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(54) Title: POLYMORPHS OF CRISABOROLE AND PRODUCTION PROCESSES THEREFOR

(57) Abstract: Provided are crisaborole polymorphs, e.g., crystalline Form A, crystalline Form B, crystalline Form C, crystalline Form D, crystalline Form E, crystalline Form F and processes for producing these polymorphs.

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POLYMORPHS OF CRISABOROLE AND PRODUCTION PROCESSES THEREFOR

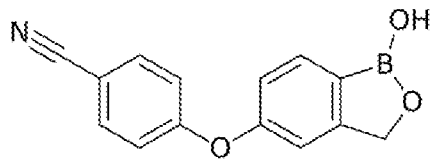
FIELD OF THE INVENTION

[0001] The present invention relates to polymorphs of crisaborole, pharmaceutical compositions thereof and production processes therefor.

BACKGROUND OF THE INVENTION

[0002] Crisaborole (code name AN2728) is a non-steroidal boron-containing drug (a phenoxybenzoxaborole) used for the topical treatment of psoriasis and atopic dermatitis (atopic eczema). Crisaborole is a phosphodiesterase-4 inhibitor acting on the phosphodiesterase 4B gene, which is a member of the type IV, cyclic AMP (cAMP)-specific, cyclic nucleotide phosphodiesterase (PDE) family (PDE4B).

[0003] The chemical name of crisaborole is (5-(4-cyanophenoxy)-1-hydroxy-1,3-dihydro-2,1-benzoxaborole. It has a molecular formula of $C_{14}H_{10}BNO_3$ and a molecular weight of 251.045. Crisaborole is soluble in organic solvents such as isopropanol (about 180 mg/mL) and ethyl acetate (about 97 mg/mL). Crisaborole is sparingly soluble in water (0.2 mg/mL). Crisaborole has the following structural formula:



[0004] Crisaborole is recited in US Patent 8,039,451 (hereinafter the '451 patent) along with pharmaceutical formulation containing it. The synthesis of crisaborole is recited, e.g., in Example 4 of the '451 patent (Compound No. 4.2.q). No polymorphs of crisaborole have been identified in the literature.

[0005] Polymorphs are crystalline materials having the same chemical composition but different molecular packing. Active pharmaceutical ingredients (APIs) may exist in different crystalline forms, each having different physical and chemical properties. While polymorphs are one type of solid form, other solid form

types include solvates, hydrates, and amorphous forms. Solvates are crystalline materials made of the same chemical substance but with molecules of solvent, such as ethanol (ethanolate solvate) incorporated into the molecular packing. When water is the solvent, these solvates are referred to as hydrates. An amorphous form of a substance has the same chemical composition, but lacks the long-range molecular order of the crystalline form of the compound.

[0006] The differences in the physical properties of different crystalline forms stem, e.g., from intermolecular interactions of adjacent chemical moieties in the bulk solid. Accordingly, polymorphs are distinct solids having the same molecular formula with different physical properties compared to other crystalline forms of the same compound.

[0007] Important physical properties of active pharmaceutical compounds are solubility in aqueous media, shelf life, processing properties and particularly the rate of absorption of the drug.

[0008] The skin is a barrier that controls the body's moisture and prevents the penetration of microorganisms because the skin is composed of superficial layers of epidermis and stratum corneum that provide most of the skin barrier properties. The stratum corneum consists of layers of overlapping cell plates containing keratin.

[0009] Usually, drug absorption via the skin is transcellular, that is, a passive diffusion process, which depends on the efficacy of the epidermal barrier and the nature of the drug itself. Drugs having low molecular weight of less than about 800 Daltons with high water and lipid solubility demonstrate the greatest skin penetration.

[0010] Different crystalline forms or polymorphs of the same pharmaceutical compounds have different aqueous solubility hence different absorption profile.

[0011] Thus, there is a need for stable crystalline forms of crisaborole having relatively higher water solubility and for processes for preparing such forms that are not cumbersome, that is, processes suitable for industrial production. The present invention provides such novel crystalline forms and processes for the preparation of the novel crisaborole crystalline forms.

SUMMARY OF THE INVENTION

[0012] The present invention provides novel crisaborole polymorphs referred to hereinafter as crystalline Form A, crystalline Form B, crystalline Form C, crystalline Form D, crystalline Form E and crystalline Form F.

[0013] In an aspect of the present invention, processes for preparing the crisaborole crystalline Form A, crystalline Form B, crystalline Form C, crystalline Form D, crystalline Form E and crystalline Form F are provided.

[0014] The present invention provides pharmaceutical compositions comprising at least one of the polymorphs of crisaborole of the present invention and at least one pharmaceutically acceptable excipient.

[0015] The present invention also provides a process for preparing the pharmaceutical compositions comprising at least one of the crisaborole polymorphs of the present invention by mixing said crisaborole polymorph with at least one pharmaceutically acceptable excipient.

[0016] The present invention further provides methods of using the crisaborole polymorphs of the present invention in the treatment of diseases or conditions including diseases or conditions for which crisaborole provides therapeutic benefit to a mammal having the disease or condition, such as, treatment of psoriasis and atopic dermatitis by topically administering to a subject in need thereof a therapeutically effective amount of at least one of said crisaborole polymorphs.

BRIEF DESCRIPTION OF THE DRAWINGS

[0017] Figure 1 depicts the XRPD pattern of crisaborole Form A.

[0018] Figure 2 depicts the IR spectrum of crisaborole Form A.

[0019] Figure 3 depicts the DSC curve of crisaborole Form A.

[0020] Figure 4 depicts the TGA curve of crisaborole Form A.

[0021] Figure 5 depicts the microscope image of crisaborole Form A.

[0022] Figure 6 depicts the XRPD pattern of crisaborole Form B.

[0023] Figure 7 depicts the IR spectrum of crisaborole Form B.

[0024] Figure 8 depicts the DSC curve of crisaborole Form B.

[0025] Figure 9 depicts the TGA curve of crisaborole Form B.

[0026] Figure 10 depicts the microscope image of crisaborole Form B.

[0027] Figure 11 depicts the XRPD pattern of crisaborole Form C.

[0028] Figure 12 depicts the IR spectrum of crisaborole Form C.

[0029] Figure 13 depicts the DSC curve of crisaborole Form C.

[0030] Figure 14 depicts the TGA curve of crisaborole Form C .

[0031] Figure 15 depicts the microscope image of crisaborole Form C.

[0032] Figure 16 depicts the XRPD pattern of crisaborole Form D.

[0033] Figure 17 depicts the IR spectrum of crisaborole Form D.

[0034] Figure 18 depicts the DSC curve of crisaborole Form D

[0035] Figure 19 depicts the TGA curve of crisaborole Form D.

[0036] Figure 20 depicts the microscope image of crisaborole Form D.

[0037] Figure 21 depicts the XRPD pattern of crisaborole Form E.

[0038] Figure 22 depicts the IR spectrum of crisaborole Form E.

[0039] Figure 23 depicts the DSC curve of crisaborole Form E.

[0040] Figure 24 depicts the TGA curve of crisaborole Form E.

[0041] Figure 25 depicts the microscope image of crisaborole Form E.

[0042] Figure 26 depicts the XRPD pattern of crisaborole Form F.

[0043] Figure 27 depicts the IR spectrum of crisaborole Form F.

[0044] Figure 28 depicts the DSC curve of crisaborole Form F.

[0045] Figure 29 depicts the microscope image of crisaborole Form F.

DETAILED DESCRIPTION OF THE INVENTION

[0046] The inventors of the present invention have surprisingly discovered novel polymorphs of crystalline crisaborole referred to hereinafter as crystalline Form A, crystalline Form B, crystalline Form C, crystalline Form D, crystalline Form E and crystalline Form F.

[0047] The present invention additionally provides processes for preparing the crisaborole crystalline Form A, crystalline Form B, crystalline Form C, crystalline Form D, crystalline Form E and crystalline Form F. The starting material in these processes can be produced by any suitable method, including synthesis methods known in the art. For example, the crisaborole starting material is obtained as described in Example 4 of US Patent 8,039,451.

[0048] The processes of the present invention produce high purity crisaborole crystalline Form A, crystalline Form B, crystalline Form C, crystalline Form D, crystalline Form E and crystalline Form F.

[0049] The X-ray powder diffraction pattern corresponding to crisaborole crystalline Form A is depicted in Fig. 1 and Table 1. The diffraction peaks at 6.0, 14.1, 15.3, 16.0, 18.1, 21.4, 24.7, 24.8, 26.0, 26.1, 26.4, 28.4 and 31.4 ±0.2 degrees 2θ are most characteristic of this form. The X-ray powder diffraction peak positions and intensities exhibited by crystalline Form A are listed in Table 1.

Table 1

No.	Position 2θ degrees	Relative Intensity, %
1	6.0	49
2	12.1	5
3	14.1	53
4	15.3	100
5	16.0	39
6	18.1	53
7	21.4	30
8	23.0	7
9	24.7	28
10	24.8	80
11	26.0	75
12	26.1	68
13	26.4	26
14	28.4	40
15	30.1	8
16	31.4	31
17	31.7	19

[0050] The DSC curve of crystalline Form A is depicted in Fig. 3 showing peak maximum at 136.8°C.

[0051] The IR spectrum and TGA curve of the crystalline Form A are depicted in Figs. 2 and 4 respectively.

[0052] The microscope image of crystalline Form A is depicted in Fig. 5.

[0053] The X-ray powder diffraction pattern corresponding to crystalline Form B is depicted in Fig. 6 and Table 2. The diffraction peaks at 16.7, 17.6, 20.7, 21.3, 21.6, 22.6, 23.2, 24.8, 26.1, 27.0 and 27.6 ± 0.2 degrees 2θ are most characteristic of this form.

Table 2

No.	Position 2θ degrees	Relative intensity, %
1	7.0	6
2	12.3	10
3	14.3	23
4	16.7	66
5	17.6	48
6	18.3	18
7	20.7	100
8	21.3	64
9	21.6	58
10	22.6	91
11	23.2	86
12	24.8	48
13	26.1	47
14	27.0	47
15	27.6	37

[0054] The DSC curve of crisaborole crystalline Form B is depicted in Fig. 8. It exhibits peak maximum at 138.97ºC.

[0055] The IR spectrum and TGA curve of crystalline Form B are depicted in Figs. 7 and 9 respectively.

[0056] The microscope image of crystalline Form B is depicted in Fig. 10.

[0057] The X-ray powder diffraction peak positions and intensities exhibited by crisaborole crystalline Form C are listed in Fig. 11 and Table 3. The diffraction peaks at 5.4, 17.3, 18.6, 20.0, 21.4, 23.1, 24.9, 26.3 and 30.3 ±0.2 degrees 2θ are most characteristic of this form.

Table 3

No.	Position 2θ degrees	Relative Intensity %
1	5.4	33
2	12.4	9
3	13.0	22
4	15.1	6
5	15.7	8
6	16.2	16
7	17.3	88
8	18.6	88
9	20.0	90
10	20.8	21
11	21.4	46
12	23.1	53
13	24.9	58
14	26.3	100
15	27.5	23
16	27.9	25
17	30.3	33

[0058] The DSC curve of crystalline Form C is depicted in Fig. 13. It exhibits peak maximum at 180ºC.

[0059] The IR spectrum and TGA curve of crystalline Form C are depicted in Figs. 12 and 14 respectively.

[0060] The microscope image of crystalline Form C is depicted in Fig. 15.

[0061] The X-ray powder diffraction peak positions and intensities exhibited by crisaborole crystalline Form D are listed in Fig. 16 and Table 4. The diffraction peaks at 14.2, 16.4, 20.0, 24.9 and 26.8 ±0.2 degrees 2θ are most characteristic of this form.

Table 4

No.	Position 2θ degrees	Relative Intensity %
1	7.6	16
2	12.4	12
3	14.2	29
4	16.4	100
5	17.7	16
6	19.0	11
7	20.0	87
8	21.6	7
9	24.9	28
10	25.6	17
11	26.8	78
12	28.0	11
13	28.7	9
14	29.5	11

[0062] The DSC curve of crystalline Form D is depicted in Fig. 18. It exhibits peak maximum at 96.1ºC.

[0063] The IR spectrum and TGA curve of crystalline Form D are depicted in Figs. 17 and 19 respectively.

[0064] The microscope image of crystalline Form D is depicted in Fig. 20.

[0065] Crystalline Form D is a methanolate solvate of crisaborole, which upon overnight evaporation under reduced pressure transforms to form A.

[0066] The X-ray powder diffraction peak positions and intensities exhibited by crisaborole crystalline Form E are listed in Fig. 21 and Table 5. The diffraction peaks at 5.8, and 23.4 ±0.2 degrees 2θ are most characteristic of this form.

Table 5

No.	Position 2θ degrees	Relative Intensity %
1	5.8	100
2	9.4	5
3	11.1	10
4	11.6	3
5	13.4	4
6	14.5	9
7	15.3	4
8	15.6	3
9	15.9	2
10	16.5	4
11	17.5	3
12	18.1	3
13	18.9	3
14	20.0	9
15	22.2	6
16	22.6	4
17	23.4	31
18	24.0	2
19	24.6	6
20	26.1	6
21	26.5	4
22	26.9	2
23	27.7	2
24	28.8	3

[0067] The DSC curve of crystalline Form E is depicted in Fig. 23. It exhibits peak maximum at 85.2ºC.

[0068] The IR spectrum and TGA curve of crystalline Form E are depicted in Figs. 22 and 24 respectively.

[0069] The microscope image of crystalline Form E is depicted in Fig. 25.

[0070] The X-ray powder diffraction peak positions and intensities exhibited by crisaborole crystalline Form F are listed in Fig. 26 and Table 6. The diffraction peaks at 6.9, 20.2, 23.9, 24.7 and 27.6 ±0.2 degrees 2θ are most characteristic of this form.

Table 6

No.	Position 2θ degrees	Relative Intensity %
1	6.9	100
2	11.1	8
3	11.9	2
4	14.0	13
5	15.4	3
6	16.3	5
7	18.4	5
8	19.7	6
9	20.2	20
10	21.0	11
11	21.8	6
12	23.9	41
13	24.7	20
14	27.6	20
15	28.0	7
16	29.0	3
17	30.8	3
18	33.7	3

[0071] The DSC curve of crystalline Form F is depicted in Fig. 28. It exhibits peak maximum at 88.41ºC.

[0072] The IR spectrum of crystalline Form F is depicted in Fig. 27.

[0073] The microscope image of crystalline Form F is depicted in Fig. 29.

[0074] Crystalline Form F is an ethanolate solvate of crisaborole, which contains about 15% ethanol (according to GC analysis). Upon overnight evaporation under reduced pressure, form F transforms to form C.

[0075] The processes of the present invention for preparing crisaborole crystalline Form A, Form B, Form C, Form D, Form E and Form F are selected from crystallization, melting, slurrying or suspending in a solvent, vapor diffusion onto solids, vapor diffusion into solutions, thermal cycling, drying or heating the starting material, evaporation or removal of a solvent or solvents under reduced pressure, exposing the material to accelerated aging conditions, grinding and combination of said methods.

[0076] According to a specific embodiment of the present invention, there is provided a process for preparing the crisaborole crystalline Form A, said process comprising:

dissolving crisaborole in a solvent selected from acetone, acetonitrile, anisole, dichloromethane, ethyl acetate, n-heptane, isopropyl alcohol, isopropyl acetate, methyl ethyl ketone (MEK), methyl isobutyl ketone (MIBK), methyl tert-butyl ether (MTBE), methyl-THF, tetrahydrofuran (THF), toluene, water and mixtures thereof, preferably under heating;

cooling the solution to a temperature of 10°C or lower and optionally mixing to afford crystals of crisaborole Form A or cooling the mixture and optionally seeding and further cooling to a temperature at which crystals of crisaborole Form A begin to precipitate; and

isolating the crystals, optionally washing the crystals and, optionally, drying.

[0077] In a specific embodiment of the present invention, heating is to a temperature of at least 50°C and the solution is left to cool to ambient temperature or cooled to a temperature of 10°C or lower.

[0078] In a specific embodiment of the present invention, cooling is carried out to a temperature of about 0°C for at least 1 hour to 5 hours.

[0079] In another specific embodiment of the present invention, heating is to a temperature of at least 50°C and cooling is carried out to a temperature of 45°C or below, preferably to about 40°C followed by seeding and further cooling to about 0°C.

[0080] In another specific embodiment of the present invention, cooling is carried out for at least 1 hour, preferably for 1.5 hours and the further cooling is carried out for at least 1 hour, preferably for 4 hours.

[0081] According to the present invention, isolating the crystals can be carried out by a method selected from drying, evaporation or removal of a solvent or solvents under reduced pressure, freeze drying or spray drying and filtration.

[0082] According to a specific embodiment of the present invention, the crystals are isolated by filtration.

[0083] According to a specific embodiment of the present invention, the crystals are washed with water.

[0084] According to a specific embodiment of the present invention, a process for preparing crisaborole crystalline Form A comprises the steps of dissolving crisaborole in ethyl acetate, preferably at a W/V ration of 1 g per about 5 mL, at a temperature of about 70°C and cooling the solution to a temperature of about 0°C and stirring for about one hour to afford crystals of crisaborole Form A.

[0085] According to the present invention, using seeding enables improving the yield and purity of the product and seeding may assist in shortening the reaction time.

[0086] According to another specific embodiment of the present invention, a process for preparing crisaborole crystalline Form A includes the steps of dissolving crisaborole in an about 1.3:1 (V/V) mixture of acetone and water at a temperature of about 55°C, preferably at a W/V ratio of 1 g per about 10 mL, cooling to about 40°C or below, seeding and further cooling to a temperature of about 0°C, stirring for about 4 hours to enable precipitation, isolating the crystals by filtration, washing the crystals with water and drying the crystals.

[0087] The present invention provides a process for preparing the crystalline crisaborole Form B, said process comprising:

dissolving crisaborole in a solvent selected from acetone, ethyl acetate, n-hexane, methyl isobutyl ketone (MIBK) and mixtures thereof, optionally under heating and mixing;

evaporating the solution optionally under vacuum and heating to afford crystalline Form B; and

isolating the crystals, optionally washing the crystals and, optionally, drying.

[0088] According to the present invention, isolating the crystals can be carried out by a method selected from drying, evaporation or removal of a solvent or solvents under reduced pressure, freeze drying or spray drying and filtration.

[0089] According to a specific embodiment of the present invention, the crystals are isolated by evaporation or removal of a solvent or solvents under reduced pressure.

[0090] According to a specific embodiment of the present invention, the Form B crystals are washed with hexane.

[0091] According to a specific embodiment of the present invention, a process for preparing crystalline crisaborole Form B comprises the steps of dissolving crisaborole in a (1:1 V/V) mixture of ethyl acetate and n-hexane at a W/V ratio of 1 g per about 100 mL at ambient temperature and evaporating the solvent mixture to afford crystals of crisaborole Form B, washing with n-hexane and drying.

[0092] Also provided by the present invention is a process for preparing crisaborole crystalline Form C, said process comprising:

heating crisaborole to a temperature in which all the solid crisaborole is melted; and

isolating crisaborole Form C upon cooling.

[0093] In a specific embodiment of the present invention, heating is to about 150°C for one hour.

[0094] The present invention provides a process for preparing crystalline crisaborole Form D, said process comprising:

dissolving crisaborole in methanol, preferably under heating and mixing;

allowing the solution to cool to ambient temperature or cooling the solution to 10°C or lower and optionally mixing to afford crystals of crisaborole Form D; and

isolating the crystals and, optionally, drying.

[0095] In a specific embodiment for obtaining Form D, heating is to a temperature of at least 50°C and cooling is carried out to a temperature of 25°C or below, preferably to about 0°C.

[0096] In a specific embodiment of the present invention for obtaining Form D, cooling is carried out for about 1 hour.

[0097] According to a specific embodiment of the present invention, a process for preparing crisaborole crystalline Form D includes the steps of dissolving crisaborole in methanol at a temperature of about 60°C at a W/V ratio of 1 g per about 30 mL, cooling to about 0°C, stirring for about 1 hour to enable precipitation, isolating the crystals by filtration and drying the crystals.

[0098] The present invention provides a process for preparing crisaborole crystalline Form E, said process comprising:

suspending crisaborole in ethanol for at least one hour; and

isolating the crystals by filtration and, optionally, drying.

[0099] In a specific embodiment of the present invention for obtaining Form E, said suspending is at ambient temperature.

[00100] According to a specific embodiment of the present invention, a process for preparing crisaborole crystalline Form E includes the steps of suspending crisaborole in ethanol at a temperature of about 20°C at a W/V ratio of 1 g per about 25 mL for at least one hour, isolating the crystals by filtration and drying the crystals.

[00101] The present invention provides a process for preparing crisaborole crystalline Form F, said process comprising:

dissolving crisaborole in ethanol, optionally at elevated temperature and stirring;

cooling to ambient temperature and mixing; and

isolating the crystals and, optionally, drying.

[00102] In a specific embodiment of the present invention, said dissolving is at a temperature of at least 50°C, preferably at a temperature of about 70°C.

[00103] According to a specific embodiment of the present invention, a process for preparing crisaborole crystalline Form F includes the steps of dissolving crisaborole in ethanol at a temperature of about 70°C at a W/V ratio of 1 g per about 10 mL, cooling with stirring to enable precipitation, isolating the crystals by filtration and drying the crystals.

[00104] The present invention provides pharmaceutical compositions comprising at least one polymorph of the present invention, i.e., crystalline Form A, crystalline Form B, crystalline Form C, crystalline Form D, crystalline Form E and crystalline Form F of crisaborole and at least one pharmaceutically acceptable excipient.

[00105] The present invention provides a process for preparing said pharmaceutical compositions by mixing at least one polymorph with at least one pharmaceutically acceptable excipient selected from absorption accelerators, binders, bulking agents, carriers, diluents, disintegrants, fillers, lubricants, surface-active agents, wetting agents and the like.

[00106] The pharmaceutical compositions of the present invention are prepared in the form of tablets, pills, powders, liquids, emulsions, granules, capsules, suppositories, injection preparations (solutions and suspensions), and the like.

[00107] The present invention further provides methods of using the crystalline forms of crisaborole of the present invention in the treatment of diseases or conditions including diseases or conditions for which crisaborole provides therapeutic benefit to a mammal having the disease or condition, such as topical treatment of psoriasis and atopic dermatitis, by administering to a subject in need thereof a therapeutically effective amount of said crisaborole forms.

EXAMPLES

[00108] The following examples further illustrate the invention but should not be construed as in any way limiting its scope.

[00109] Example 1- Preparation of crisaborole crystalline Form A by crystallization from ethyl acetate.

[00110] Ethyl acetate (15 mL) was added to crisaborole (3 g) and the mixture was heated to 70°C. The thus formed solution was cooled for an hour from a temperature of 70°C to 0°C, and after reaching 0°C, the mixture was stirred at 0°C for an hour. The precipitated crystals were collected by filtration and dried at 50°C under reduced pressure to afford crisaborole crystalline Form A (1.8 g, 60% yield) containing 3300 ppm residual ethyl acetate.

Example 2- Preparation of crisaborole crystalline Form A by crystallization from acetone and water

[00111] Acetone (87.5 mL) and water (67.5 mL) were added to crisaborole (15 g) and heated to 55°C. The thus formed solution was cooled under stirring from 55°C to 40°C for about 1.5 hours and seeded with Form A crystals. The solution was further

cooled for 4 hours to 0°C under stirring and after reaching 0°C, the mixture was further stirred at 0°C for 1 hour. The precipitated crystals were collected by filtration, washed with water (30 mL), and dried at 50°C under reduced pressure to afford crystalline Form A (13 g, 86.7% yield) containing 630 ppm of residual acetone.

Example 3- Preparation of crisaborole crystalline Form B by evaporation

[00112] Ethyl acetate (50 mL) and n-hexane (50 mL) were added to crisaborole (1 g) and stirred for 30 minutes at ambient temperature to complete dissolution. The thus formed solution was evaporated at 50°C to dryness. The precipitated crystals were collected, washed with hexane (20 mL), and dried at 50°C under reduced pressure to afford crystalline Form B (0.6 g, 60% yield).

Example 4- Preparation of crisaborole crystalline Form C by melting

[00113] Crisaborole crystalline Form B (0.2 g) was heated to 150°C in a tray oven for an hour. The obtained crystals were collected to afford crystalline Form C (0.2 g, 100% yield).

Example 5- Preparation of crisaborole crystalline Form D by crystallization from methanol

[00114] Methanol (30 mL) was added to crisaborole (1g) and heated to 60°C. The thus formed solution was cooled from 60°C to 0°C during 1 hour, and after reaching 0°C, the mixture was stirred at 0°C for 1 hour. The precipitated crystals were collected by filtration to afford crystalline Form D (0.8 g, 80% yield) containing 1072 ppm of residual methanol. Upon overnight evaporation under reduced pressure Form D transformed to form A.

Example 6- Preparation of crisaborole crystalline Form E by suspending in ethanol at ambient temperature

[00115] Ethanol (5 mL) was added to crisaborole Form B (0.2 g). The thus formed suspension was stirred for 4 days at ambient temperature. The precipitated crystals were collected by filtration to afford crystalline Form E (0.15 g, 75%).

Example 7- Preparation of crisaborole crystalline Form F by crystallization from ethanol

Ethanol (10 mL) was added to crisaborole (1g) and heated to a temperature of 70°C. The solution was cooled to 25°C for about an hour and stirred at 25°C for hour. The precipitated crystals were collected by filtration to afford crystalline Form F (0.5 g, 50% yield). Crystalline Form F contains about 15% ethanol (according to GC analysis). Upon overnight evaporation under reduced pressure, form F transformed to form C.

CLAIMS

1. Crisaborole crystalline Form A characterized by an X-ray diffraction pattern exhibiting characteristic diffraction peaks at 6.0, 14.1, 15.3, 16.0, 18.1, 21.4, 24.7, 24.8, 26.0, 26.1, 26.4, 28.4 and 31.4 ±0.2 degrees 2θ.

2. The crystalline Form A of claim 1 having the X-ray powder diffraction peak positions and intensities as depicted in Fig. 1 and Table 1.

3. The crystalline Form A of claim 1 further characterized by DSC curve as depicted in Fig. 3 exhibiting peak maximum at 136.8°C.

4. A process for preparing the crisaborole crystalline Form A of claim 1, comprising:

dissolving crisaborole in a solvent selected from acetone, acetonitrile, anisole, dichloromethane, ethyl acetate, n-heptane, isopropyl alcohol, isopropyl acetate, methyl ethyl ketone (MEK), methyl isobutyl ketone (MIBK), methyl tert-butyl ether (MTBE), methyl-THF, tetrahydrofuran (THF), toluene, water and mixtures thereof, preferably under heating;

cooling the solution to a temperature of 10°C or lower and optionally mixing to afford crystals of crisaborole Form A or cooling the solution and optionally seeding and further cooling to a temperature at which crystals of crisaborole Form A begin to precipitate; and

isolating the crystals, optionally washing the crystals and, optionally, drying.

5. The process of claim 4, wherein heating is to a temperature of at least 50°C and the solution is left to cool to ambient temperature or cooled to a temperature of 10°C or lower.

6. The process of claim 4, wherein cooling is carried out for at least 1 hour to 5 hours.

7. The process of claim 4, wherein heating is to a temperature of at least 50°C and cooling is carried out to a temperature of 45°C or below, preferably to about 40°C and the further cooling is to about 0°C.

8. The process of claim 4, wherein cooling is carried out for at least 1 hour, preferably for 1.5 hours and the further cooling is carried out for at least 1 hour, preferably for 4 hours.

9. The process of claim 4, wherein isolating the crystals is carried out by a method selected from drying, evaporation or removal of a solvent or solvents under reduced pressure, freeze drying or spray drying and filtration.

10. The process of claim 9, wherein the crystals are isolated by filtration.

11. Crisaborole crystalline Form B characterized by an X-ray powder diffraction exhibiting characteristic diffraction peaks at 16.7, 17.6, 20.7, 21.3, 22.1, 21.6, 22.6, 23.2, 24.8, 26.1, 27.0 and 27.6 ± 0.2.

12. The crystalline Form B of claim 11 having the X-ray powder diffraction peak positions and intensities as depicted in Fig. 6 and Table 2.

13. The crystalline Form B of claim 11 further characterized by a DSC curve as depicted in Fig. 8, exhibiting peak maximum at 138.97ºC.

14. A process for preparing the crystalline Form B of claim 11, said process comprising:

dissolving crisaborole in a solvent selected from acetone, ethyl acetate, n-hexane, methyl isobutyl ketone (MIBK) and mixtures thereof, preferably under heating and mixing;

evaporating the mixture optionally under vacuum and heating; and

isolating the crystals of Form B optionally washing the crystals and, optionally, drying.

15. The process of claim 14, wherein isolating the crystals is carried out by a method selected from drying, evaporation or removal of a solvent or solvents under reduced pressure, freeze drying or spray drying and filtration.

16. The process of claim 15, wherein the crystals are isolated by evaporation or removal of a solvent or solvents under reduced pressure.

17. Crisaborole crystalline Form C characterized by an X-ray powder diffraction exhibiting characteristic diffraction peaks at 5.4, 17.3, 18.6, 20.0, 21.4, 23.1, 24.9, 26.3 and 30.3 ±0.2 degrees 2θ.

18. The crystalline Form C of claim 17 having the X-ray powder diffraction peak positions and intensities as depicted in Fig. 11 and Table 3.

19. The crystalline Form C of claim 17 further characterized by a DSC curve as as depicted in Fig. 13 exhibiting peak maximum at 180ºC.

20. A process for preparing the crisaborole crystalline Form C of claim 17, said process comprising:

heating crisaborole to a temperature in which all the solid cristaborole is melted; and

isolating crisaborole Form C upon cooling.

21. The process of claim 20, wherein heating is to a temperature of 150°C for one hour.

22. Crisaborole crystalline Form D characterized by an X-ray diffraction pattern exhibiting characteristic diffraction peaks at 14.2, 16.4, 20.0, 24.9 and 26.8 ±0.2 degrees 2θ.

23. The crystalline Form D of claim 22 having the X-ray powder diffraction peak positions and intensities as depicted in Fig. 16 and Table 4.

24. The crystalline Form D of claim 22 further characterized by DSC curve as depicted in Fig. 18 exhibiting peak maximum at 96.1°C.

25. A process for preparing the crisaborole crystalline Form D of claim 22, said process comprising:

dissolving crisaborole in methanol, preferably under heating and mixing;

allowing the solution to cool to ambient temperature or cooling the solution to 10°C or lower and optionally mixing to afford crystals of Form D; and

isolating the crystals and, optionally, drying.

26. The process of claim 25, wherein heating is to a temperature of at least 50° and cooling is carried out to a temperature of 25°C or below, preferably to about 0°C.

27. The process of claim 25, wherein cooling is carried out for about 1 hour.

28. Crisaborole crystalline Form E characterized by an X-ray diffraction pattern exhibiting characteristic diffraction peaks at 5.8, and 23.4 ±0.2 degrees 2θ.

29. The crystalline Form E of claim 28 having the X-ray powder diffraction peak positions and intensities as depicted in Fig. 21 and Table 5.

30. The crystalline Form E of claim 28 further characterized by DSC curve as depicted in Fig. 23 exhibiting peak maximum at 85.2°C.

31. A process for preparing the crisaborole crystalline Form E of claim 28, comprising:

suspending crisaborole in ethanol for at least one hour; and

isolating the crystals of Form E by filtration and, optionally, drying.

32. The process of claim 31, wherein said suspending is at at ambient temperature.

33. Crisaborole crystalline Form F characterized by an X-ray diffraction pattern exhibiting characteristic diffraction peaks at 6.9, 20.2, 23.9, 24.7 and 27.6±0.2 degrees 2θ.

34. The crystalline Form F of claim 33 having the X-ray powder diffraction peak positions and intensities as depicted in Fig. 26 and Table 6.

35. The crystalline Form F of claim 33 further characterized by DSC curve as depicted in Fig. 28 exhibiting peak maximum at 88.4°C.

36. A process for preparing crisaborole crystalline Form F of claim 33, said process comprising:

dissolving crisaborole in ethanol, optionally at elevated temperature and stirring;

cooling to ambient temperature and mixing; and

isolating the crystals and, optionally, drying.

37. The process of claim 36, wherein said dissolving is at a temperature of at least 50°C, preferably at a temperature of about 70°C.

38. A pharmaceutical composition comprising crisaborole crystalline Form A, crystalline Form B, crystalline Form C, crystalline Form D, crystalline Form E or crystalline Form F and at least one pharmaceutically acceptable excipient.

39. The use of crisaborole crystalline Form A, crystalline Form B, crystalline Form C, crystalline Form D, crystalline Form E or crystalline Form F for the preparation of a pharmaceutical composition comprising at least one of said crisaborole crystalline forms and at least one pharmaceutically acceptable excipient for the treatment of psoriasis and atopic dermatitis.

Fig. 1

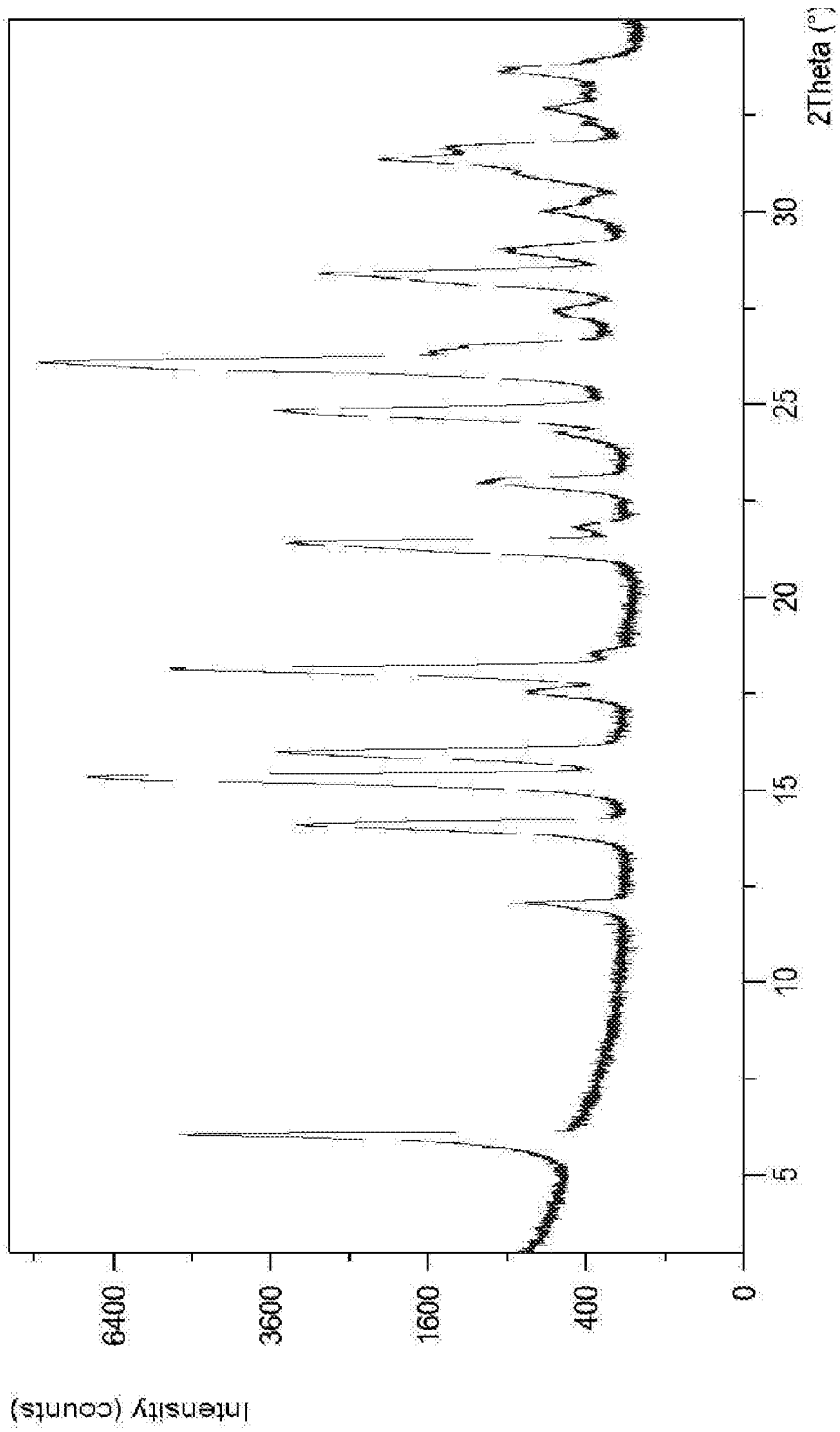


Fig. 2

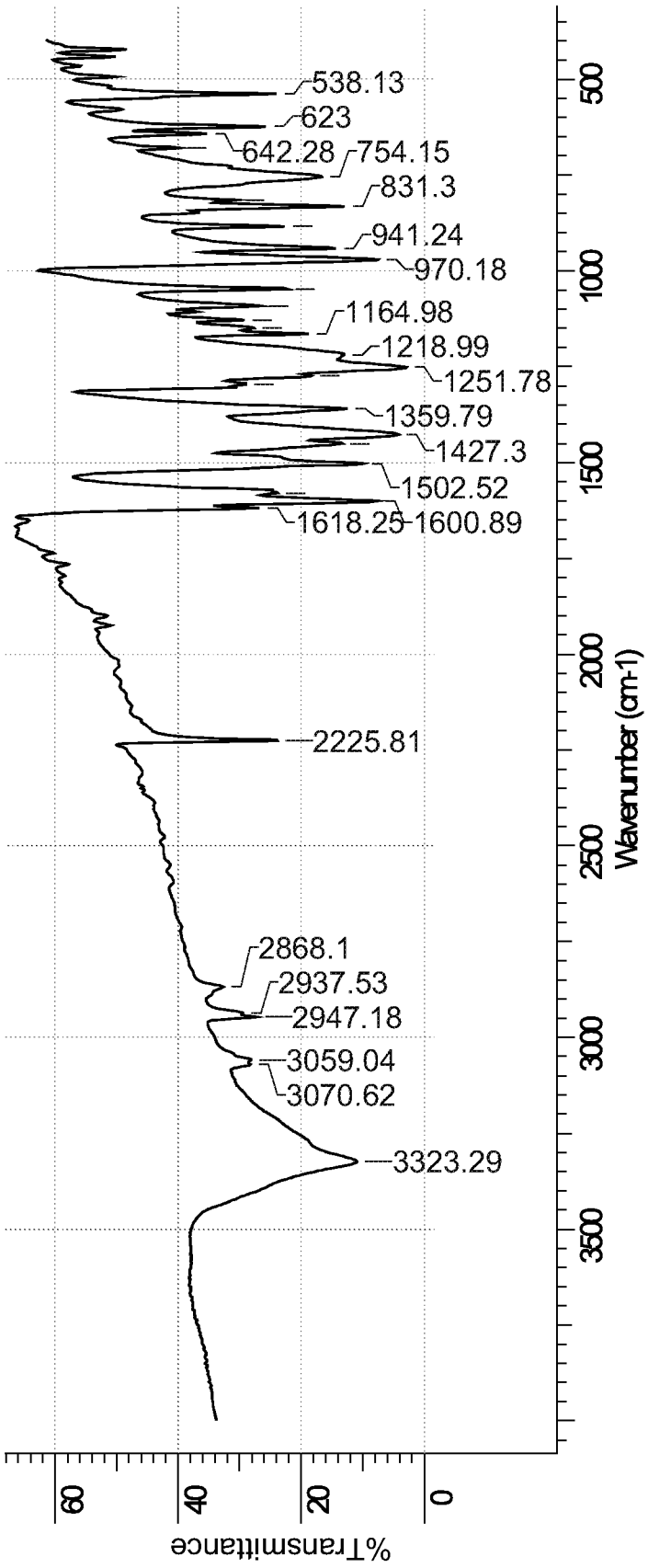

538.13
623
642.28
754.15
831.3
941.24
970.18
1164.98
1218.99
1251.78
1359.79
1427.3
1502.52
1618.25
1600.89
2225.81
2868.1
2937.53
2947.18
3059.04
3070.62
3323.29
Wavenumber (cm-1)
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1000
1500
2000
2500
3000
3500
%Transmittance
0
20
40
60

Fig. 3

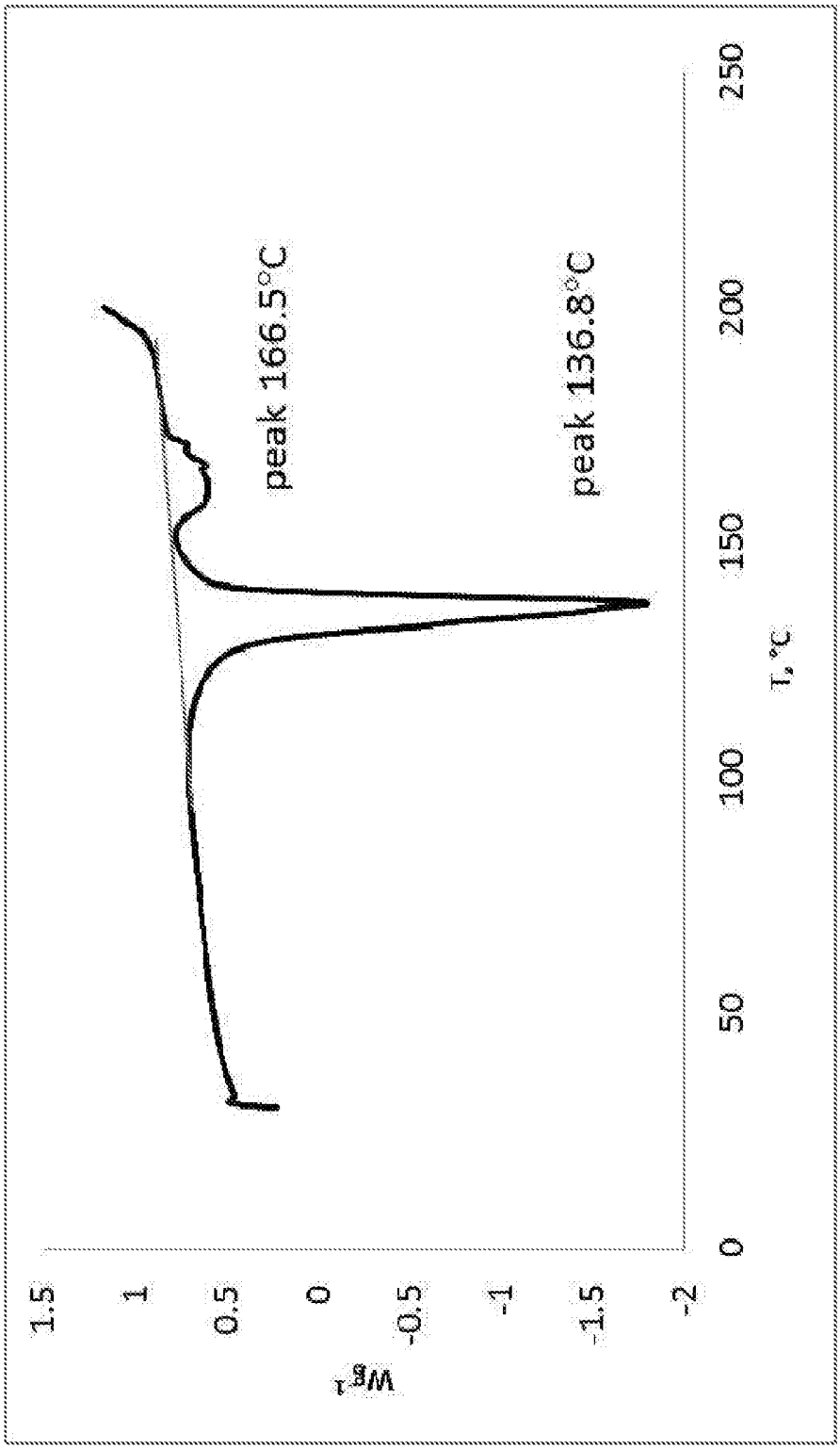


Fig. 4

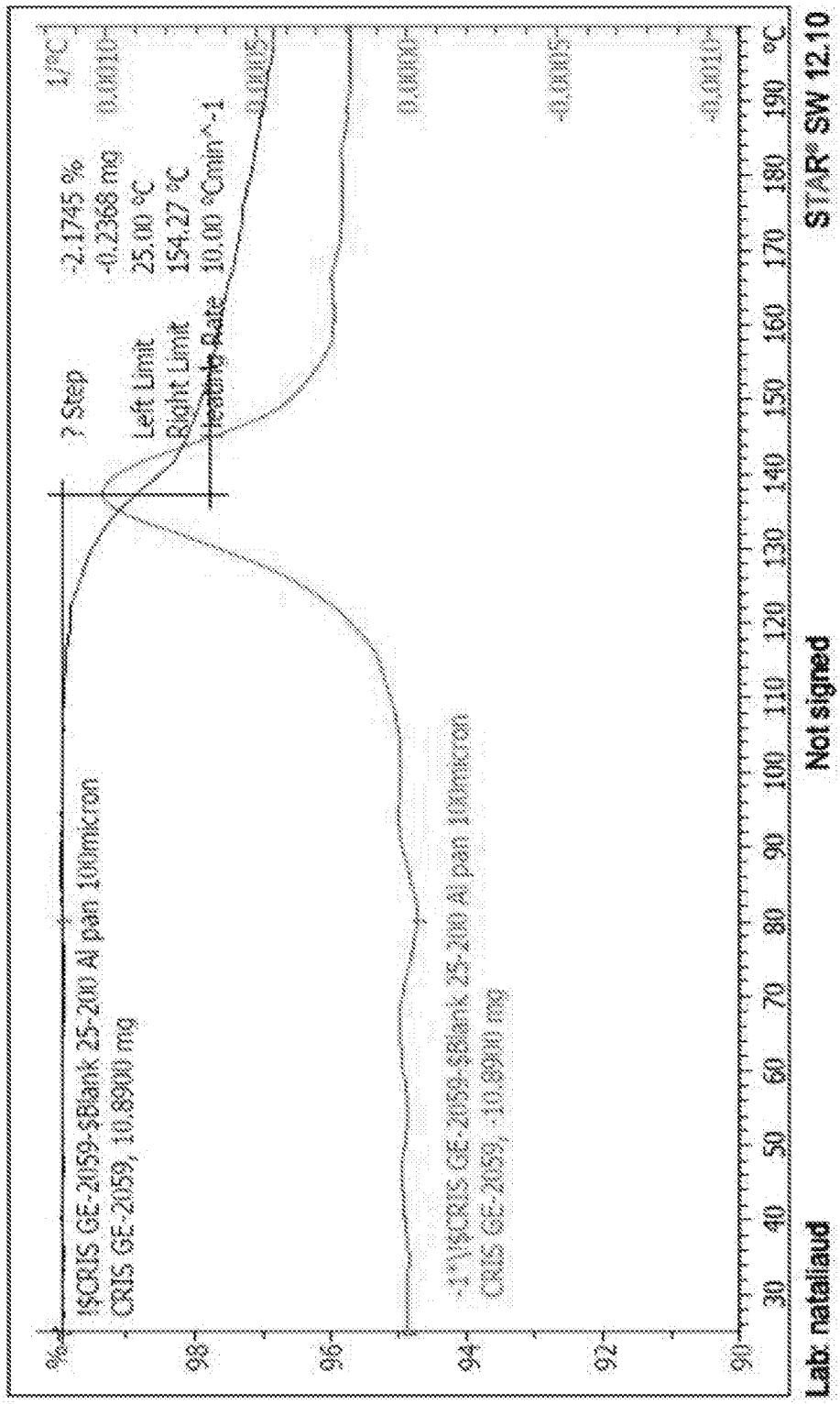

I§CRIS GE-2059-§Blank 25-200 Al pan 10Micron
CRIS GE-2059, 10.8900 mg
-1^1§CRIS GE-2059-§Blank 25-200 Al pan 10Micron
CRIS GE-2059, -10.8900 mg
? Step
Left Limit
Right Limit
Heating Rate
-2.1745 %
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154.27 °C
10.00 °Cmin^-1
Lab: nataliaud
Not signed
STAR® SW 12.10

Fig. 5

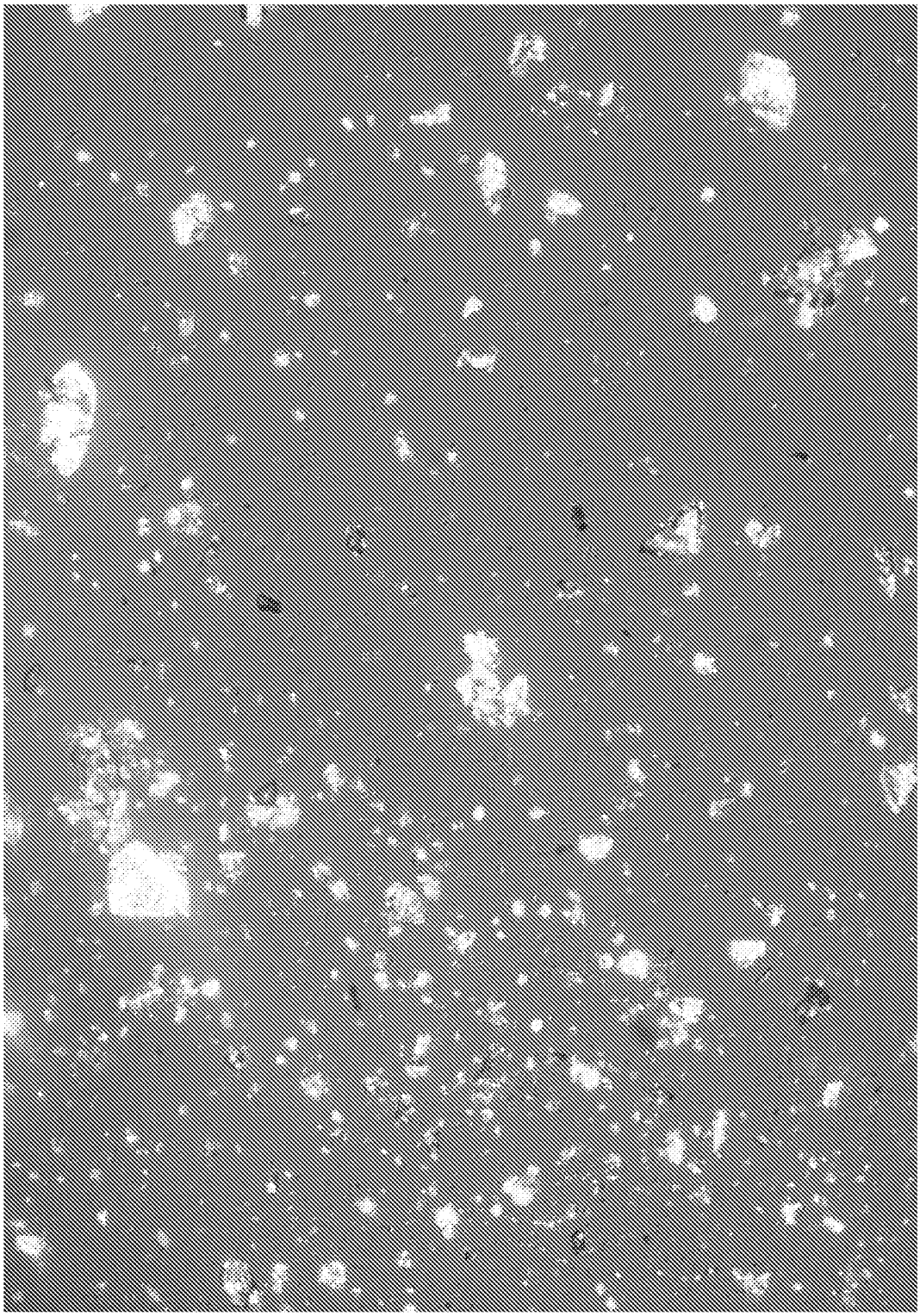


Fig. 6

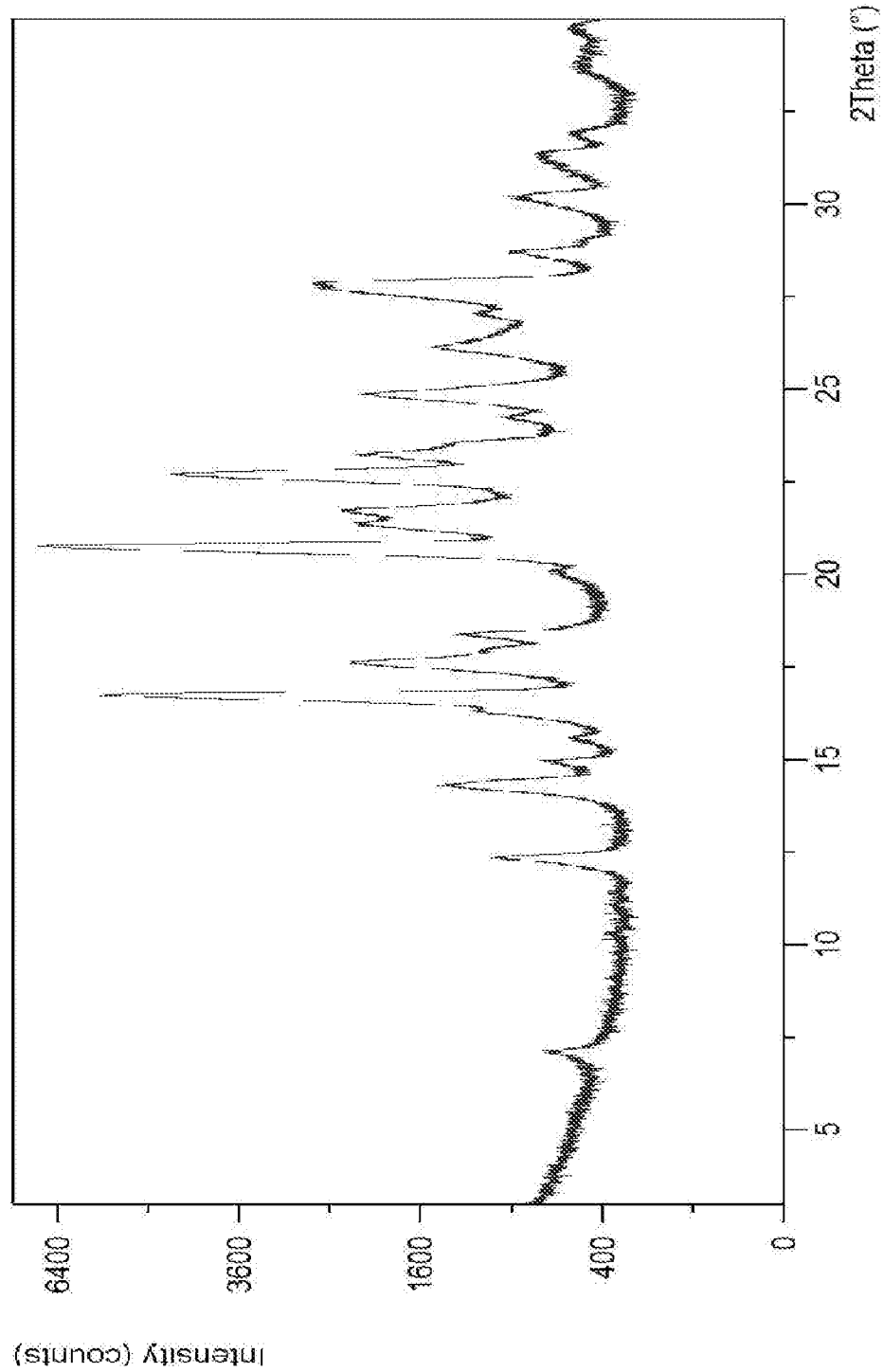


Fig. 7

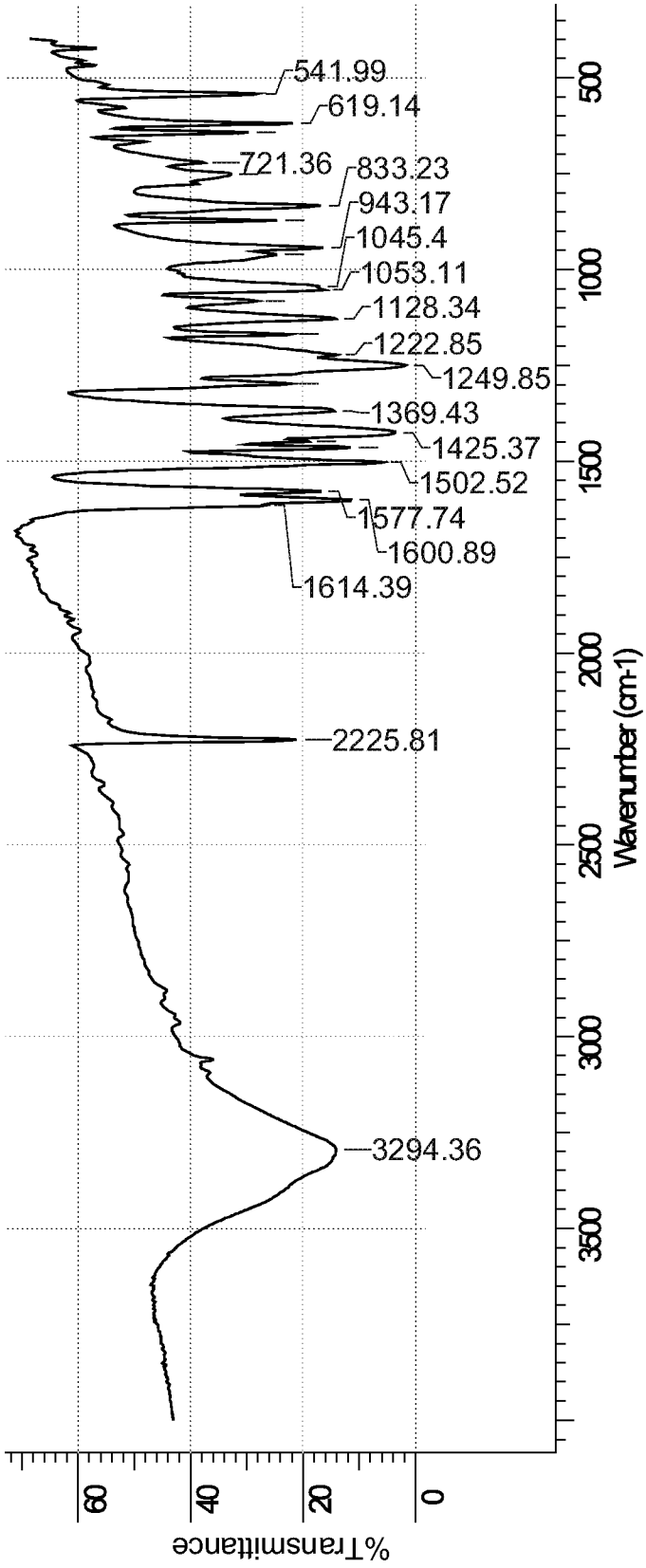

541.99
619.14
721.36
833.23
943.17
1045.4
1053.11
1128.34
1222.85
1249.85
1369.43
1425.37
1502.52
1577.74
1600.89
1614.39
2225.81
3294.36
500
1000
1500
2000
2500
3000
3500
Wavenumber (cm-1)
60
40
20
0
%Transmittance

Fig. 8

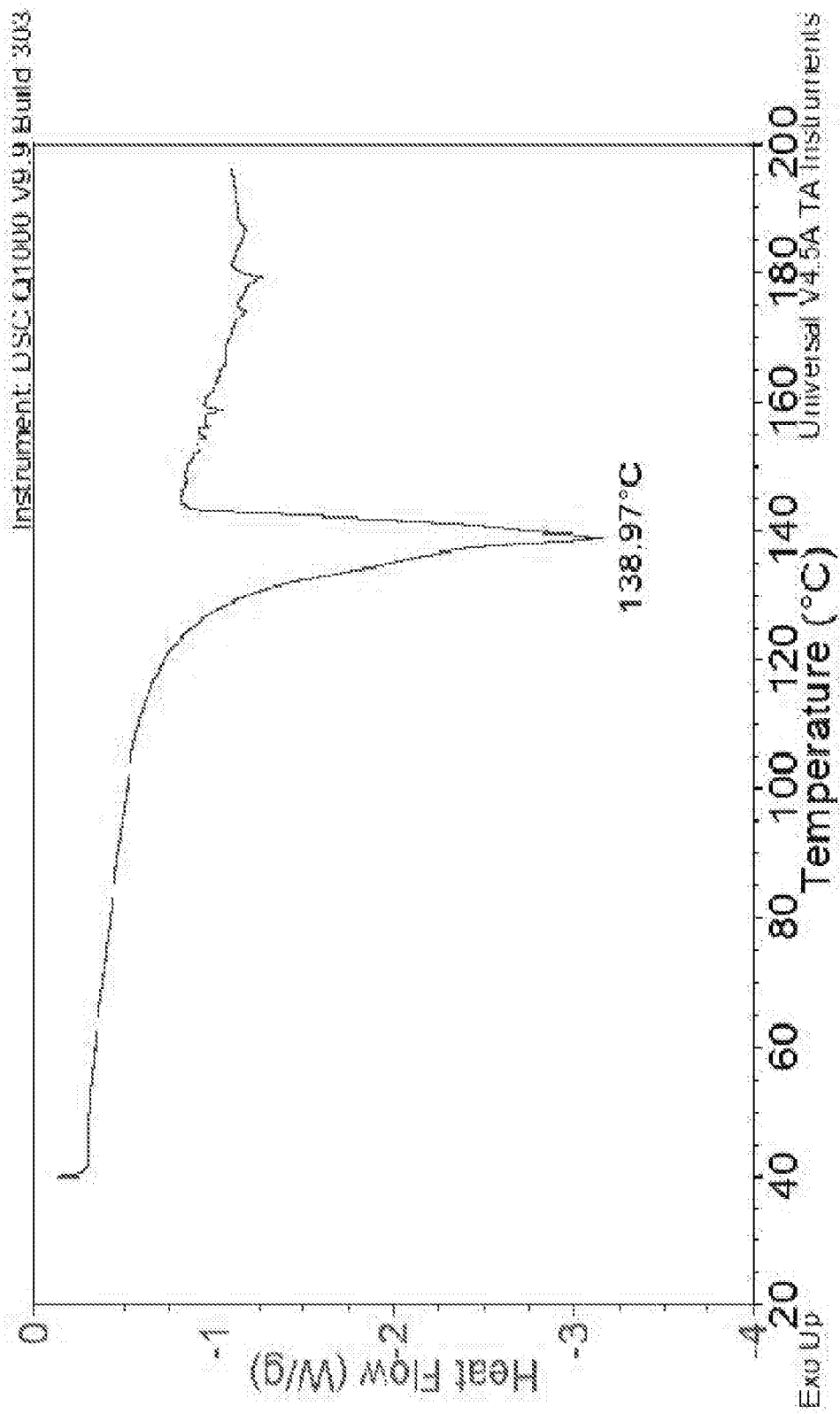

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138.97°C
Heat Flow (W/g)
Temperature (°C)
Universal V4.5A TA Instruments
Exo Up

Fig. 9

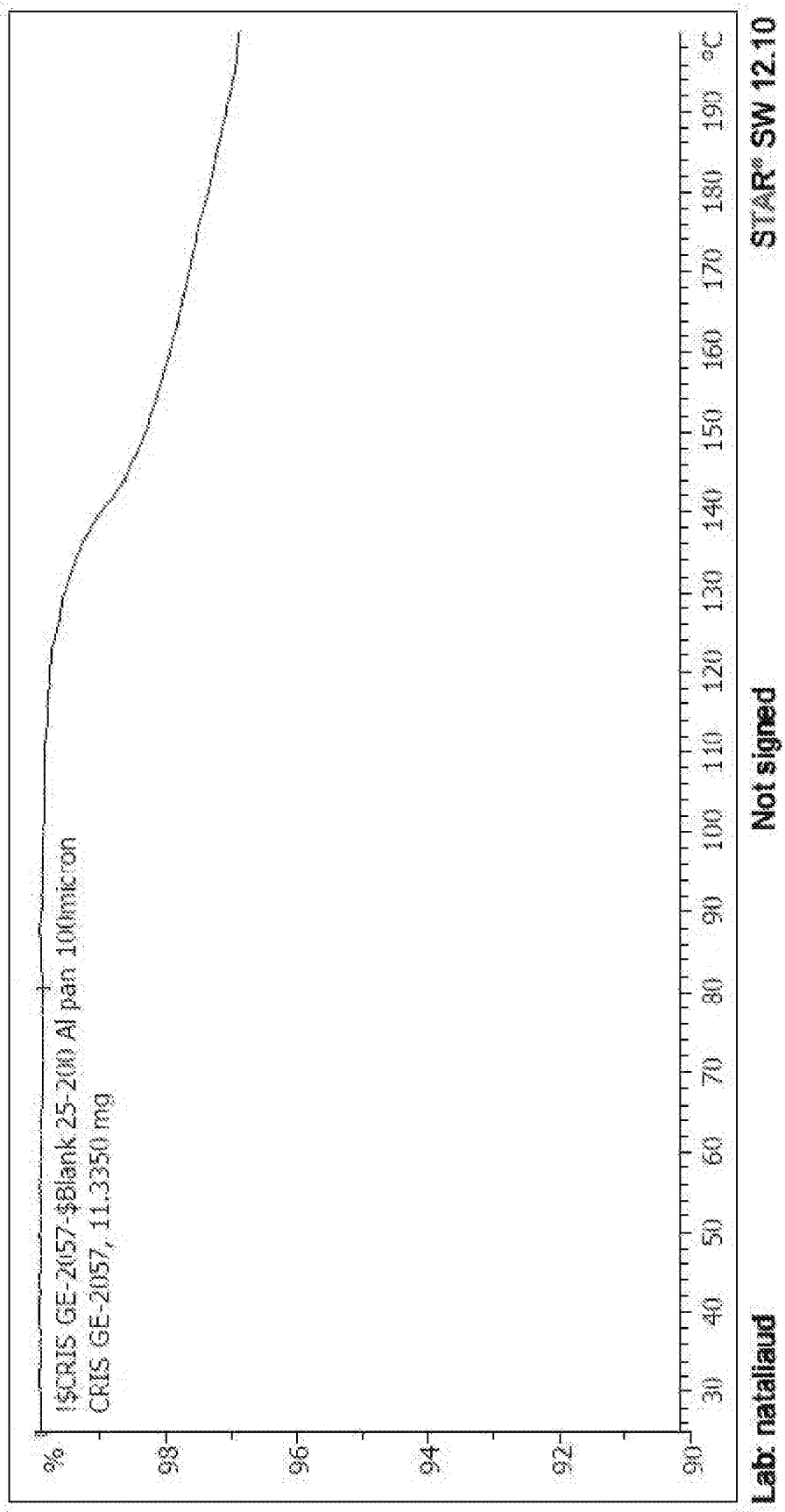

%
98
96
94
92
90
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
°C
!$CRIS GE-2057-$Blank 25-200 Al pan 100micron
CRIS GE-2057, 11.3350 mg
Lab: nataliaud
Not signed
STAR° SW 12.10

Fig. 10

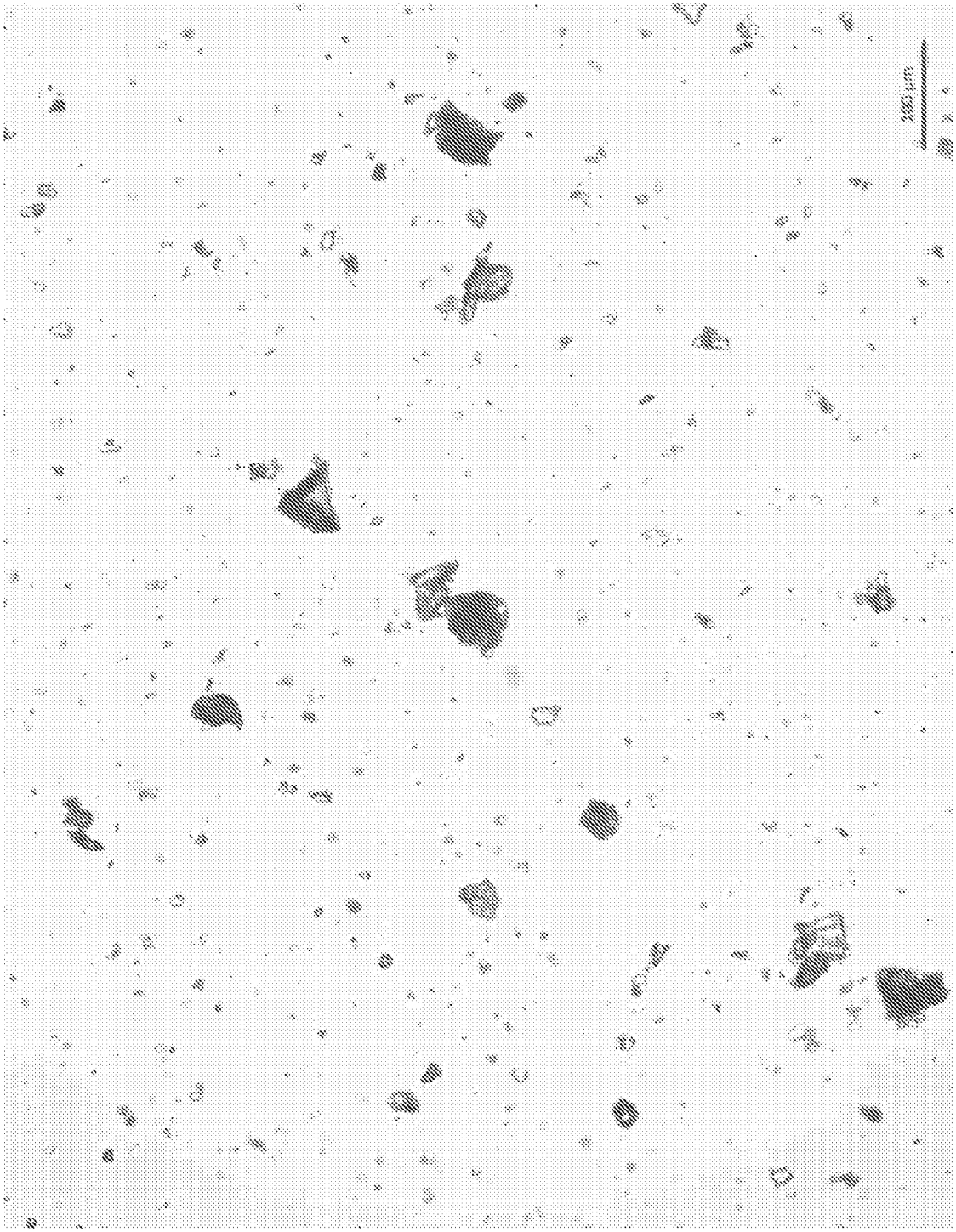


Fig. 11

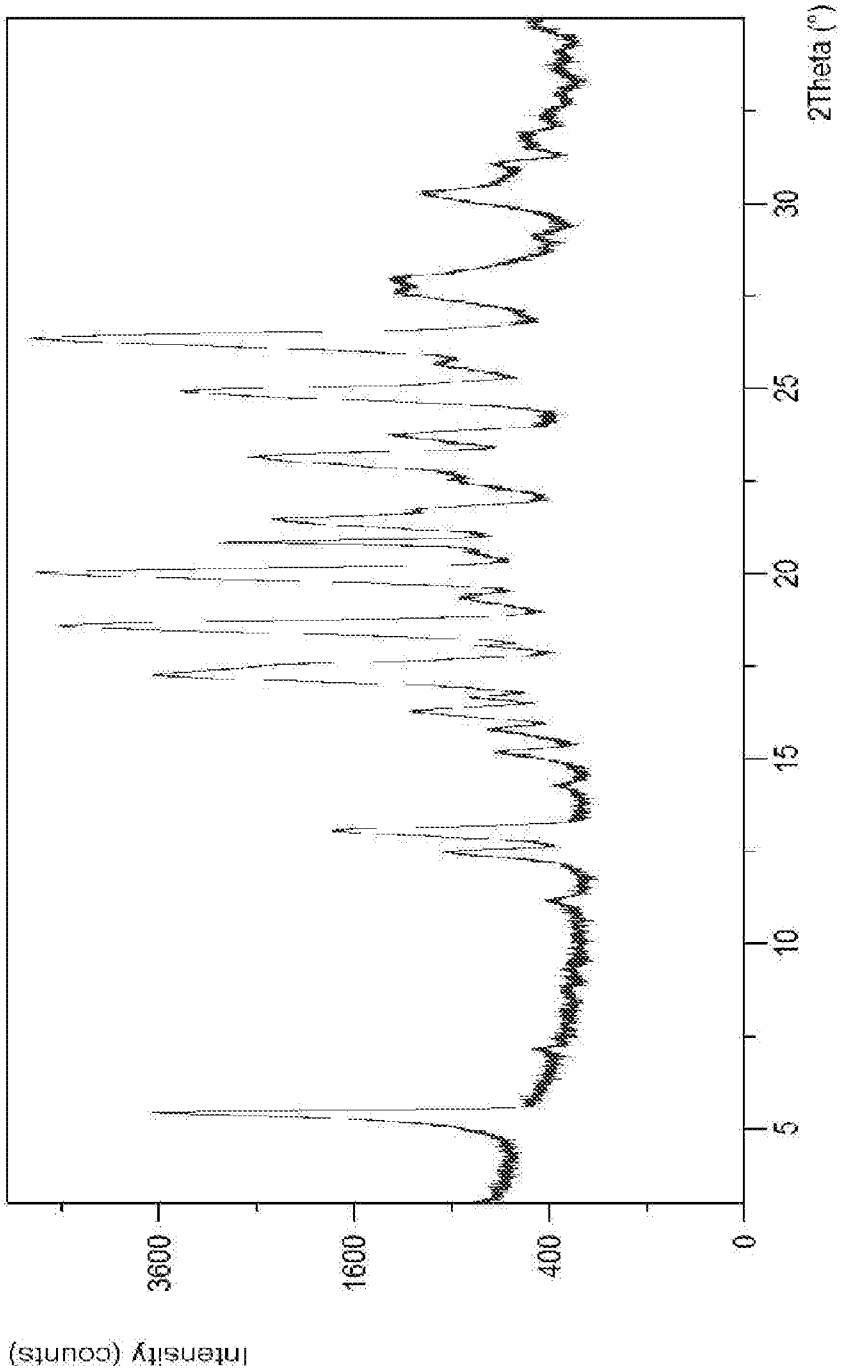


Fig. 12

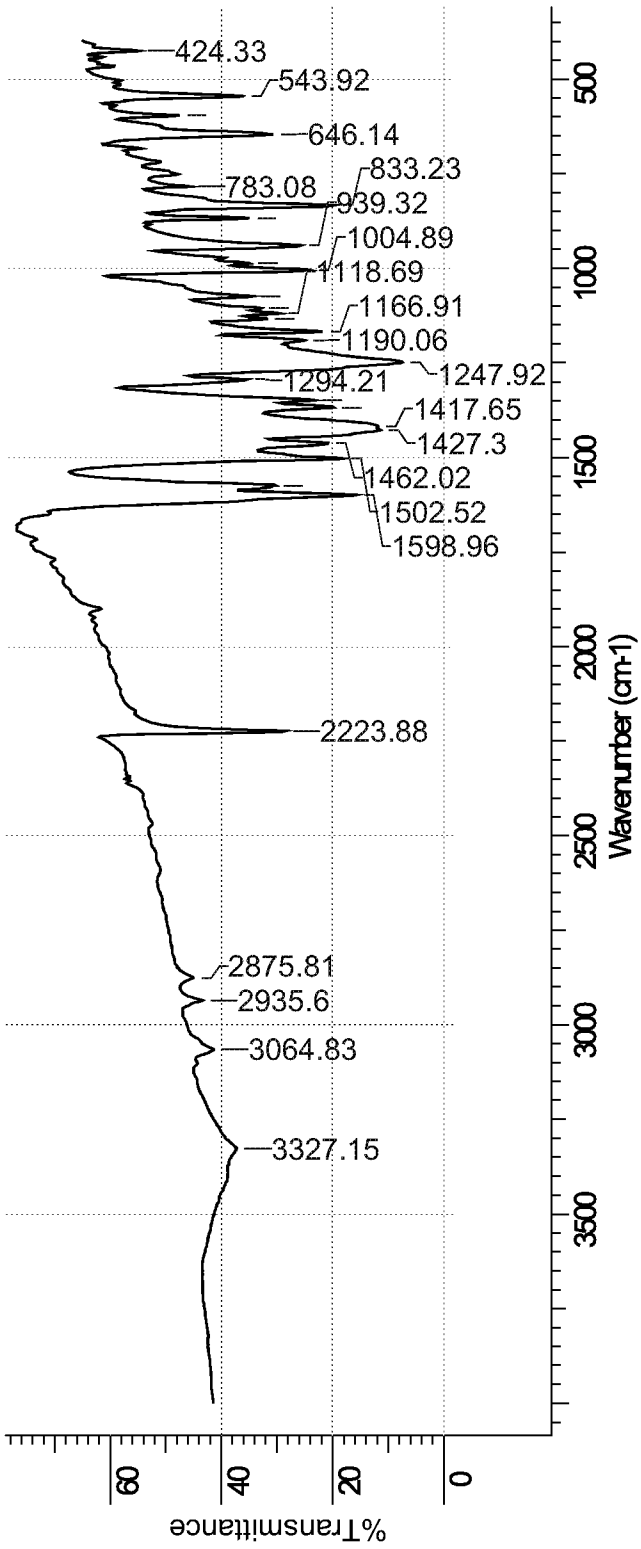

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646.14
783.08
833.23
939.32
1004.89
1118.69
1166.91
1190.06
1247.92
1294.21
1417.65
1427.3
1462.02
1502.52
1598.96
2223.88
2875.81
2935.6
3064.83
3327.15
500
1000
1500
2000
2500
3000
3500
Wavenumber (cm-1)
60
40
20
0
%Transmittance

Fig. 13

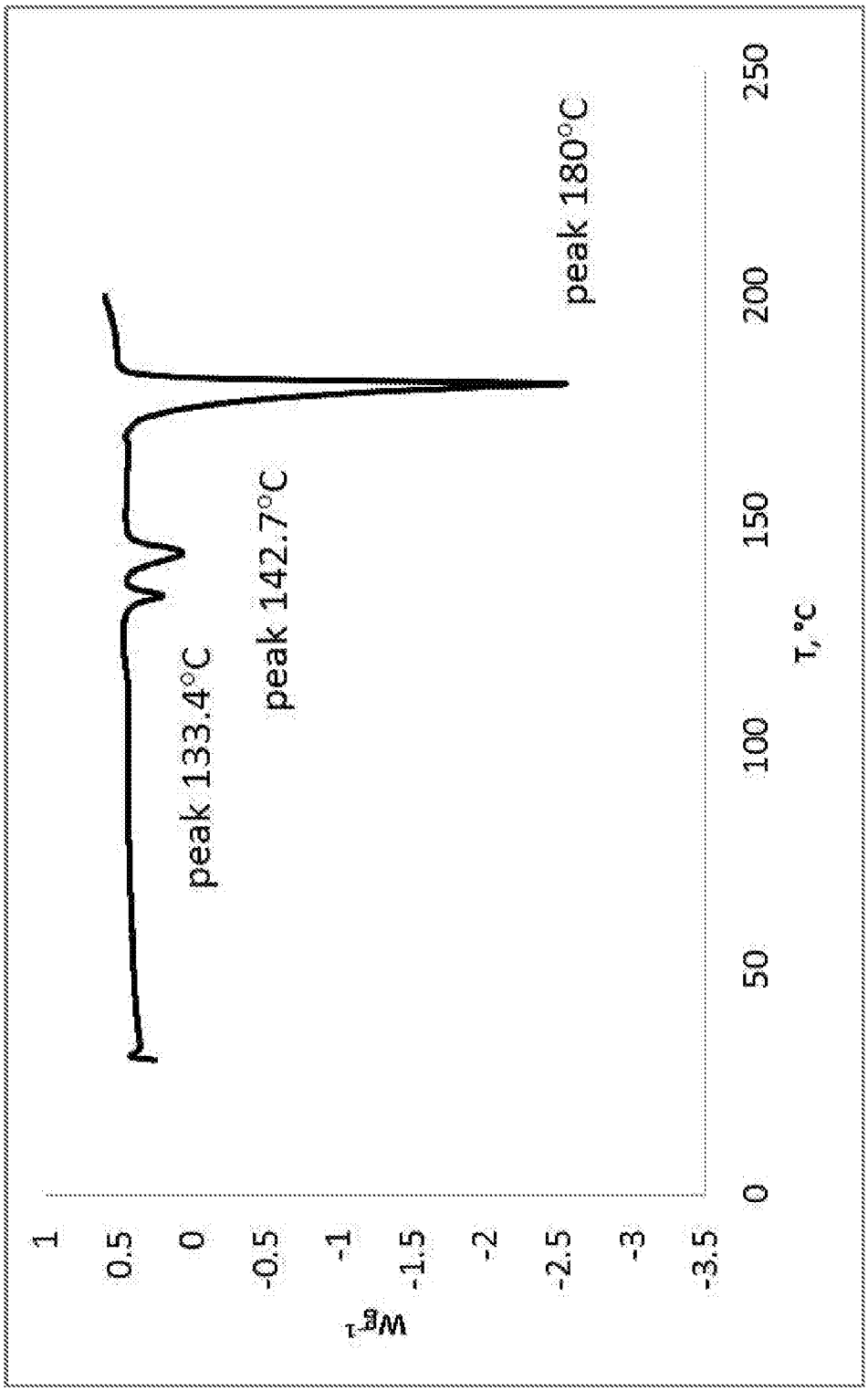

peak 133.4°C
peak 142.7°C
peak 180°C
T, °C
W_E, -1
1
0.5
0
-0.5
-1
-1.5
-2
-2.5
-3
-3.5
0
50
100
150
200
250

Fig. 14

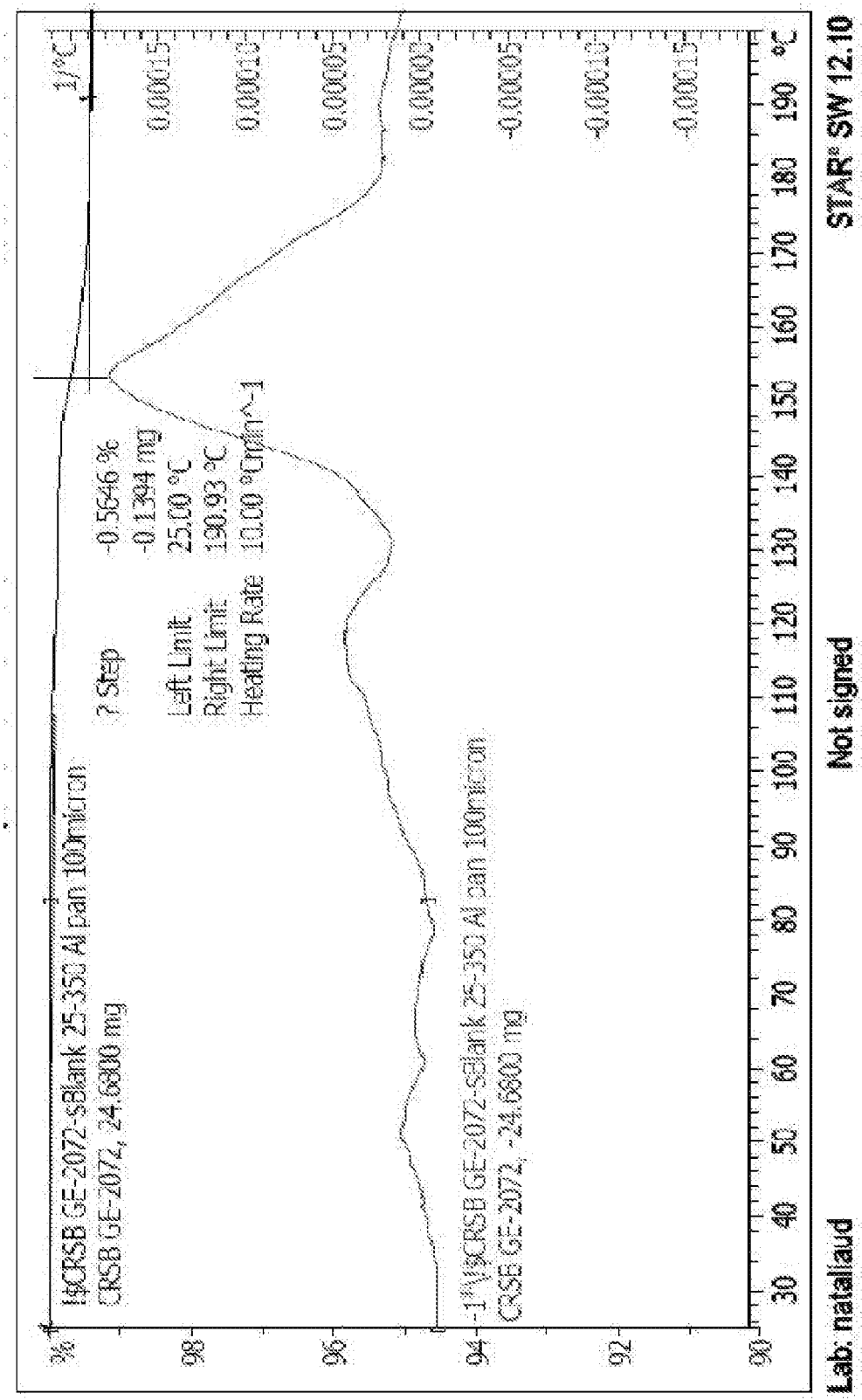

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Right Limit -0.1394 mg
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190.93 °C
10.00 °C/min^-1
-1 \\pCRSB GE-2072-sBank 25-350 Al pan 100micron
CRSB GE-2072, 24.6600 mg
1/°C
%
°C
Lab: nataliaud
Not signed
STAR® SW 12.10

Fig. 15

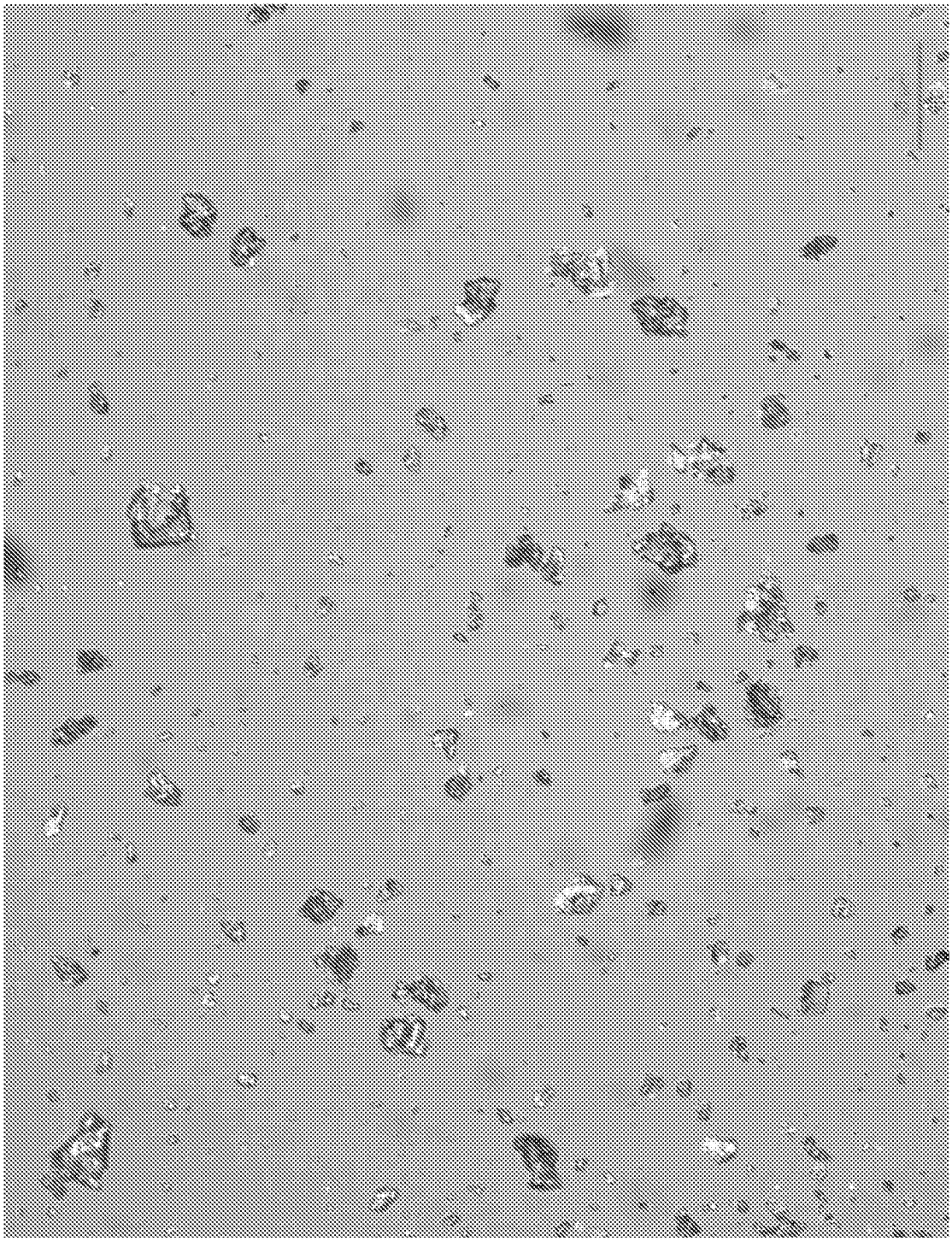


Fig. 16

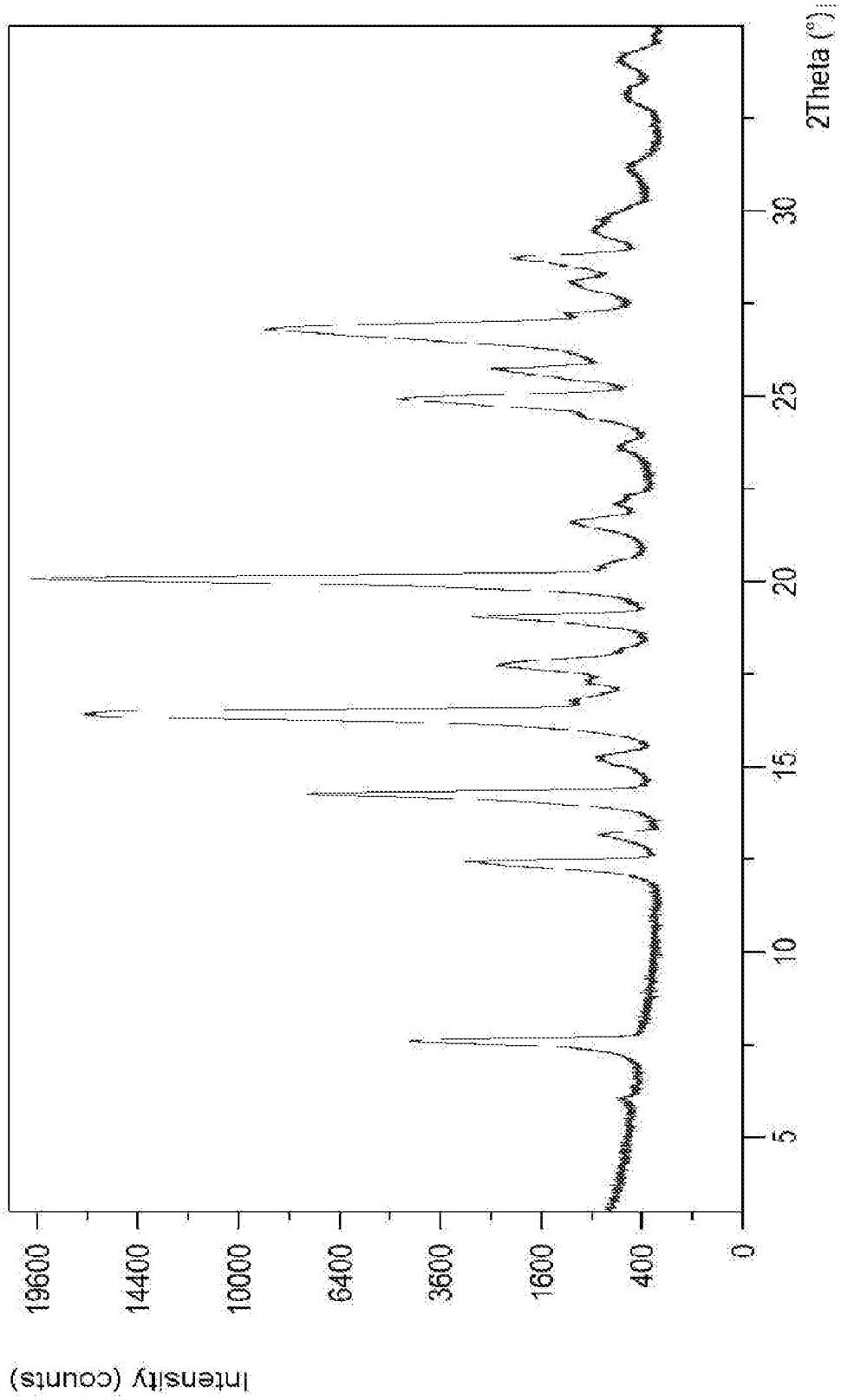

Intensity (counts)
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10000
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3600
1600
400
0
5
10
15
20
25
30
2Theta (°)

Fig. 17

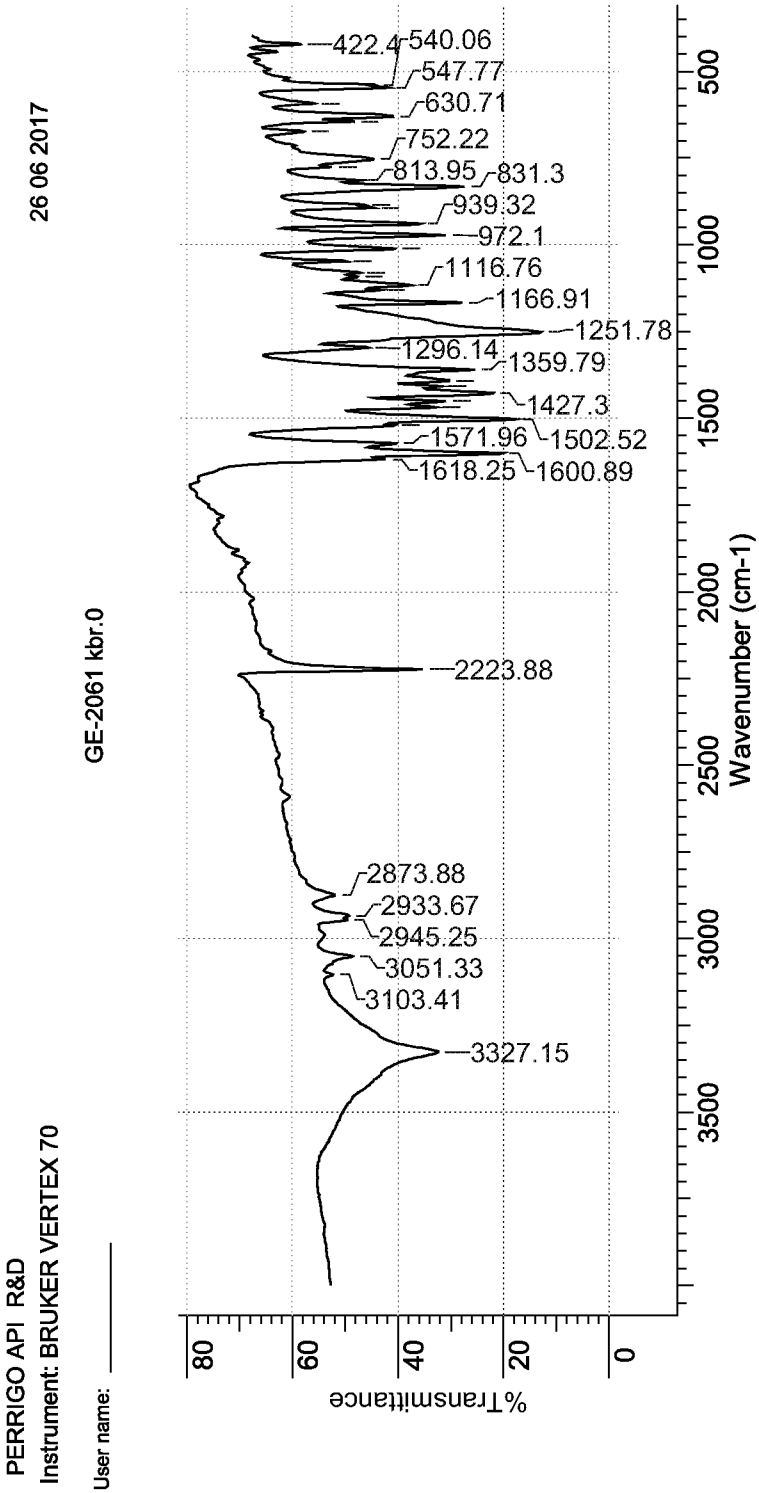

PERRIGO API R&D
Instrument: BRUKER VERTEX 70
User name: _____
GE-2061 kbr.0
26 06 2017
%Transmittance
80
60
40
20
0
Wavenumber (cm-1)
500
1000
1500
2000
2500
3000
3500
422.4
540.06
547.77
630.71
752.22
813.95
831.3
939.32
972.1
1116.76
1166.91
1251.78
1296.14
1359.79
1427.3
1502.52
1571.96
1600.89
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3051.33
3103.41
3327.15

Fig. 18

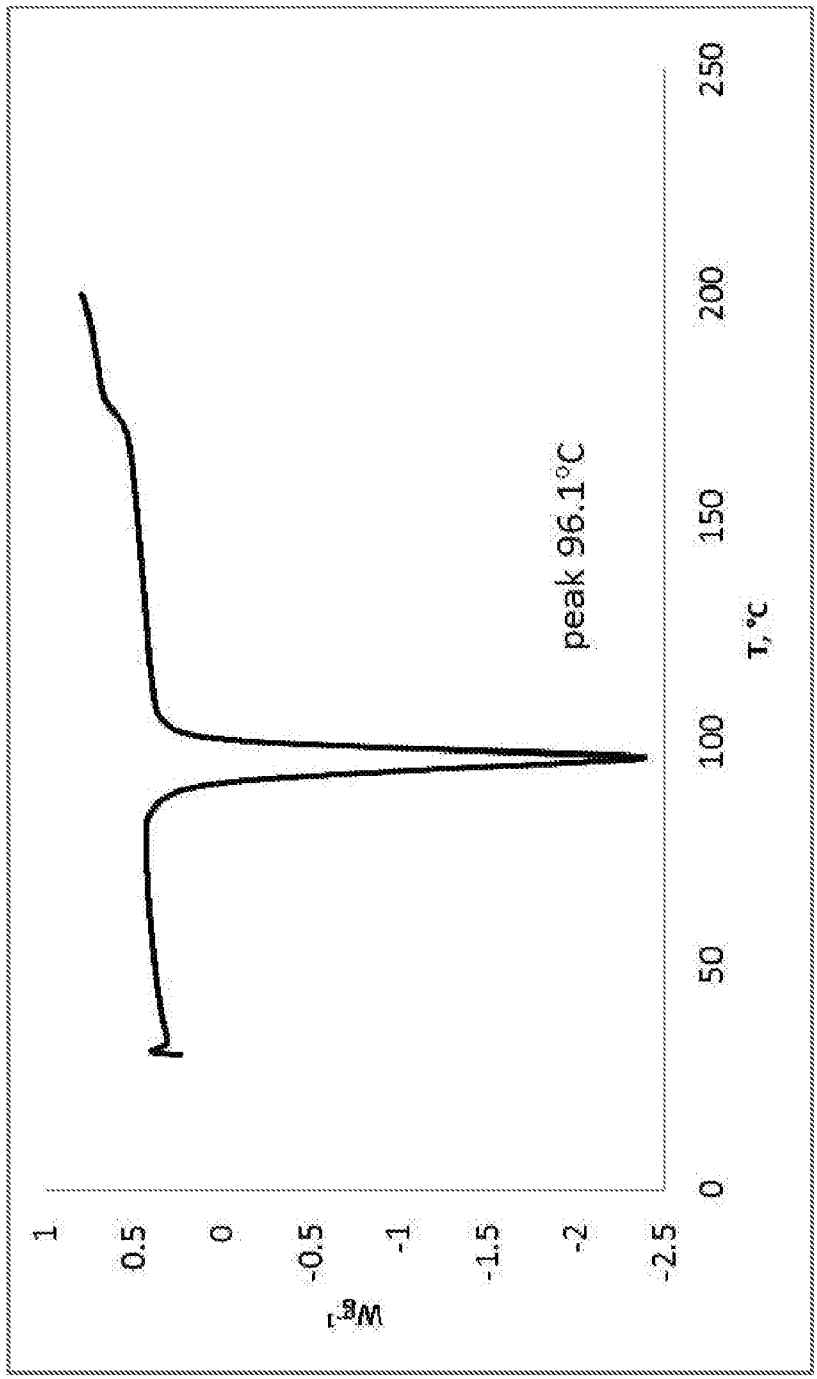


Fig. 19

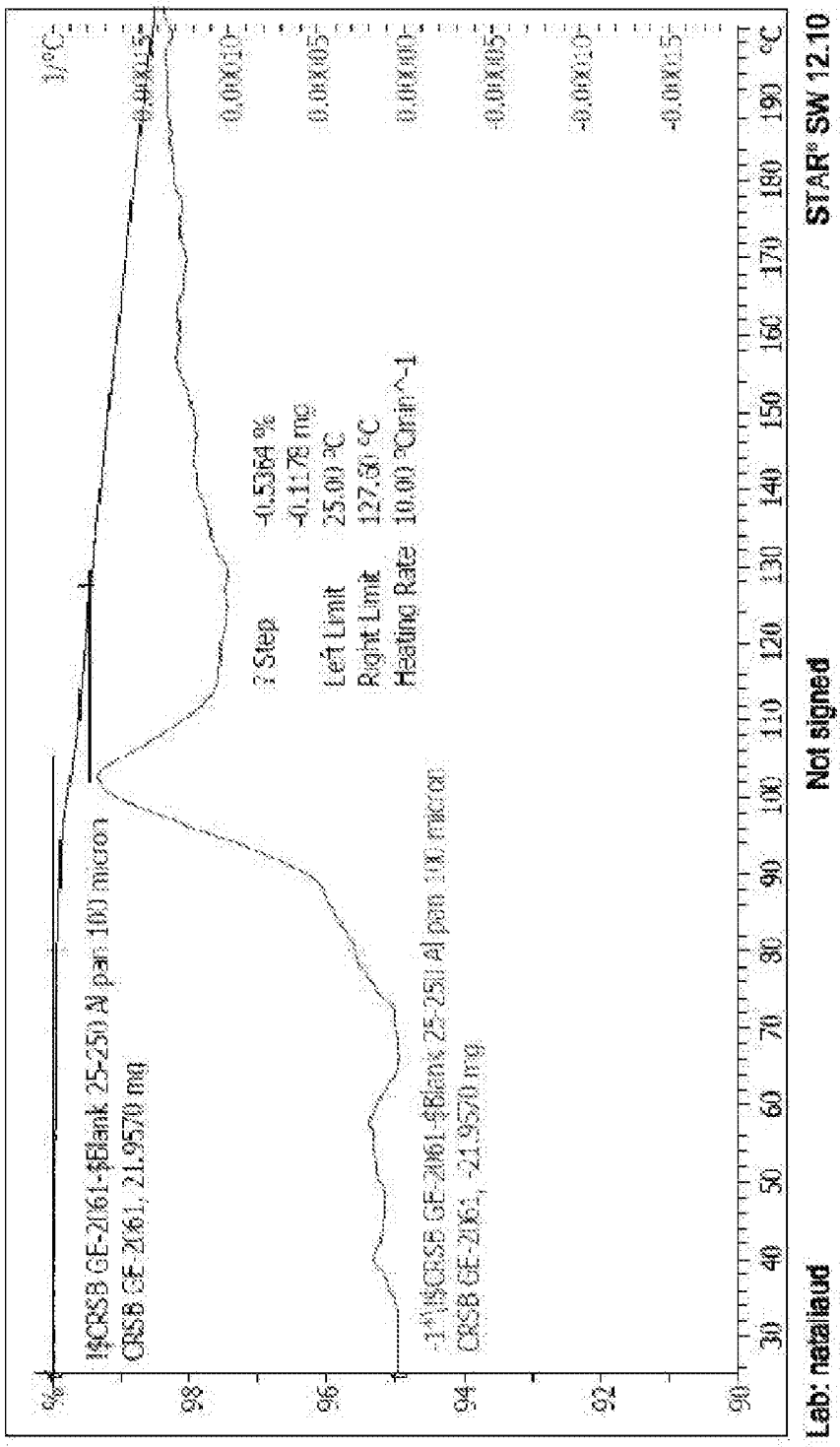

1/°C
%
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96
94
92
90
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
°C
0.00010
0.00005
0.00000
-0.00005
-0.00010
-0.00015
1 !!!CRSB GE-2161-1Blank 25-250 Al pan 100 micron
CRSB GE-2161, 21.9570 mg
-1 !!!CRSB GE-2161-1Blank 25-250 Al pan 100 micron
CRSB GE-2161, -21.9570 mg
T Step
-0.5364 %
-0.1178 mg
Left Limit
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Right Limit
127.30 °C
Heating Rate
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Lab: nataliaud
Not signed
STAR° SW 12.10

Fig. 20

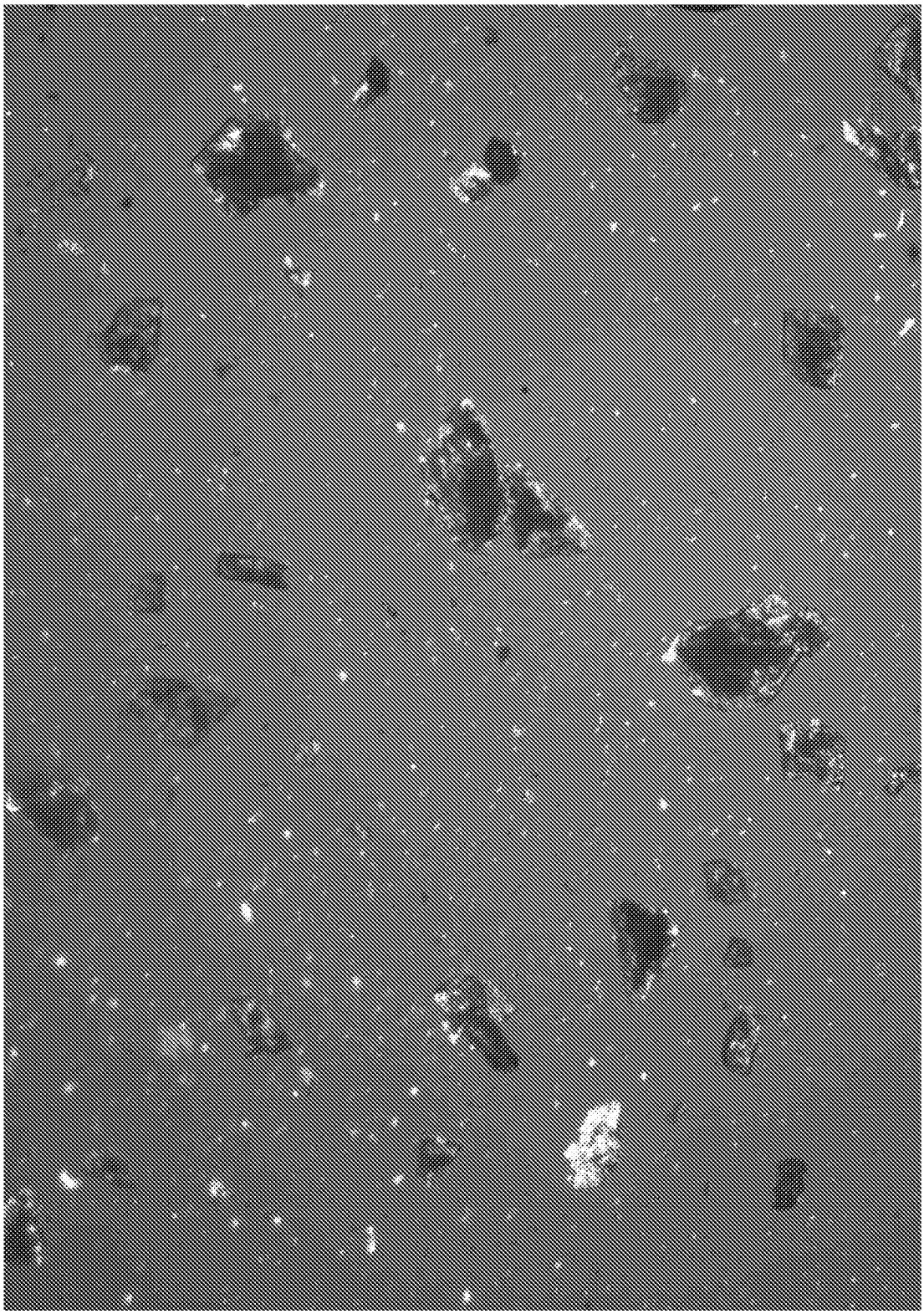


Fig. 21

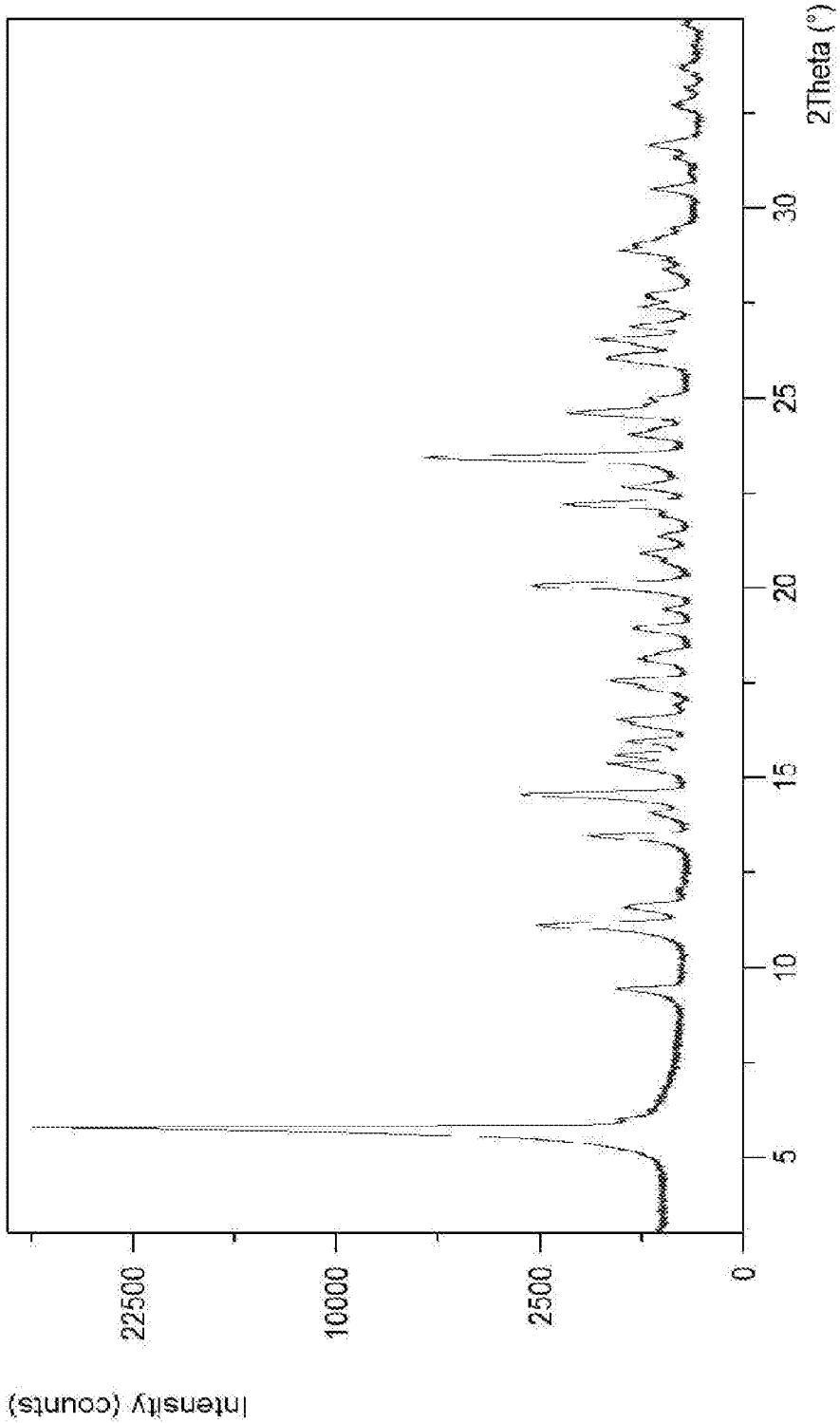


Fig. 22

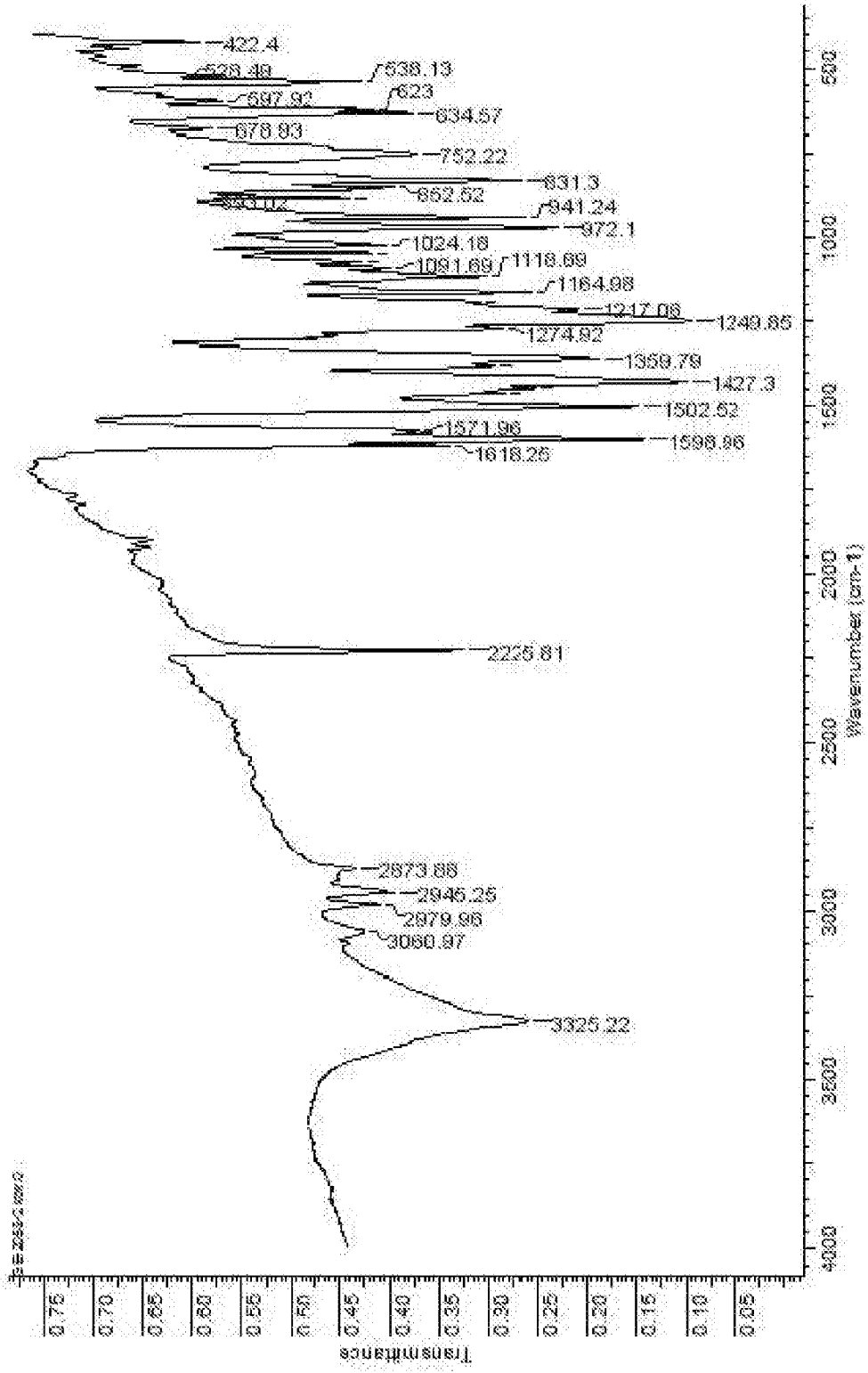
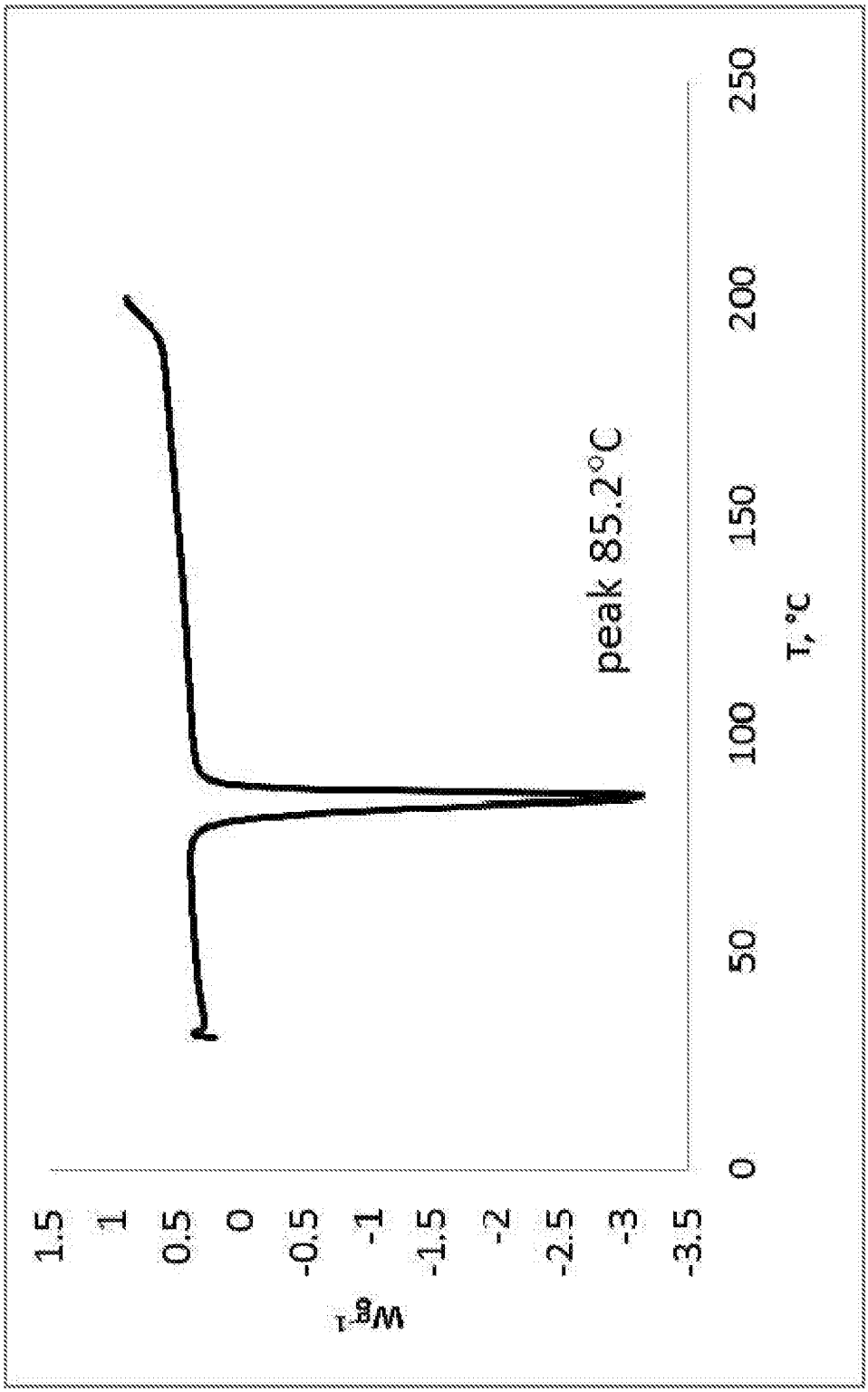

422.4
638.13
623
634.57
752.22
831.3
941.24
972.1
1024.18
1118.69
1164.98
1240.85
1274.92
1359.79
1427.3
1502.62
1598.96
1618.26
2225.81
2873.88
2946.25
2979.96
3060.97
3325.22
Transmittance
Wavenumber (cm-1)

Fig. 23



SUBSTITUTE SHEET (RULE 26)

Fig. 24

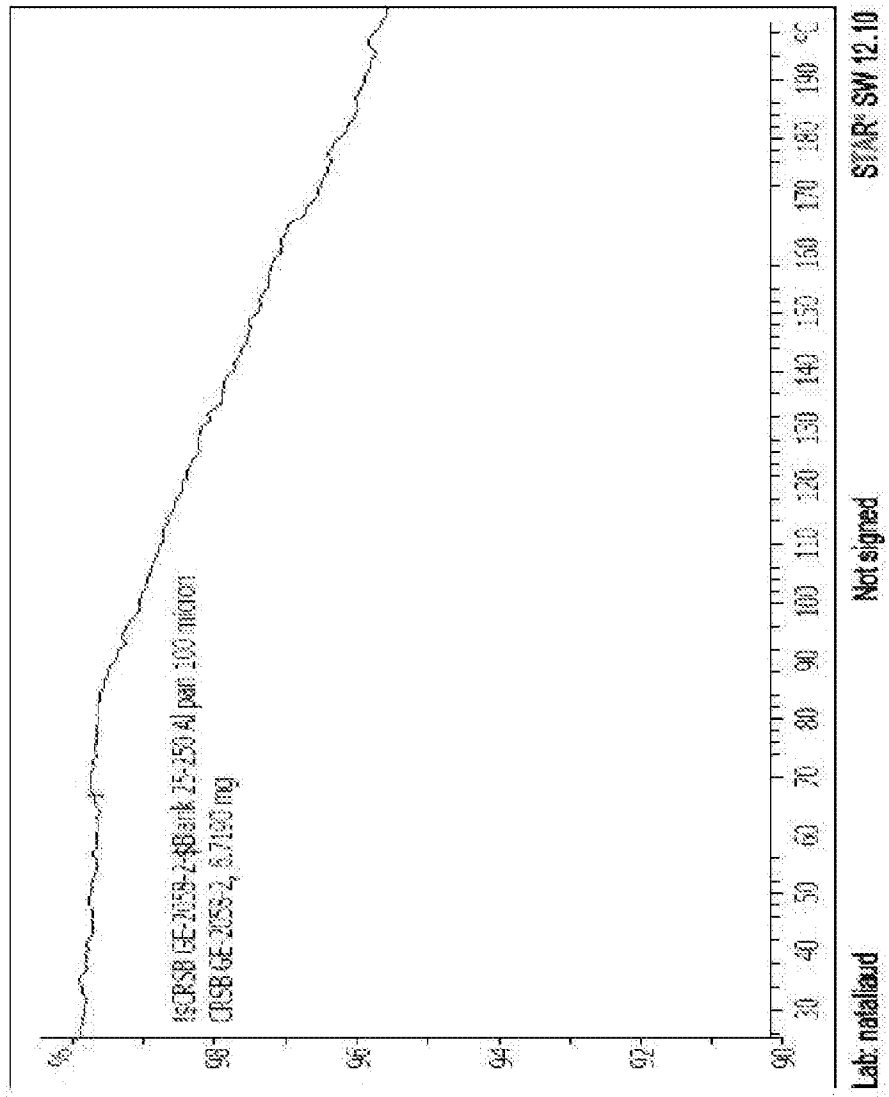

%
100
98
96
94
92
90
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
°C
CRSB GE 2055-2, 5.7100 mg
Lab: nataliaud
Not signed
STAR° SW 12.10

Fig. 25

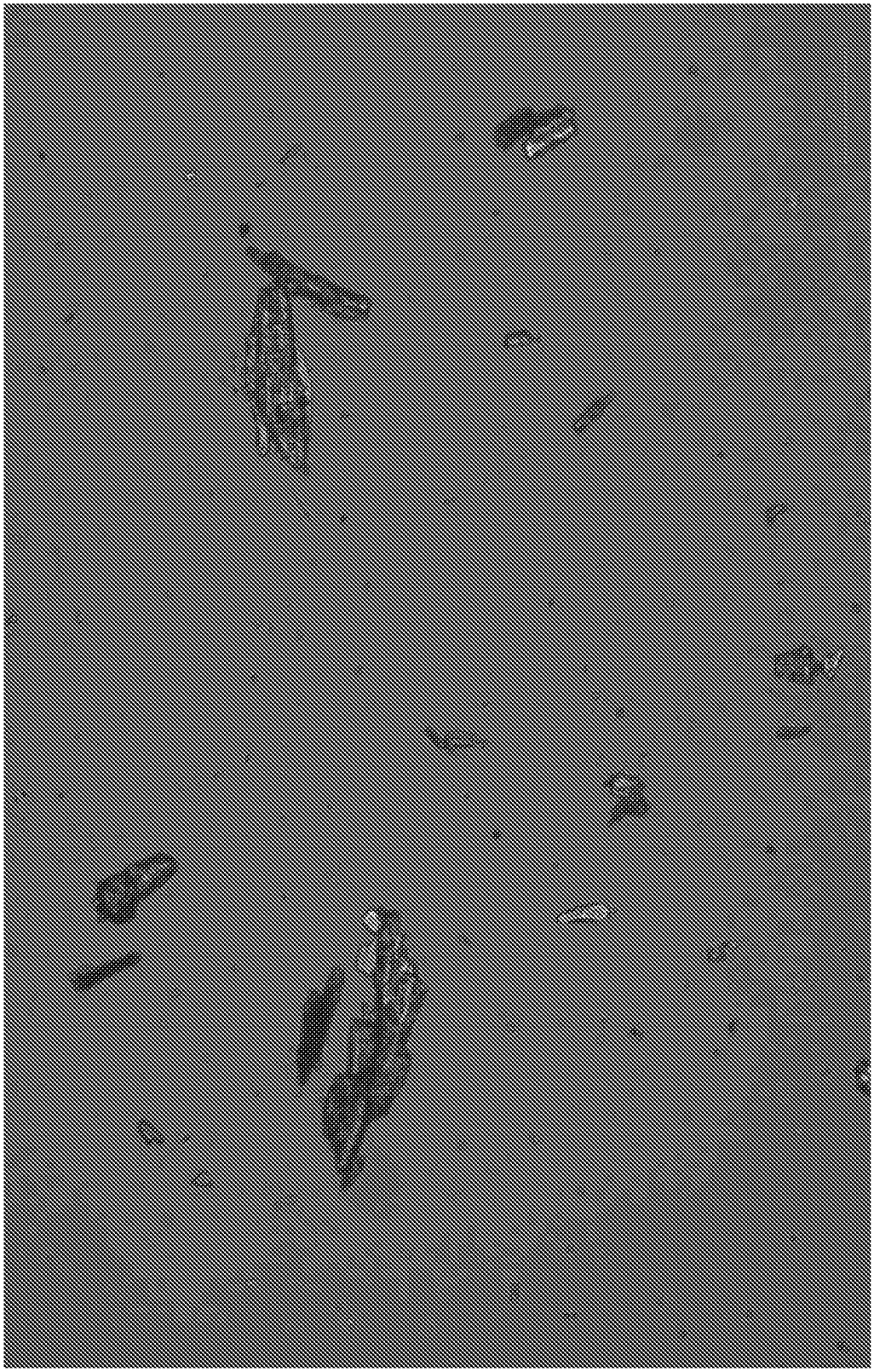
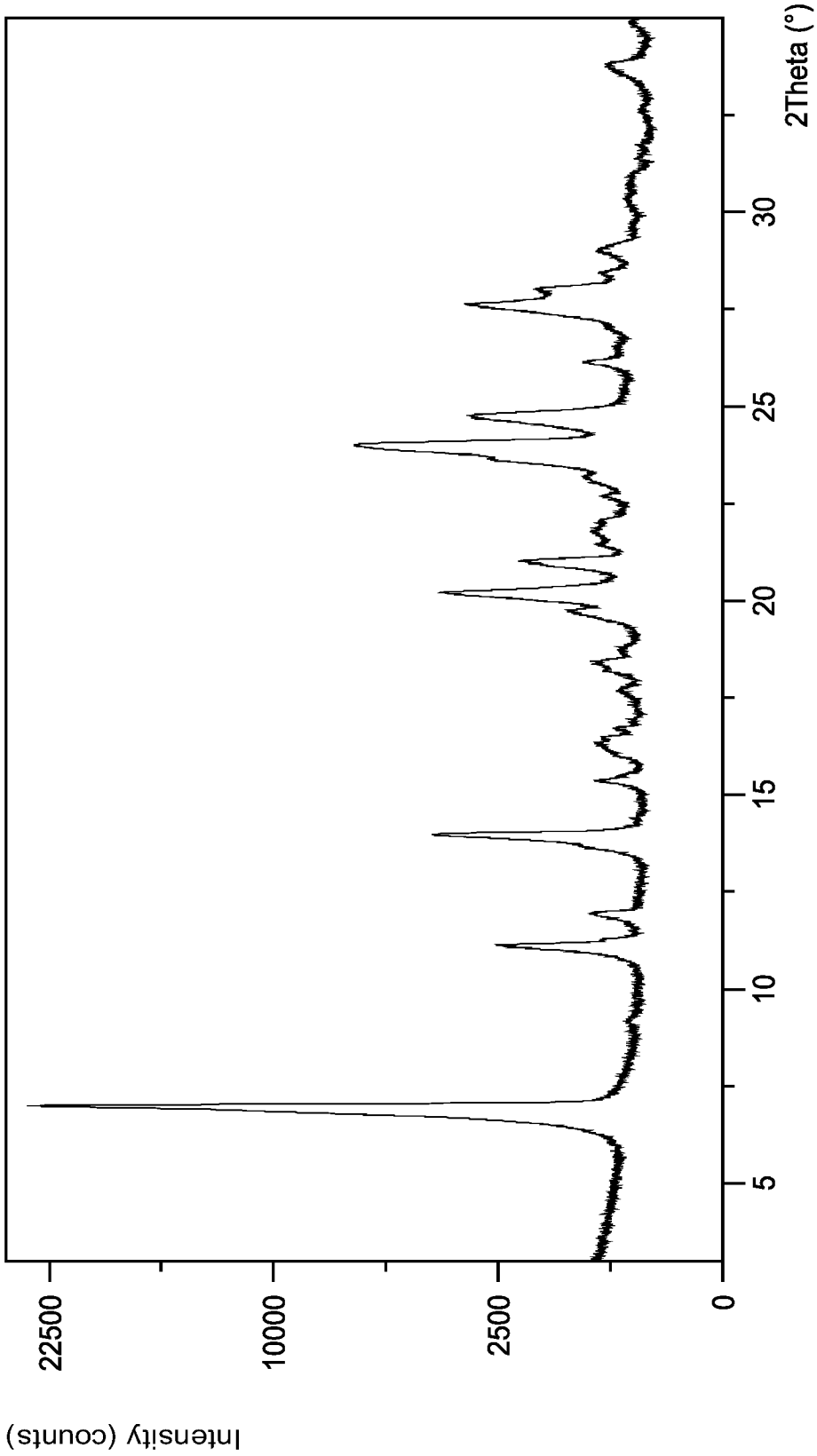


Fig. 26



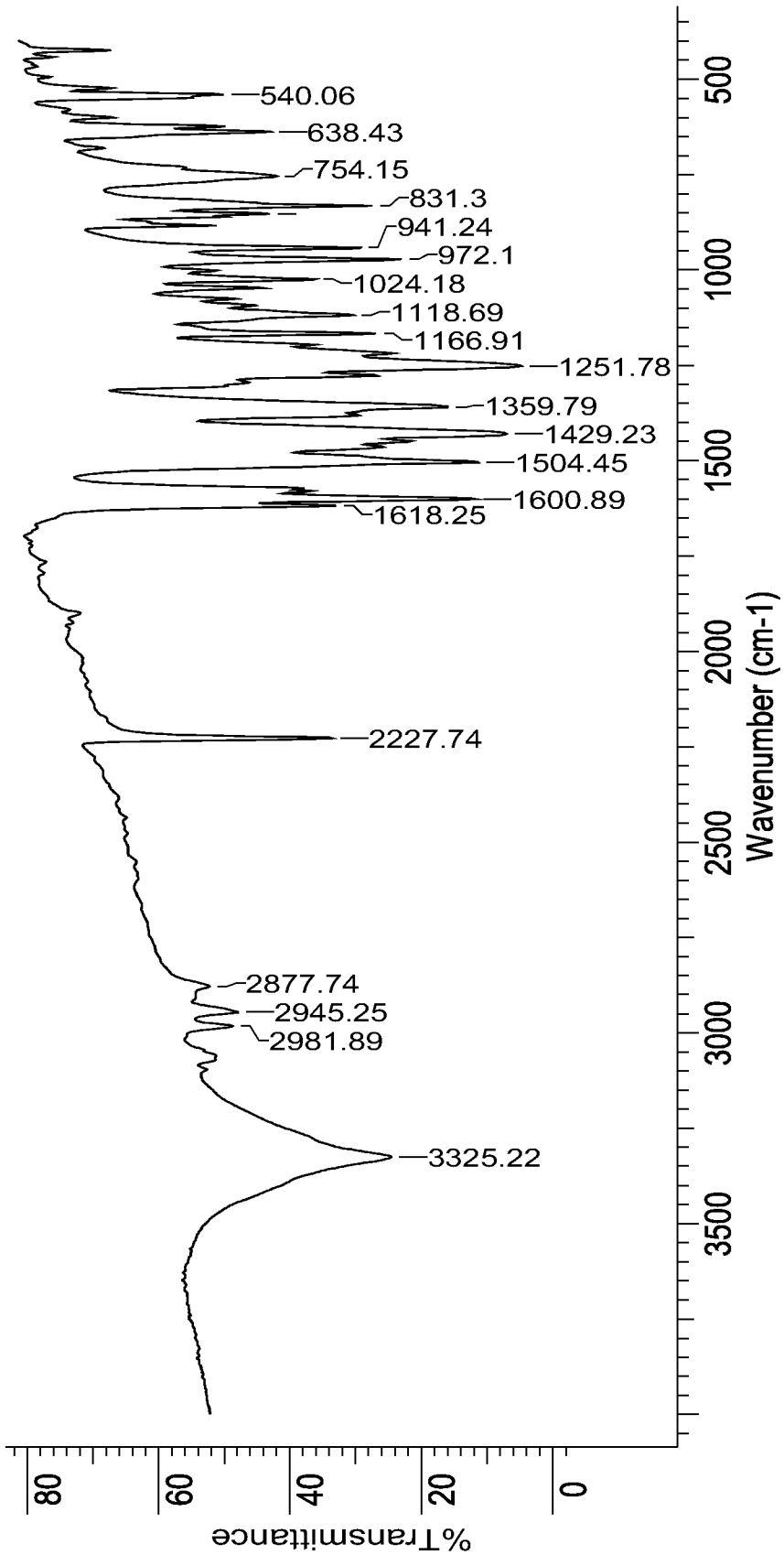

540.06
638.43
754.15
831.3
941.24
972.1
1024.18
1118.69
1166.91
1251.78
1359.79
1429.23
1504.45
1600.89
1618.25
2227.74
2877.74
2945.25
2981.89
3325.22
500
1000
1500
2000
2500
3000
3500
Wavenumber (cm-1)
0
20
40
60
80
%Transmittance

Fig. 27

Fig. 28

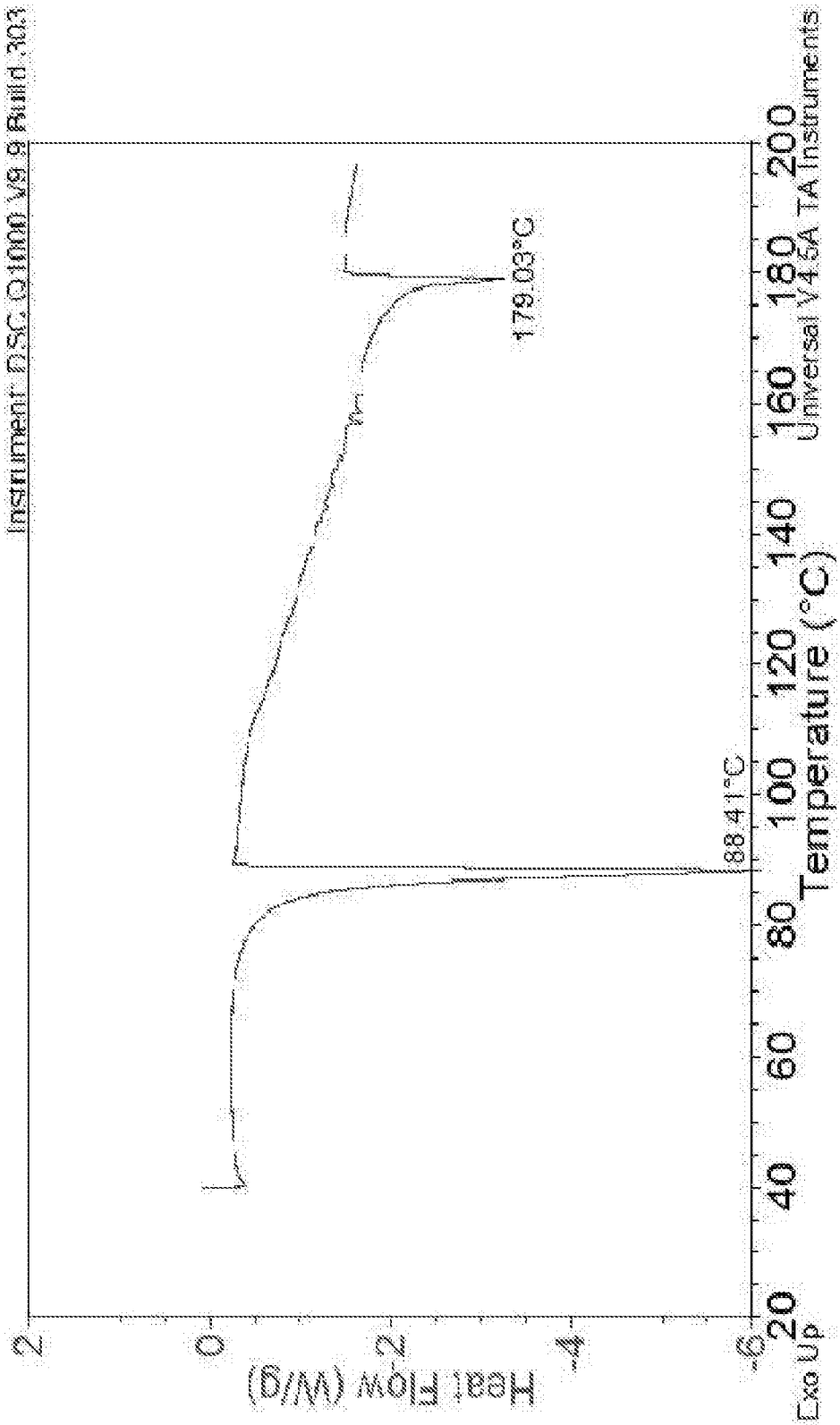
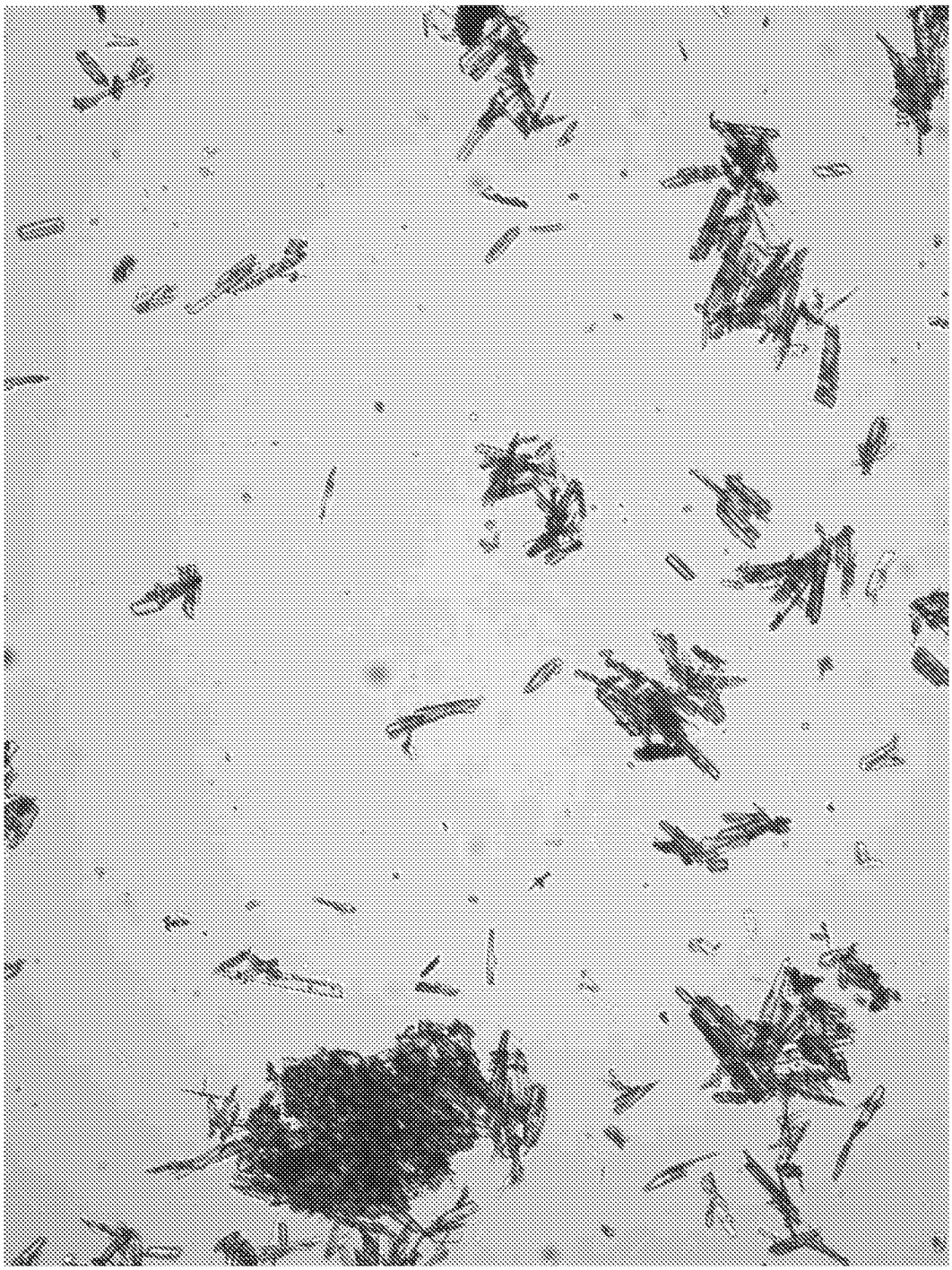

Instrument: DSC Q1000 V9.9 Build 303
179.03°C
88.41°C
Universal V4.5A TA Instruments
Temperature (°C)
Heat Flow (W/g)
Exo Up

Fig. 29



INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL2017/050558

A. CLASSIFICATION OF SUBJECT MATTER
IPC (2017.01) A61K 31/69, C07F 5/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC (2017.01) A61K 31/69, C07F 5/02

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	US 2017152273 A1 (Anacor Pharmaceuticals Inc [US]; Merchant Tejal [US]); 01 Jun 2017 (2017/06/01) paragraphs 0454-0488, example 1-7, tables 1-5	1-39
P,X	Cayman chemicals, AN 2728 product information 03 Aug 2017 (2017/08/03) whole document	1-3,11-13,17-19, 22-24,28-30,33-35,38,39
Y	WO 2009111676 A2 (Anacor Pharmaceuticals Inc [US]; Tsutomu Akama [US] et.al); 11 Sep 2009 (2009/09/11) abstract, paragraphs 0355, 0066 examples 13, 23-24, 27	1-3,11-13,17-19, 22-24,28-30,33-35,38,39
Y	Tsutomu Akama et.al,"Discovery and structure–activity study of a novel benzoxaborole anti-inflammatory agent (AN2728) for the potential topical treatment of psoriasis and atopic dermatitis", Journal Bioorganic & Medicinal Chemistry Letters, vol. 19, P.2129–2132; 15 Apr 2009 (2009/04/15) abstract, schemes 1-2	1-39

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
06 Aug 2017	08 Aug 2017
Name and mailing address of the ISA: Israel Patent Office Technology Park, Bldg.5, Malcha, Jerusalem, 9695101, Israel Facsimile No. 972-2-5651616	Authorized officer SHAPIRA Elena Telephone No. 972-2-5657823

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL2017/050558

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Byrn Stephan et.al.; "Pharmaceutical solids: a strategic approach to regulatory consideration"; Vol. 12, No.7, p.945-954 ISSN: 0724-8741; 31 Jul 1995 (1995/07/31) pages 945-954	1-39
Y	Edited by Brittain H. G.; "Polymorphism in pharmaceutical solids"; p.7-8, P.184-208, Marcel Dekker, first ed. ISBN: Ol84-8247-0237-9; 03 Mar 1999 (1999/03/03) pages 7-8, 184-220	1-39

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Information on patent family members

International application No.
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		JP 2017105763 A	15 Jun 2017
		WO 2017093857 A1	08 Jun 2017

B. FIELDS SEARCHED:

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

Databases consulted: BLAST, THOMSON INNOVATION, Google Patents, CAPLUS, BIOSIS, EMBASE, MARPAT, REGISTRY, Google Scholar, DWPI, Derwent Innovation

Search terms used: 5-(4-Cyanophenoxy)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole, crisaborole, AN 2728, 906673-24-3, crystal, solid, psoriasis, atopic dermatitis, stable, polymorph, form