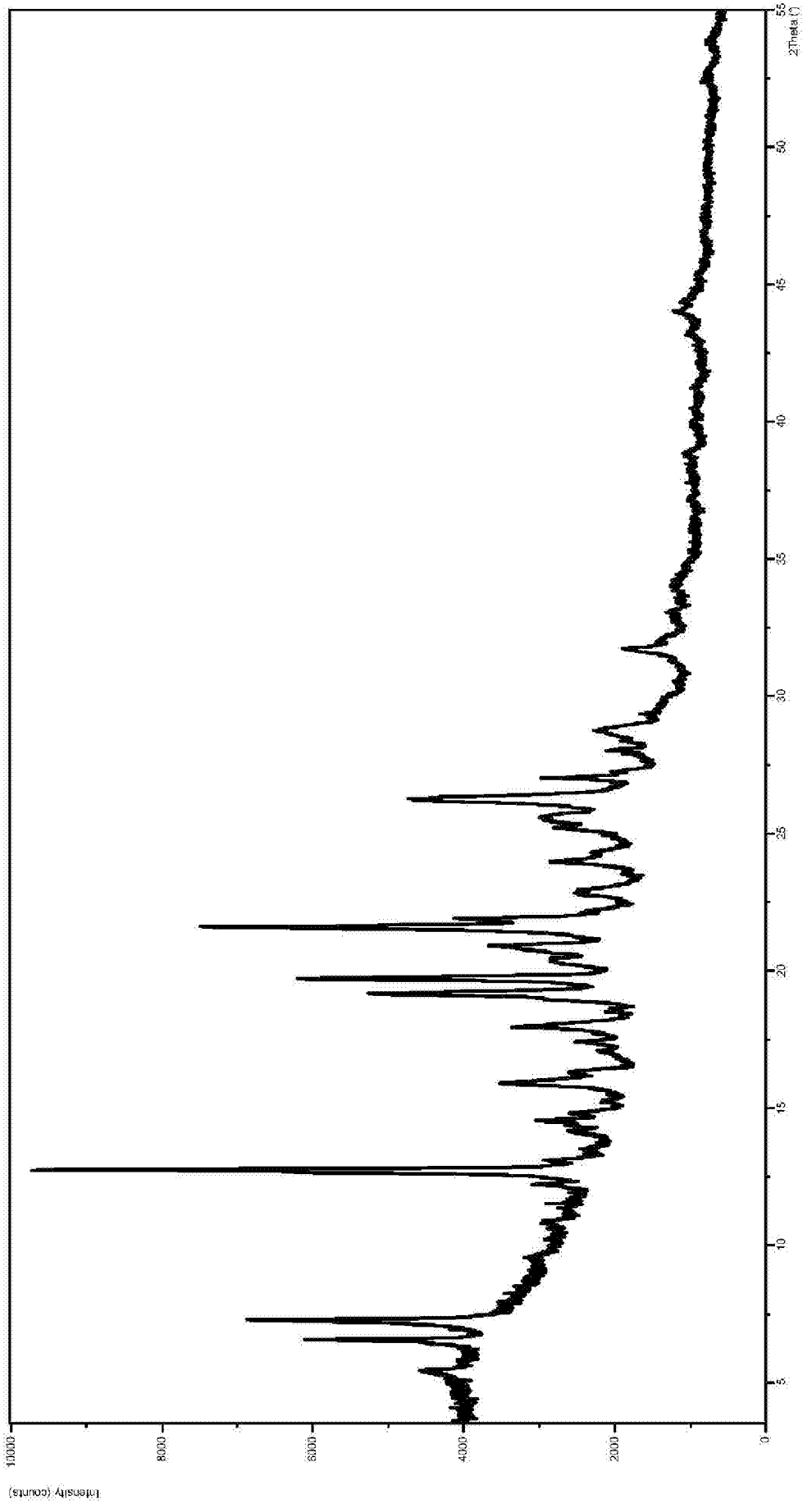

Intensity (counts)
10000
8000
6000
4000
2000
0
5
10
15
20
25
30
35
40
45
50
55
2Theta (°)

FIG. 2

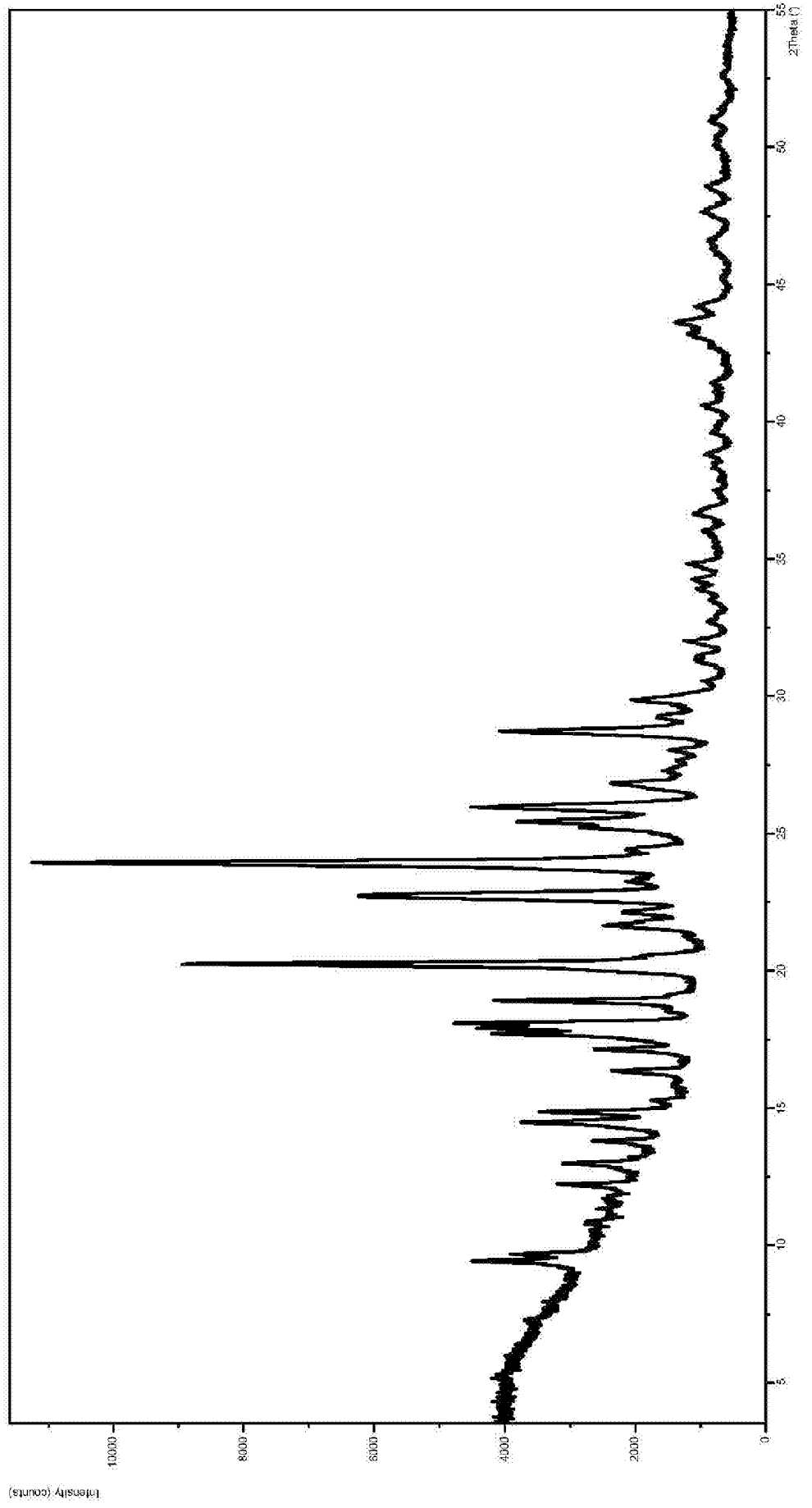

Intensity (counts)
10000
8000
6000
4000
2000
0
5
10
15
20
25
30
35
40
45
50
55
2Theta (°)

FIG. 3

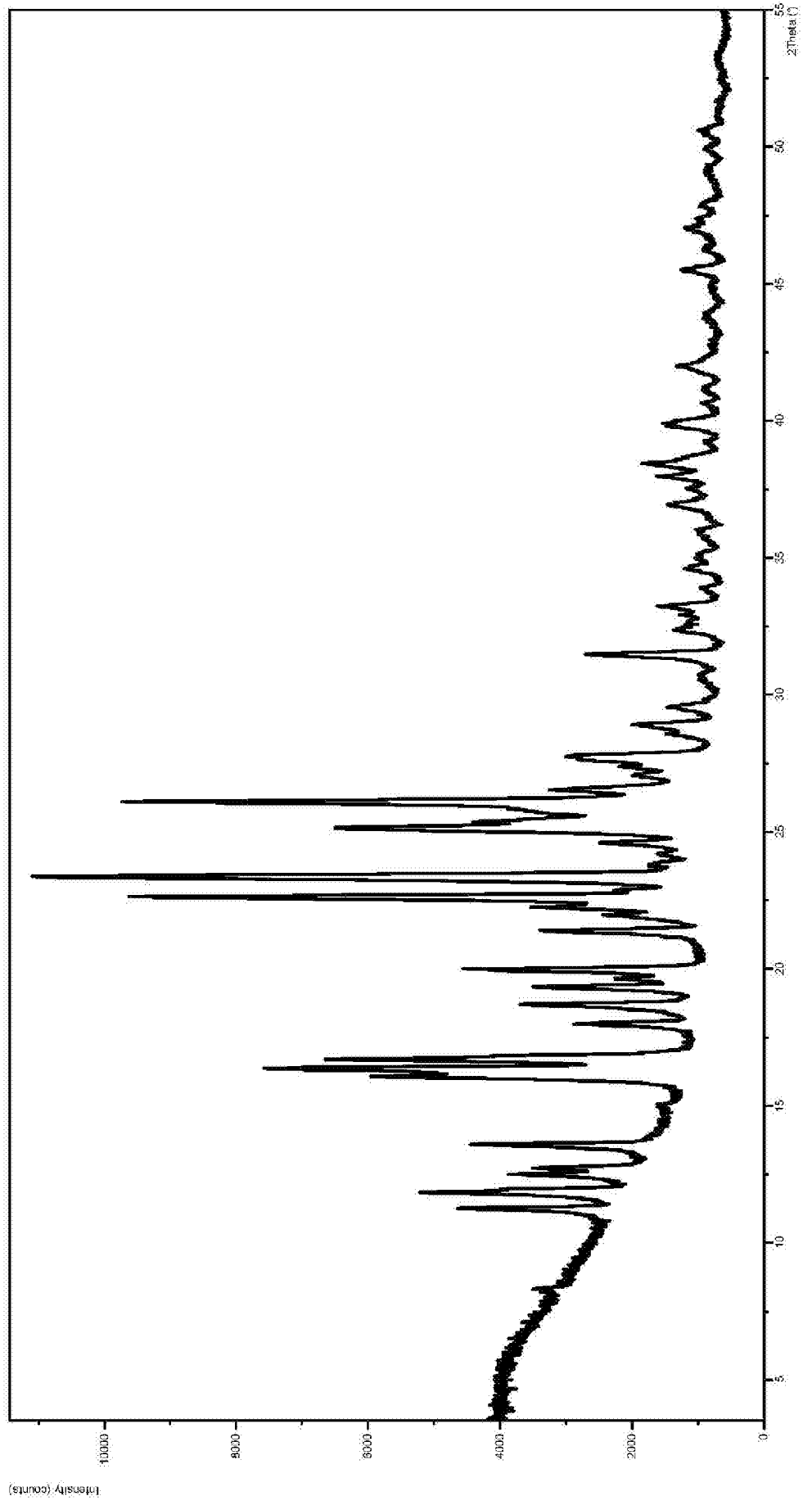

Intensity (counts)
10000
8000
6000
4000
2000
0
5
10
15
20
25
30
35
40
45
50
55
2Theta (°)

FIG. 4

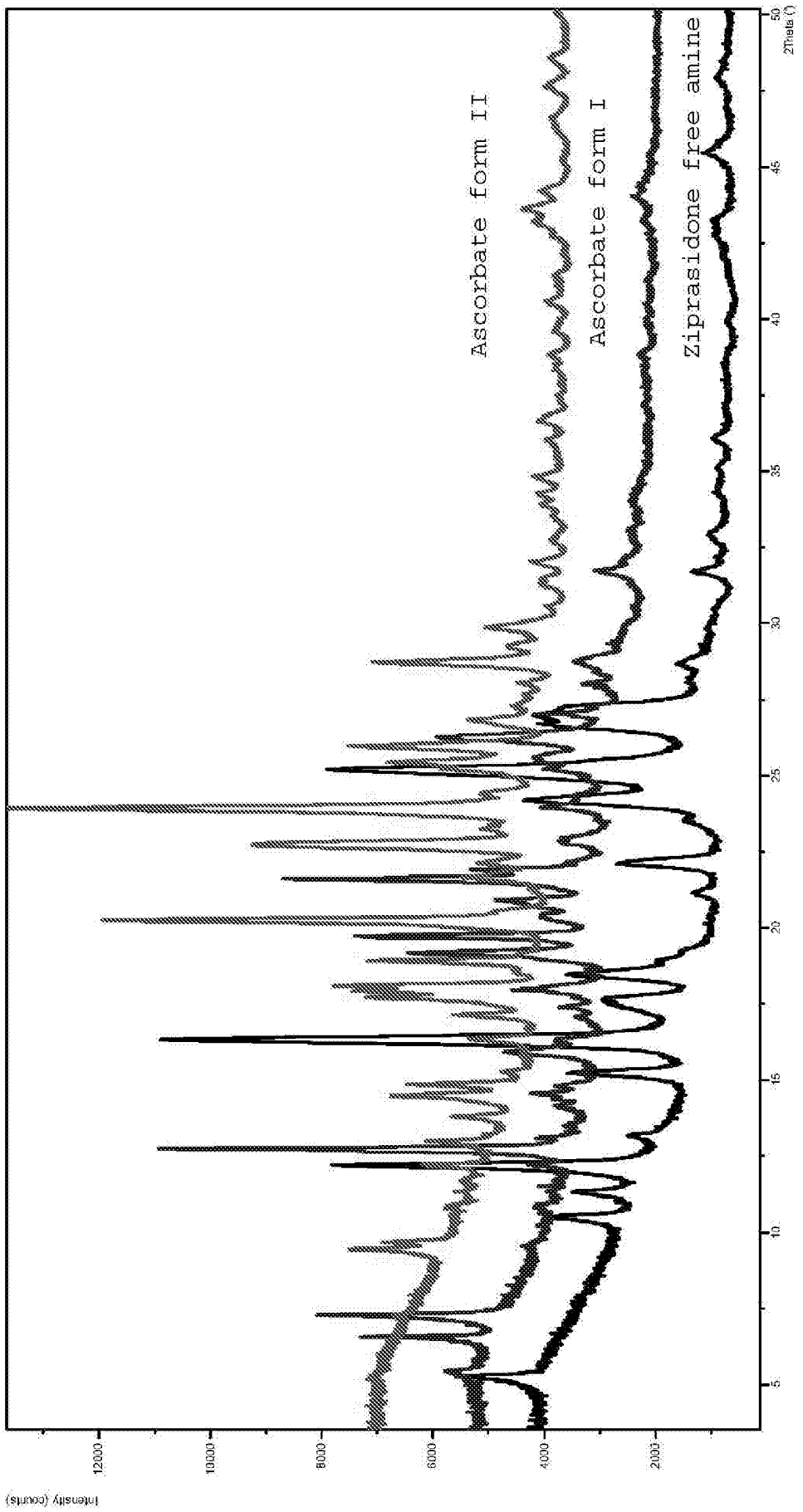

Ascorbate form II
Ascorbate form I
Ziprasidone free amine
Intensity (counts)
2Theta (°)

FIG.5

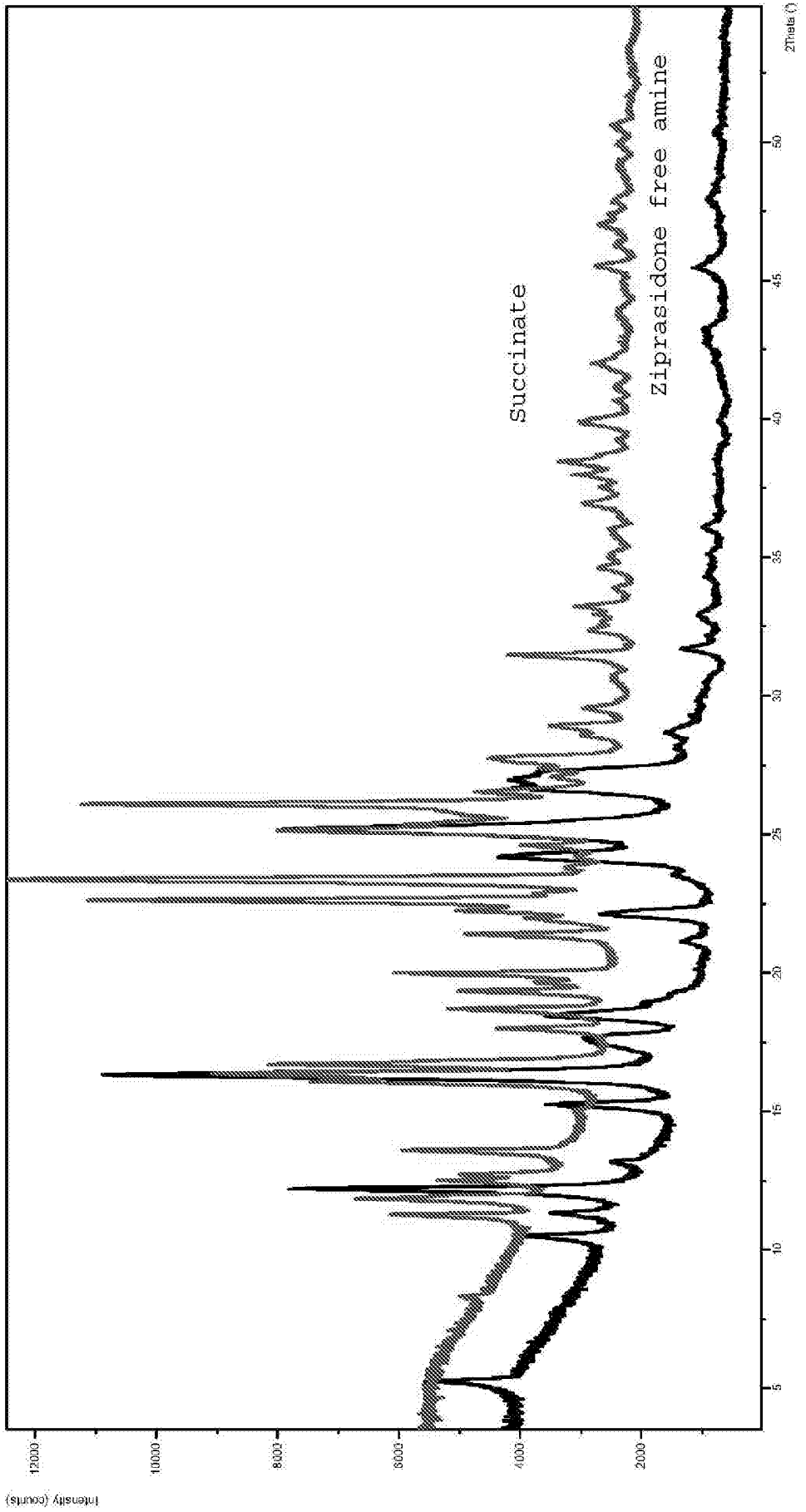

Succinate
Ziprasidone free amine
Intensity (counts)
2Theta (°)
12000
10000
8000
6000
4000
2000
5
10
15
20
25
30
35
40
45
50

FIG. 6

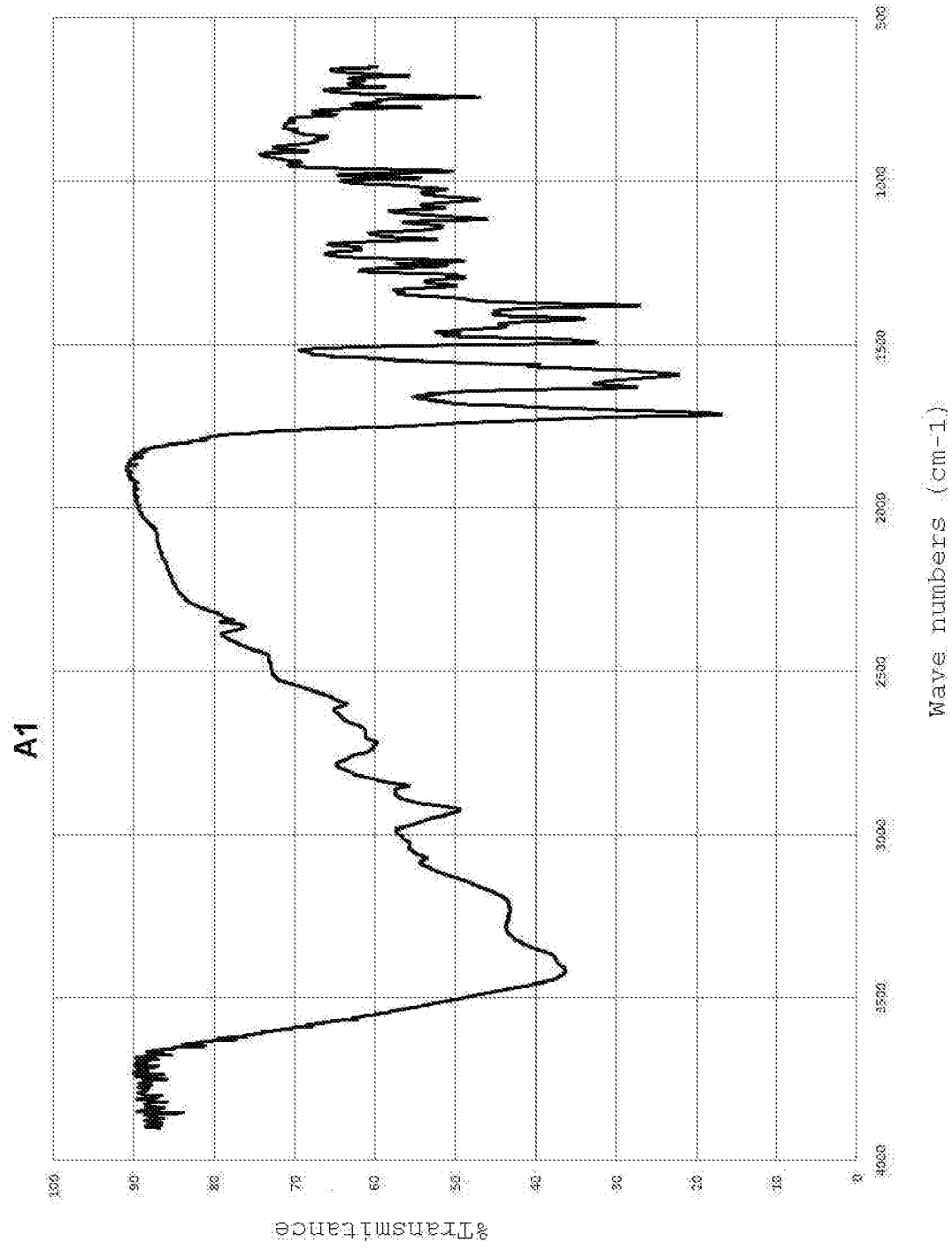

A1
%Transmittance
100
90
80
70
60
50
40
30
20
10
0
4000
3500
3000
2500
2000
1500
1000
500
Wave numbers (cm-1)

FIG. 7

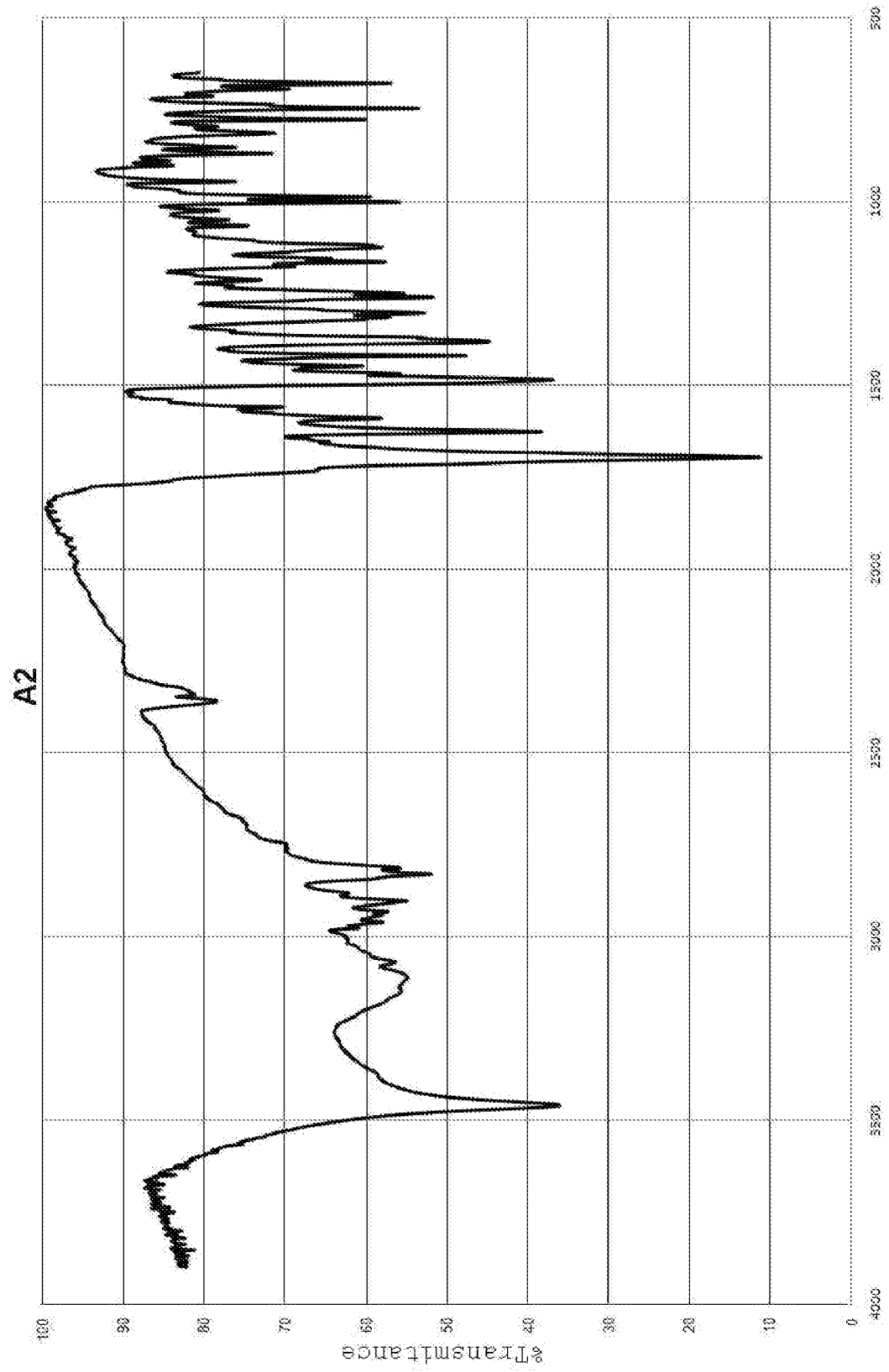

A2
%Transmittance
Wave numbers (cm-1)
100
90
80
70
60
50
40
30
20
10
0
4000
3500
3000
2500
2000
1500
1000
500

FIG.8

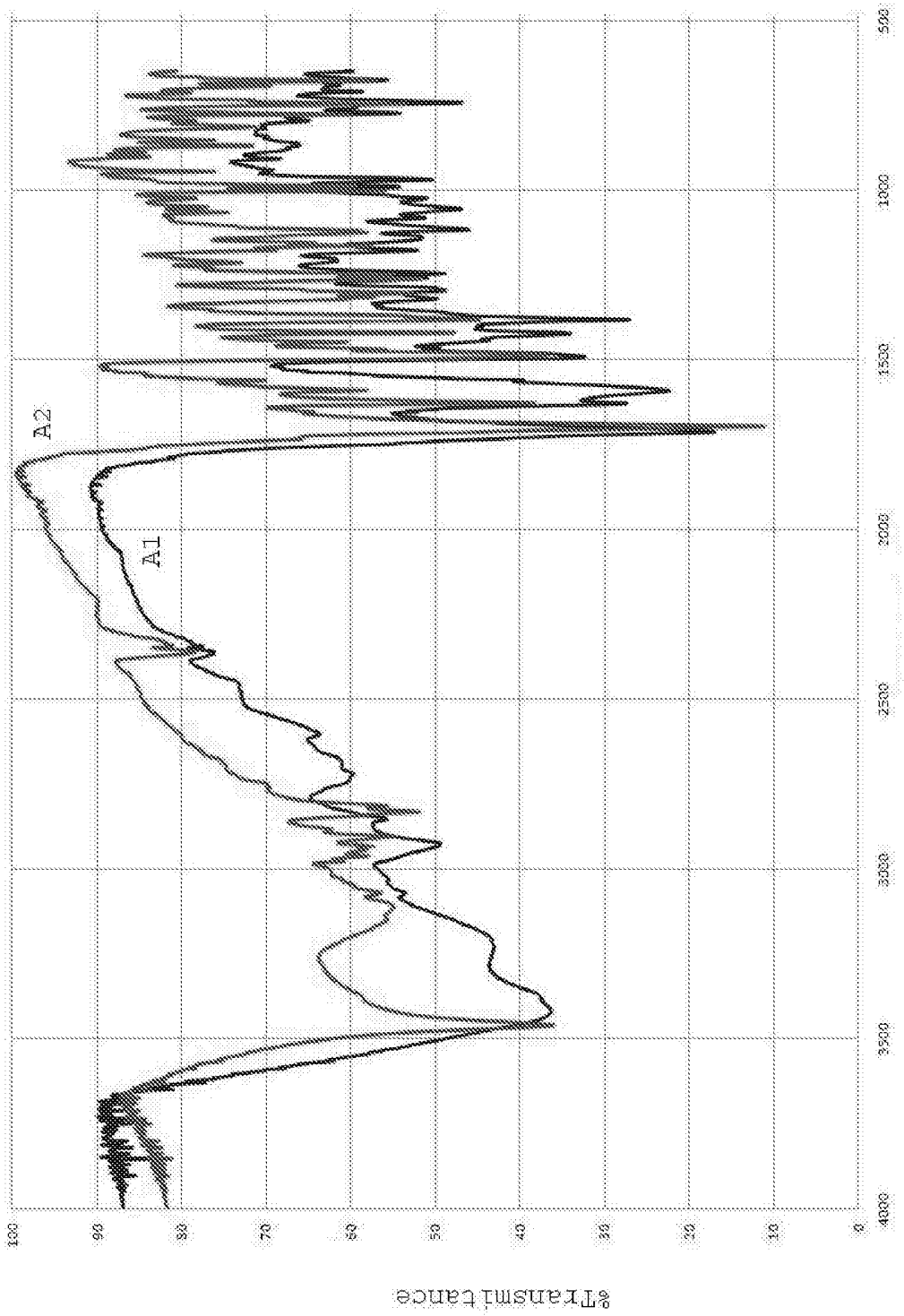

%Transmittance
Wave numbers (cm-1)
A1
A2
100
90
80
70
60
50
40
30
20
10
0
4000
3500
3000
2500
2000
1500
1000
500

FIG. 9

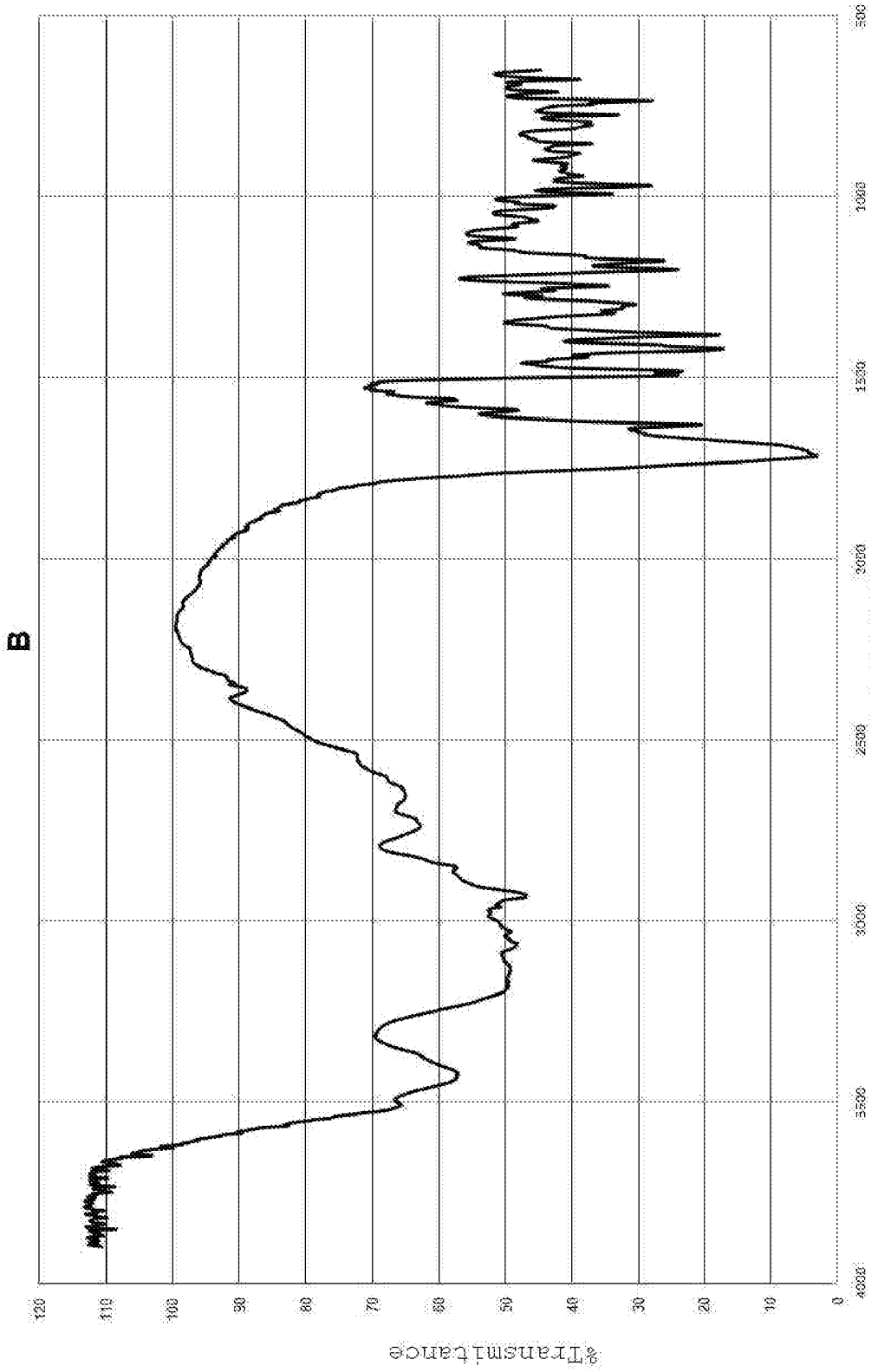


FIG. 10

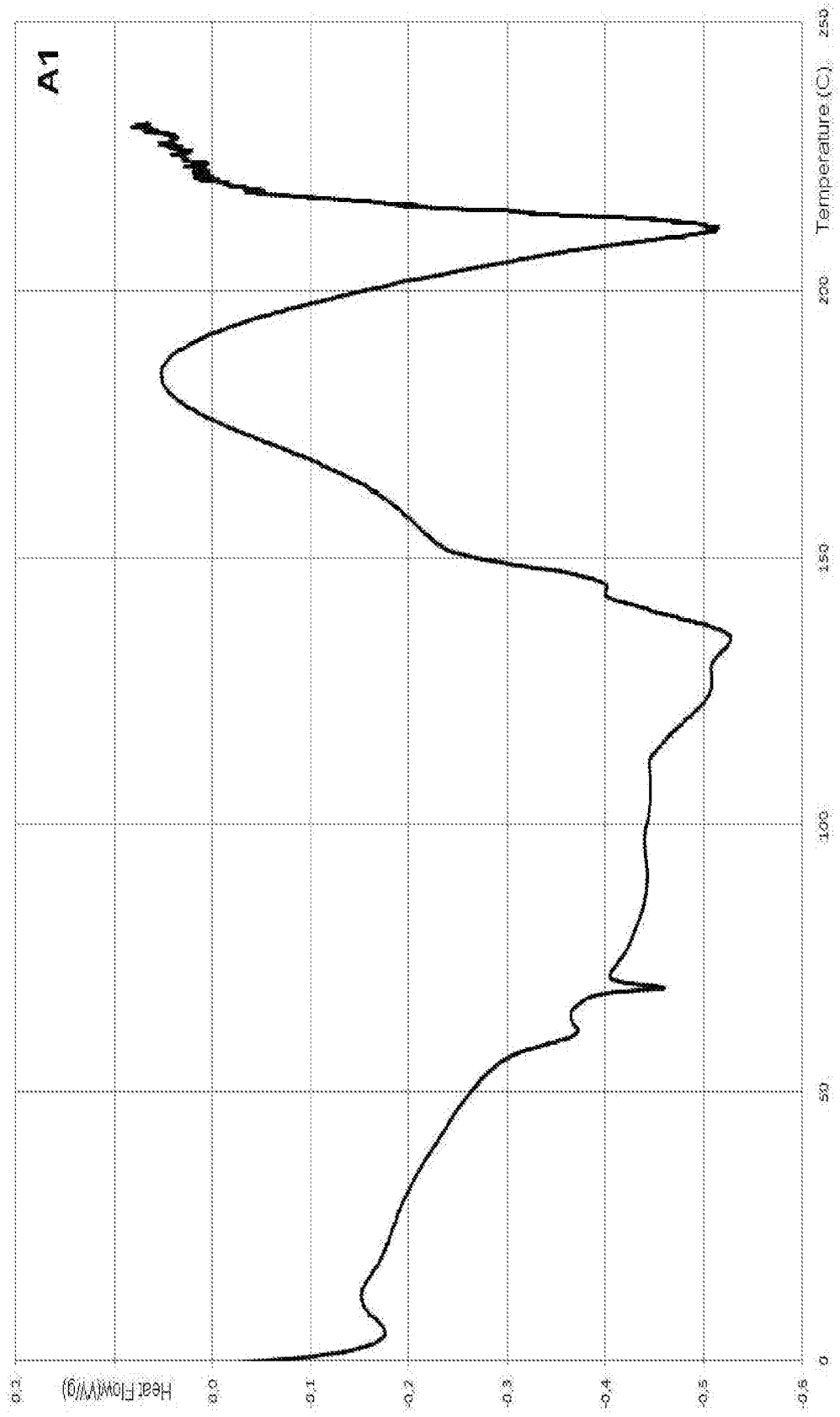

A1
Heat Flow(W/g)
0.2
0.0
-0.1
-0.2
-0.3
-0.4
-0.5
-0.6
0
50
100
150
200
250
Temperature (C)

FIG. 11

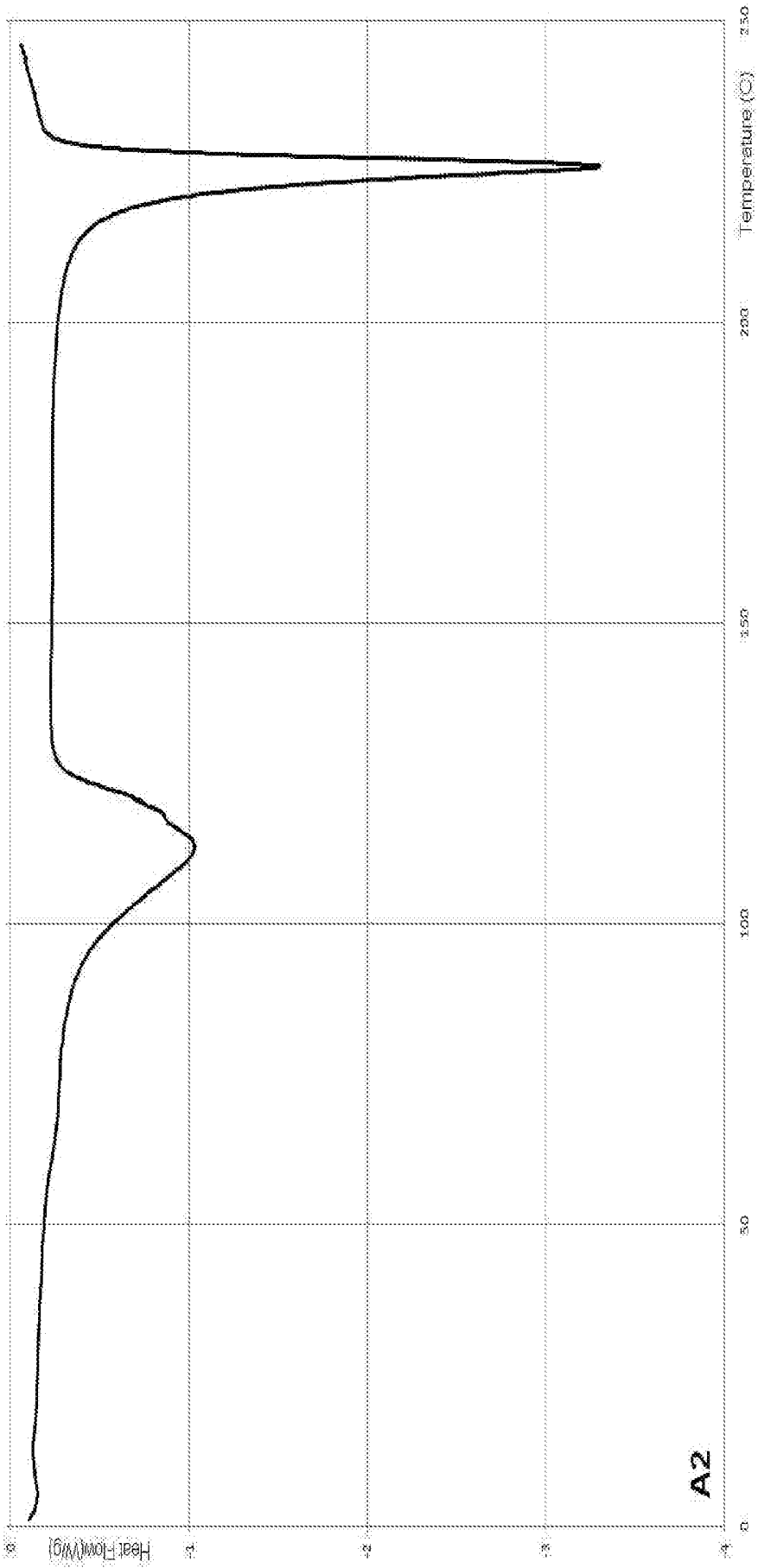


FIG. 12

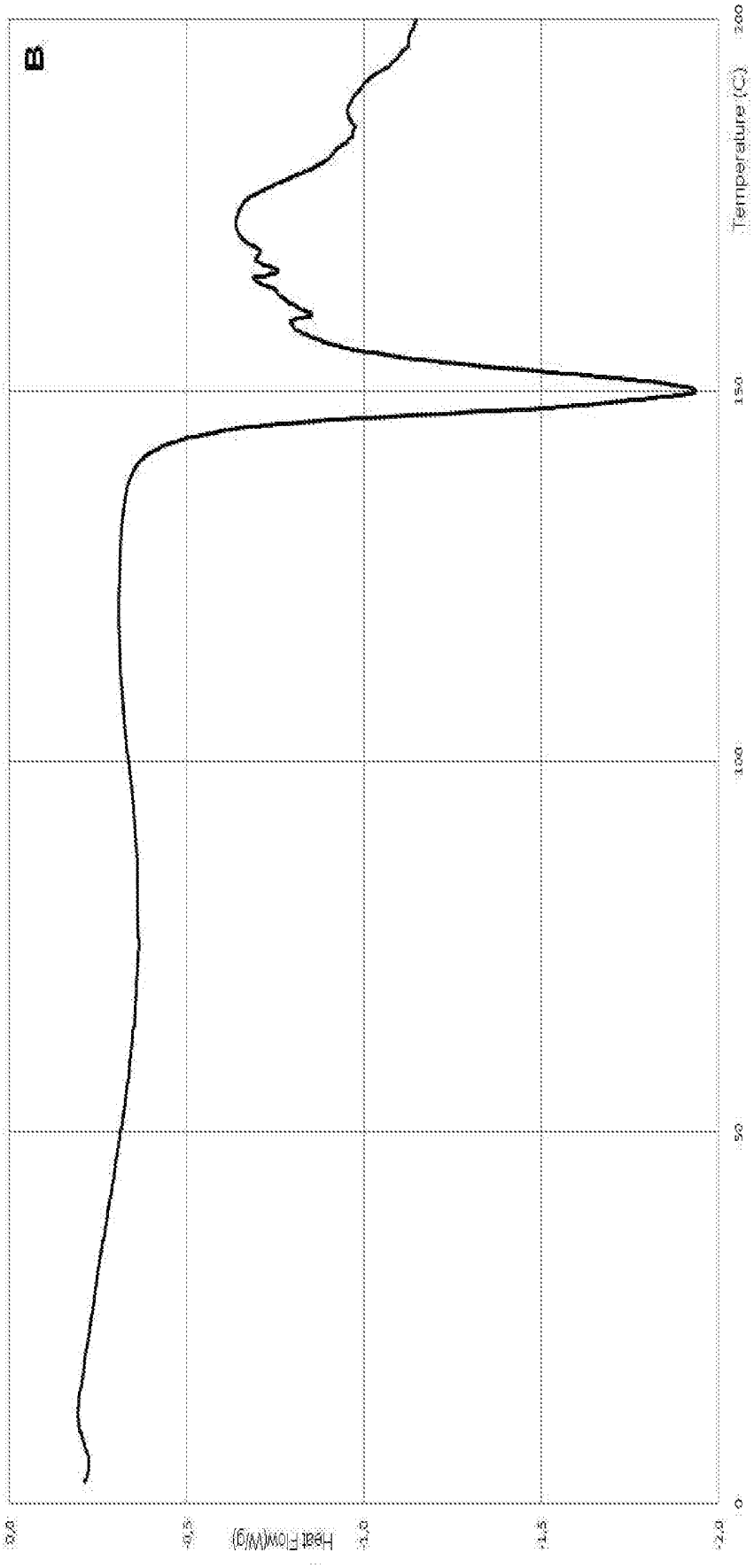
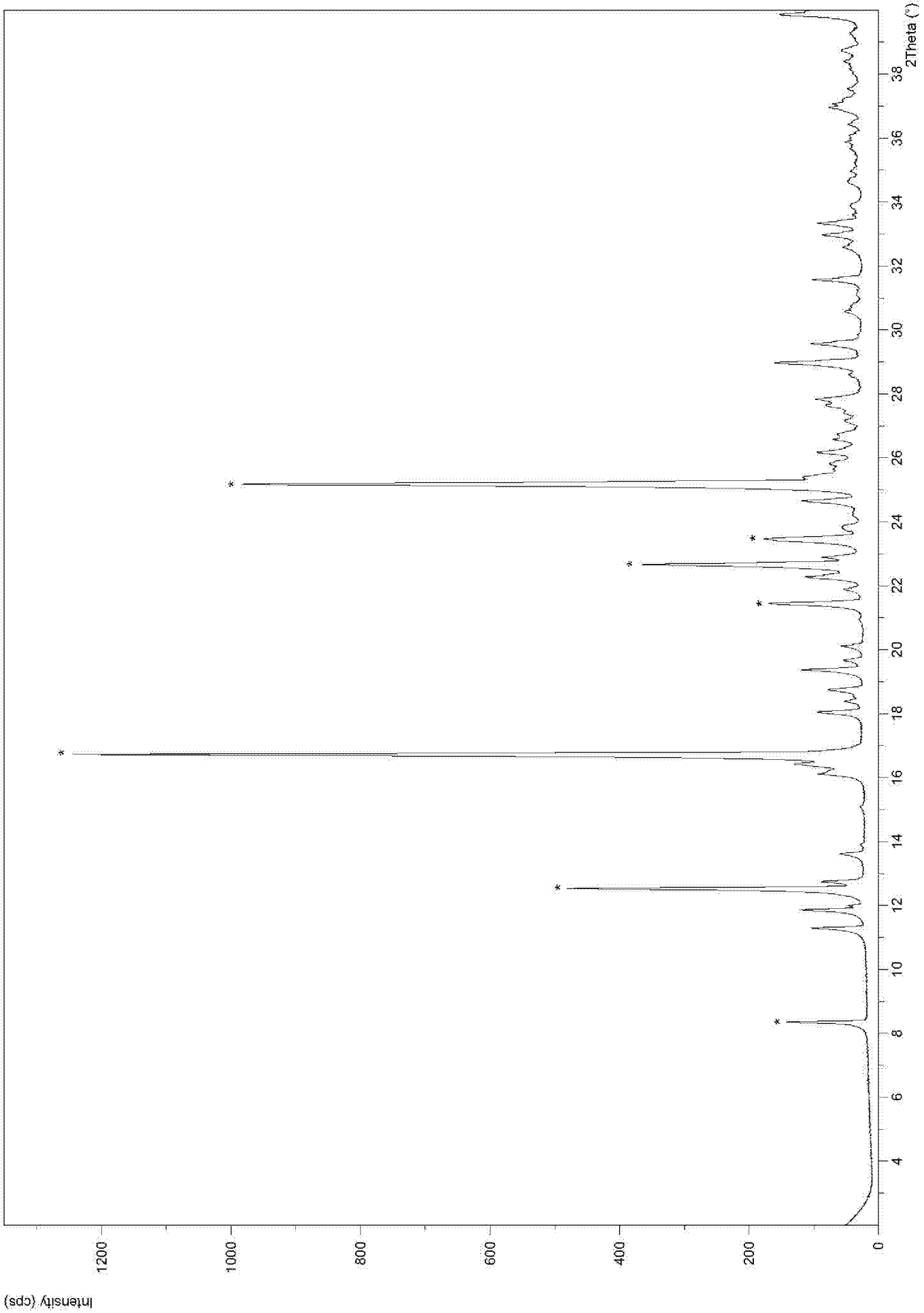


FIG. 13


Intensity (cps)
1200
1000
800
600
400
200
0
2Theta (°)
4
6
8
10
12
14
16
18
20
22
24
26
28
30
32
34
36
38
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*
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