(19) DANMARK

(10) DK/EP 3596042 T3

Patent- og Varemærkestyrelsen

(12) Oversættelse af europæisk patentskrift

(51) Int.Cl.: *C 07 C 229/12 (2006.01)* *C 07 C 229/16 (2006.01)*

(45) Oversættelsen bekendtgjort den: **2022-04-11**

(80) Dato for Den Europæiske Patentmyndigheds bekendtgørelse om meddelelse af patentet: **2022-01-12**

(86) Europæisk ansøgning nr.: **18715414.1**

(86) Europæisk indleveringsdag: **2018-03-15**

(87) Den europæiske ansøgnings publiceringsdag: **2020-01-22**

(86) International ansøgning nr.: **US2018022740**

(87) Internationalt publikationsnr.: **WO2018170322**

(30) Prioritet: **2017-03-15 US 201762471908 P**

(84) Designerede stater: **AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR**

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(54) Benævnelse: **KRYSTALFORMER AF AMINOLIPIDER**

(56) Fremdragne publikationer:
WO-A1-2012/000104
WO-A1-2015/011633
WO-A1-2016/176330
WO-A2-2012/054365
MUTHUSAMY JAYARAMAN ET AL: "Maximizing the Potency of siRNA Lipid Nanoparticles for Hepatic Gene Silencing In Vivo", ANGEWANDTE CHEMIE INTERNATIONAL EDITION, vol. 51, no. 34, 20 August 2012 (2012-08-20), pages 8529-8533, XP055063645, ISSN: 1433-7851, DOI: 10.1002/anie.201203263
MORISSETTE SHERRY L ET AL: "HIGH-THROUGHPUT CRYSTALLIZATION: POLYMORPHS, SALTS, CO-CRYSTALS AND SOLCATES OF PHARMACEUTICAL SOLIDS", ADVANCED DRUG DELIVERY REV, ELSEVIER, AMSTERDAM, NL, vol. 56, no. 3, 1 January 2004 (2004-01-01), pages 275-300, XP009072233, ISSN: 0169-409X, DOI: 10.1016/J.ADDR.2003.10.020

DESCRIPTION

RELATED APPLICATIONS

[0001] This application claims priority to, and the benefit of, U.S. Provisional Application No. 62/471,908, filed March 15, 2017.

TECHNICAL FIELD

[0002] This disclosure relates to solid crystalline forms of each of three compounds: (1) heptadecan-9-yl 8-((2-hydroxyethyl)amino)octanoate ("Compound 1"), (2) heptadecan-9-yl 8-((2-hydroxyethyl)(6-oxo-6-(undecyloxy)hexyl)amino)octanoate ("Compound 2"), and (3) heptadecan-9-yl 8-((2-hydroxyethyl)(8-(nonyloxy)-8-oxooctyl)amino)octanoate ("Compound 3"), and related compositions and methods. This disclosure also relates to solid crystalline forms of (6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl 4-(dimethylamino)butanoate ("MC3"), and related compositions and methods.

BACKGROUND

[0003] The effective targeted delivery of biologically active substances such as small molecule drugs, proteins, and nucleic acids represents a continuing medical challenge. In particular, the delivery of nucleic acids to cells is made difficult by the relative instability and low cell permeability of such species. Thus, there exists a need to develop methods and compositions to facilitate the delivery of therapeutic and/or prophylactics such as nucleic acids to cells.

[0004] Lipid-containing nanoparticle compositions, liposomes, and lipoplexes have proven effective as transport vehicles into cells and/or intracellular compartments for biologically active substances such as small molecule drugs, proteins, and nucleic acids. Such compositions generally include one or more "cationic" and/or amino (ionizable) lipids, phospholipids including polyunsaturated lipids, structural lipids (e.g., sterols), and/or lipids containing polyethylene glycol (PEG lipids). Cationic and/or ionizable lipids include, for example, aminecontaining lipids that can be readily protonated. Though a variety of such lipid-containing nanoparticle compositions have been demonstrated, improvements in safety, efficacy, and specificity are still lacking. In addition, the physical and chemical properties of lipid materials often present challenges relating to the practice of making and using lipid-containing nanoparticles for drug delivery.

[0005] WO2016/176330A1 discloses nucleoside-modified RNA for inducing an adaptive immune response. WO2012/000104A1 discloses non-liposomal systems for nucleic acid delivery. WO2012/054365A2 discloses novel low molecular weight cationic lipids for oligonucleotide delivery. Muthusamy Jayaraman et al disclose, in ANGEWANDTE CHEMIE INTERNATIONAL EDITION, (2012), vol. 51, no. 34, pages 8529 - 8533, "Maximizing the Potency of siRNA Lipid

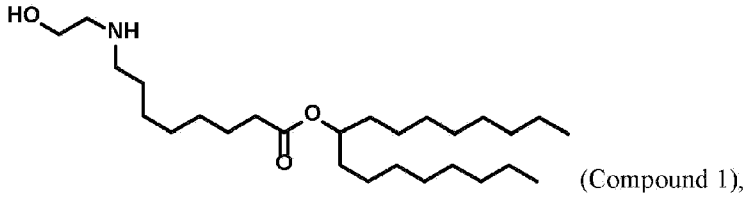
Nanoparticles for Hepatic Gene Silencing In Vivo". WO2015/011633A1 discloses compositions and methods for delivering messenger RNA.

SUMMARY

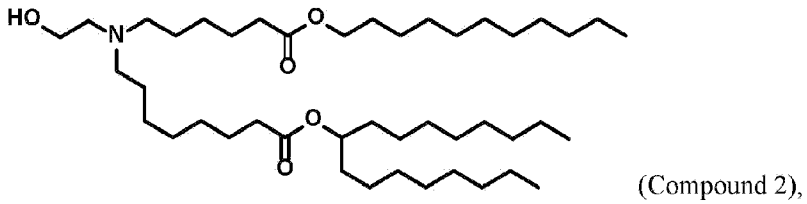
[0006] The following description and figures may encompass subject-matter and embodiments which are not intended to be included within the scope of the invention. The scope of the invention, and hence the scope of protection intended, is solely defined by the appended claims and does not extend beyond the scope defined by them.

[0007] Long-chain amino lipids are usually viscous oils at room temperature. Solid forms of these lipids are desirable for e.g., improving handling, improving stability (such as storage stability) and/or control of physical/chemical properties, simplifying purification process, simplifying large-scale production process and/or increasing accuracy in measurements and characterization of lipids.

[0008] Accordingly, provided herein are novel solid forms (e.g., crystalline forms) of each of three compounds (1) heptadecan-9-yl 8-((2-hydroxyethyl)amino)octanoate ("Compound 1"), (2) heptadecan-9-yl 8-((2-hydroxyethyl)(6-oxo-6-(undecyloxy)hexyl)amino)octanoate ("Compound 2"), and (3) heptadecan-9-yl 8-((2-hydroxyethyl)(8-(nonyloxy)-8-oxooctyl)amino)octanoate ("Compound 3"), the structure of each of which is provided below:

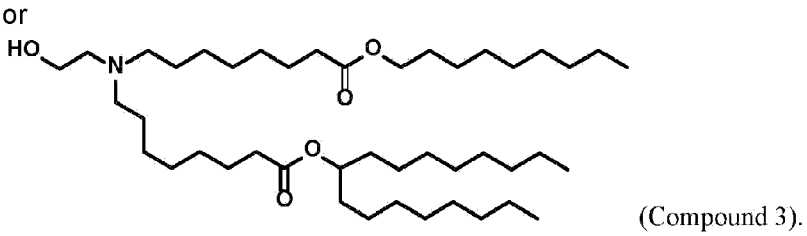


(Compound 1),



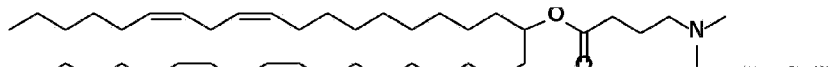
(Compound 2),

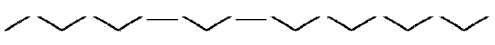
or



(Compound 3).

[0009] In another aspect, provided herein are novel solid forms (e.g., crystalline forms) of (6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl 4-(dimethylamino)butanoate ("MC3"), the structure of which is provided below:





("MC3").

[0010] In one aspect, provided herein is salt or cocrystal which is 4-hydroxybenzoate of heptadecan-9-yl 8-((2-hydroxyethyl)amino)octanoate ("Compound 1"), and which has a melting point of about 50 °C or greater (e.g., about 60 °C, about 70 °C or greater), wherein the salt or cocrystal exhibits an X-ray powder diffraction pattern obtained using Cu Kα radiation, having two, three, four, or more characteristic peaks expressed in degrees 2-theta (+/- 0.2) selected from the group consisting of 4.5, 6.8, 9.1, 11.4, and 13.7.

[0011] In some embodiments, the stoichiometry of Compound 1 and 4-hydroxybenzoic acid is within the range of from 1:0.2 to 1:5; from 1:0.5 to 1:2; or is 1:1.

[0012] In some embodiments, the salt or cocrystal which is 4-hydroxybenzoate of Compound 1 exhibits an X-ray powder diffraction pattern obtained using Cu Kα radiation, having:
(a) characteristic peaks expressed in degrees 2-theta (+/- 0.2) at 4.5, 6.8, 9.1, 11.4, 13.7, 18.3, 20.1, and 20.6; or
(b) at least eight characteristic peaks expressed in degrees 2-theta (+/- 0.2), selected from the group consisting of 4.5, 6.8, 9.1, 11.4, 13.7, 16.0, 18.3, 20.1, and 20.6; or
(c) at least nine characteristic peaks expressed in degrees 2-theta (+/- 0.2), selected from the group consisting of 4.5, 6.8, 9.1, 11.4, 13.7, 16.0, 16.6, 18.3, 20.1, and 20.6; or
(d) at least ten characteristic peaks expressed in degrees 2-theta (+/- 0.2), selected from the group consisting of 4.5, 6.8, 9.1, 11.4, 13.7, 16.0, 16.6, 18.3, 20.1, 20.6, and 21.5; or
(e) peaks with 2-theta values in accordance with the table below:

Peak	Pos. [°2Th.]
1	4.6
2	6.8
3	9.1
4	11.4
5	13.7
6	16.0
7	16.6
8	18.3
9	20.1
10	20.6
11	21.5
12	23.8

[0013] In some embodiments, the salt or cocrystal which is 4-hydroxybenzoate of Compound 1 exhibits a differential scanning calorimetry thermogram showing a primary endotherm expressed in units of °C at a temperature of 103 +/- 2 °C. In some embodiments, the salt or cocrystal shows

a second primary endotherm expressed in units of °C at a temperature of 68 +/- 2 °C.

[0014] In one aspect, provided herein is a salt or cocrystal which is trimesate of (6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl 4-(dimethylamino)butanoate ("MC3"), wherein the salt or cocrystal exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta (+/- 0.2) at 5.2, 7.8, 10.4, 18.3, 20.9, 23.6, and 26.2. In some embodiments, the stoichiometry of MC3 and trimesic acid is within the range of from 1:0.5 mol/mol to 1:2 mol/mol. In some embodiments, the stoichiometry of MC3 and trimesic acid is 1:1.2 mol/mol, 1:1.1 mol/mol, or 1:1.5 mol/mol. In some embodiments, the salt or cocrystal exhibits a differential scanning calorimetry thermogram showing: (a) a primary endotherm expressed in units of °C at a temperature of 184 +/- 2 °C; or (b) a primary endotherm expressed in units of °C at a temperature of 186 +/- 2 °C; and optionally a second primary endotherm expressed in units of °C at a temperature of 90 +/- 2 °C. In some embodiments, the salt or cocrystal exhibits an X-ray powder diffraction pattern obtained using Cu Kα radiation, having
(a) at least seven characteristic peaks expressed in degrees 2-theta (+/- 0.2), selected from the group consisting of 5.2, 7.8, 9.7, 10.4, 18.3, 20.9, 23.6, and 26.2;
(b) at least nine characteristic peaks expressed in degrees 2-theta (+/- 0.2), selected from the group consisting of 5.2, 7.8, 9.7, 10.4, 11.5, 13.0, 18.3, 20.9, 23.6, and 26.2; or
(c) peaks with 2-theta values in accordance with the table below:

Peak	Position [°2Th.]
1	5.2
2	7.8
3	9.7
4	10.4
5	11.5
6	13.0
7	18.3
8	20.9
9	23.6
10	26.2

[0015] In another aspect, provided herein is a salt or cocrystal which is trimesate of (6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl 4-(dimethylamino)butanoate ("MC3"), wherein the salt or cocrystal exhibits an X-ray powder diffraction pattern obtained using Cu Kα radiation, having characteristic peaks expressed in degrees 2-theta (+/- 0.2) at 4.8, 5.4, 7.2, 9.7, 19.4, 24.3, 26.8, and 29.3. In some embodiments, the salt or cocrystal exhibits an X-ray powder diffraction pattern obtained using Cu Kα radiation, having:
(a) at least seven characteristic peaks expressed in degrees 2-theta (+/- 0.2), selected from the group consisting of 4.8, 5.4, 7.2, 9.7, 12.1, 19.4, 21.9, 24.3, 26.8, and 29.3;
(b) at least nine characteristic peaks expressed in degrees 2-theta (+/- 0.2), selected from the group consisting of 4.8, 5.4, 7.2, 9.7, 12.1, 14.5, 17.0, 19.4, 21.9, 24.3, 26.8, 29.3, and 31.8; or

(c) peaks with 2-theta values in accordance with the table below.

Peak	Position [°2Th.]
1	4.8
2	5.4
3	7.2
4	9.7
5	12.1
6	14.5
7	17.0
8	19.4
9	21.9
10	24.3
11	26.8
12	29.3
13	31.8

[0016] In another aspect, provided herein is a salt or cocrystal which is:

1. (a) dibenzoyl-L-tartrate of heptadecan-9-yl 8-((2-hydroxyethyl)(6-oxo-6-(undecyloxy)hexyl)amino)octanoate ("Compound 2"), wherein the salt or cocrystal exhibits an X-ray powder diffraction pattern obtained using Cu Kα radiation, having two characteristic peaks expressed in degrees 2-theta (+/- 0.2) at 6.1 and 9.1;
2. (b) trimesate of Compound 2, wherein the salt or cocrystal exhibits an X-ray powder diffraction pattern obtained using Cu Kα radiation, having four or more characteristic peaks expressed in degrees 2-theta (+/- 0.2), selected from the group consisting of 3.4, 6.8, 10.2, 20.5, and 23.8;
3. (c) L-tartrate of Compound 2, wherein the salt or cocrystal exhibits an X-ray powder diffraction pattern obtained using Cu Kα radiation, having two characteristic peaks expressed in degrees 2-theta (+/- 0.2) at 5.4 and 8.1; or
4. (d) mesylate of Compound 2, wherein the salt or cocrystal exhibits an X-ray powder diffraction pattern obtained using Cu Kα radiation, having four characteristic peaks expressed in degrees 2-theta (+/- 0.2), selected from the group consisting of 4.0, 11.4, 11.8, and 19.8.

[0017] In yet another aspect, provided herein is a salt or cocrystal which is trimesate of heptadecan-9-yl 8-((2-hydroxyethyl)(8-(nonyloxy)-8-oxooctyl)amino)octanoate ("Compound 3"), wherein the salt or cocrystal exhibits an X-ray powder diffraction pattern obtained using Cu Kα radiation, having at least five characteristic peaks expressed in degrees 2-theta (+/- 0.2), selected from the group consisting of 6.2, 10.8, 12.4, 16.5, 18.7, 22.5 and 26.7. In some

embodiments, the stoichiometry of Compound 3 and trimesic acid is within the range of from 1:0.2 mol/mol to 1:5 mol/mol; from 1:0.5 mol/mol to 1:2 mol/mol; or is 1:1 mol/mol.

[0018] In some embodiments, the salt or cocrystal which is trimesate of Compound 3 exhibits:
(a) an X-ray powder diffraction pattern obtained using Cu Kα radiation, having at least six characteristic peaks expressed in degrees 2-theta (+/- 0.2), selected from the group consisting of 6.2, 10.8, 12.4, 16.5, 18.7, 22.5 and 26.7; or
(b) an X-ray powder diffraction pattern obtained using Cu Kα radiation, having peaks with 2-theta values in accordance with the table below:

Peak	Pos. [°2Th.]
1	6.2
2	10.8
3	12.4
4	16.5
5	18.7
6	22.5
7	26.7

[0019] In some embodiments, the salt or cocrystal which is trimesate of Compound 3 exhibits a differential scanning calorimetry thermogram showing a primary endotherm expressed in units of °C at a temperature of 305 +/- 2 °C; and optionally a second primary endotherm expressed in units of °C at a temperature of 240 +/- 2 °C.

[0020] The salts or cocrystals disclosed herein may be anhydrous and/or essentially solvent-free form, or be in hydrate and/or solvate form. For example, 4-hydroxybenzoate of Compound 1 is anhydrous. For example, trimesate of MC3 may be anhydrous or in a hydrate or solvate form.

[0021] The salts or cocrystals disclosed herein may be free of impurities.

[0022] The salts or cocrystals disclosed herein may be a crystalline solid free of other crystalline forms of the salt or cocrystal.

[0023] The salts or cocrystals disclosed herein may be non-hygroscopic. For example, the 4-hydroxybenzoate of Compound 1 is non-hygroscopic. For example, the trimesate of MC3 is non-hygroscopic.

[0024] It has been found that under suitable conditions some of the salts or cocrystals of Compounds 1-3 and some of the salts or cocrystals of MC3 can be obtained in the form of different polymorphs. For example, 4-hydroxybenzoate of Compound 1 has at least two polymorphs, Polymorphs A and B. For example, trimesate of Compound 3 has at least two polymorphs, Polymorphs A and B. For example, trimesate of MC3 has at least two polymorphs, Polymorphs A and B.

[0025] The polymorphs disclosed herein may be substantially pure, i.e., substantially free of impurities. Non-limiting examples of impurities include other polymorph forms, or residual organic and inorganic molecules such as related impurities (e.g., intermediates used to make the compounds), solvents, water or salts. As used herein "substantially pure" or "substantially free of impurities" means there is not a significant amount of impurities (e.g., other polymorph forms, or residual organic and inorganic molecules such as related impurities, solvents, water or salts) present in a sample of the salt, cocrystal, or polymorph. For example, a salt, cocrystal, or polymorph disclosed herein contains less than 10% weight by weight (wt/wt) total impurities, less than 5% wt/wt total impurities, less than 2% wt/wt total impurities, less than 1% wt/wt total impurities, less than 0.5% wt/wt total impurities, or not a detectable amount of impurities.

[0026] The present invention provides Polymorph A of 4-hydroxybenzoate of Compound 1. In one embodiment, Polymorph A of 4-hydroxybenzoate of Compound 1 is substantially free of impurities, meaning there is not a significant amount of impurities present in the sample of Polymorph A. In another embodiment, Polymorph A is a crystalline solid substantially free of Compound 1 (or any of its amorphous salt forms). In yet another embodiment, Polymorph A is a crystalline solid substantially free of other polymorphs of 4-hydroxybenzoate of Compound 1 and substantially free of amorphous Compound 1 (or any of its amorphous salt forms). For example, Polymorph A is a crystalline solid substantially free of Polymorph B of 4-hydroxybenzoate of Compound 1 and substantially free of amorphous Compound 1 (or any of its amorphous salt forms). The skilled artisan understands that a solid sample of Polymorph A may also include other polymorphs (e.g., Polymorph B), and/or amorphous Compound 1 (or any of its amorphous salt forms).

[0027] Polymorph A of 4-hydroxybenzoate of Compound 1 can be defined according to its X-ray powder diffraction pattern. Polymorph A of 4-hydroxybenzoate of Compound 1 exhibits an X-ray powder diffraction pattern obtained using Cu Kα radiation, having two, three, four, or more characteristic peaks expressed in degrees 2-theta (+/- 0.2) selected from the group consisting of 4.5, 6.8, 9.1, 11.4, and 13.7. In one embodiment, Polymorph A exhibits an X-ray powder diffraction pattern obtained using Cu Kα radiation, having peaks with 2-theta values substantially in accordance with Figure 1. In another embodiment, Polymorph A exhibits an X-ray powder diffraction pattern obtained using Cu Kα radiation, having peaks with 2-theta values substantially in accordance with Table I.

[0028] Polymorph A of 4-hydroxybenzoate of Compound 1 can also be defined according to its differential scanning calorimetry thermogram. In one embodiment, the polymorph exhibits a differential scanning calorimetry thermogram showing a primary endotherm expressed in units of °C at a temperature of 103 +/- 2 °C and a second primary endotherm expressed in units of °C at a temperature of 68 +/- 2 °C. In another embodiment, Polymorph A exhibits a differential scanning calorimetry thermogram substantially in accordance with the lower curve shown in Figure 3.

[0029] Also disclosed herein are a salt or cocrystal of heptadecan-9-yl 8-((2-hydroxyethyl)amino)octanoate ("Compound 1") and a compound (e.g., a coformer compound)

selected from the group consisting of oxalic acid, trimellitic acid, orotic acid, trimesic acid, and sulfuric acid. These salts or cocrystals can also be obtained in the form of different polymorphs. For example, orotate of Compound 1 has at least two polymorphs, Polymorphs A and B. Polymorph B of Compound 1 orotate may be substantially free of impurities (e.g., phase or form impurities), meaning there is not a significant amount of impurities present in the sample of Polymorph B. Polymorph B of Compound 1 orotate may be a crystalline solid substantially free of amorphous Compound 1 (or any of its amorphous salt forms). Polymorph B of Compound 1 orotate may be a crystalline solid substantially free of other polymorphs of Compound 1 orotate and substantially free of amorphous Compound 1 (or any of its amorphous salt forms). For example, Polymorph B of Compound 1 orotate may be a crystalline solid substantially free of Polymorph A of Compound 1 orotate and substantially free of amorphous Compound 1 (or any of its amorphous salt forms). The skilled artisan understands that a solid sample of Polymorph B of Compound 1 orotate may also include other polymorphs (e.g., Polymorph A), and/or amorphous Compound 1 (or any of its amorphous salt forms).

[0030] Polymorph B of Compound 1 orotate can be defined according to its X-ray powder diffraction pattern. Accordingly, Polymorph B of Compound 1 orotate exhibits an X-ray powder diffraction pattern obtained using Cu Kα radiation, having two, three, four, or more characteristic peaks expressed in degrees 2-theta (+/- 0.2) selected from the group consisting of 5.1, 7.5, 10.1, 12.7, 15.2, and 17.8. Polymorph B of Compound 1 orotate may exhibit an X-ray powder diffraction pattern obtained using Cu Kα radiation, having peaks with 2-theta values substantially in accordance with Figure 18, upper profile. Polymorph B of Compound 1 orotate may exhibit an X-ray powder diffraction pattern obtained using Cu Kα radiation, having peaks with 2-theta values substantially in accordance with Table III.

[0031] The present invention provides Polymorph B of trimesate of Compound 3. In one embodiment, Polymorph B of trimesate of Compound 3 is substantially free of impurities, meaning there is not a significant amount of impurities present in the sample of Polymorph B. In another embodiment, Polymorph B is a crystalline solid substantially free of Compound 3 (or any of its amorphous salt forms). In yet another embodiment, Polymorph B is a crystalline solid substantially free of other polymorphs of trimesate of Compound 3 and substantially free of amorphous trimesate of Compound 3 (or any of its amorphous salt forms). For example, Polymorph B is a crystalline solid substantially free of Polymorph A of trimesate of Compound 3 and substantially free of amorphous trimesate of Compound 3 (or any of its amorphous salt forms). The skilled artisan understands that a solid sample of Polymorph B may also include other polymorphs (e.g., Polymorph A) and/or amorphous Compound 3 (or any of its amorphous salt forms).

[0032] Polymorph B of Compound 3 trimesate can be defined according to its X-ray powder diffraction pattern. Accordingly, Polymorph B of Compound 3 trimesate exhibits an X-ray powder diffraction pattern obtained using Cu Kα radiation, having at least five characteristic peaks expressed in degrees 2-theta (+/- 0.4) at 6.2, 10.8, 12.4, 16.5, 18.7, 22.5, and 26.7. In one embodiment, Polymorph B exhibits an X-ray powder diffraction pattern obtained using Cu Kα radiation, having peaks with 2-theta values substantially in accordance with Figure 48. In another embodiment, Polymorph B exhibits an X-ray powder diffraction pattern obtained using Cu Kα

radiation, having peaks with 2-theta values substantially in accordance with Table XII.

[0033] In other embodiments, Polymorph B of trimesate of Compound 3 is identifiable on the basis of a characteristic peak observed in a differential scanning calorimetry thermogram. In one embodiment, the polymorph exhibits a differential scanning calorimetry thermogram showing a characteristic melting endotherm peak expressed in units of °C with an onset temperature of about 305 +/- 2 °C. In another embodiment, the polymorph exhibits a differential scanning calorimetry thermogram showing a second primary endotherm expressed in units of °C at a temperature of 240 +/- 2 °C. In another embodiment, the polymorph exhibits a differential scanning calorimetry thermogram substantially in accordance with Figure 49.

[0034] The present invention provides Polymorph A of trimesate of MC3, which exhibits an X-ray powder diffraction pattern obtained using Cu Kα radiation, having characteristic peaks expressed in degrees 2-theta (+/- 0.4) at 5.2, 7.8, 10.4, 18.3, 20.9, 23.6, and 26.2, In one embodiment, Polymorph A of trimesate of MC3 is substantially free of impurities, meaning there is not a significant amount of impurities present in the sample of Polymorph A. In another embodiment, Polymorph A is a crystalline solid substantially free of MC3 (or any of its amorphous salt forms). In yet another embodiment, Polymorph A is a crystalline solid substantially free of other polymorphs of trimesate of MC3 and substantially free of amorphous MC3 (or any of its amorphous salt forms). For example, Polymorph A is a crystalline solid substantially free of Polymorph B of trimesate of MC3 and substantially free of amorphous MC3 (or any of its amorphous salt forms). The skilled artisan understands that a solid sample of Polymorph A may also include other polymorphs (e.g., Polymorph B), and/or amorphous MC3 (or any of its amorphous salt forms).

[0035] In one embodiment, Polymorph A exhibits an X-ray powder diffraction pattern obtained using Cu Kα radiation, having peaks with 2-theta values substantially in accordance with Figure 52. In another embodiment, Polymorph A exhibits an X-ray powder diffraction pattern obtained using Cu Kα radiation, having peaks with 2-theta values substantially in accordance with Table XIII.

[0036] Polymorph A of MC3 trimesate can also be defined according to its differential scanning calorimetry thermogram. In one embodiment, the polymorph exhibits a differential scanning calorimetry thermogram showing a primary endotherm expressed in units of °C at a temperature of 184 +/- 2 °C. In one embodiment, the polymorph exhibits a differential scanning calorimetry thermogram showing a primary endotherm expressed in units of °C at a temperature of 186 +/- 2 °C and a second primary endotherm expressed in units of °C at a temperature of 90 +/- 2 °C. In yet another embodiment, the polymorph exhibits a differential scanning calorimetry thermogram substantially in accordance with Figure 53 or Figure 54.

[0037] The present invention also provides Polymorph B of trimesate of MC3, which exhibits an X-ray powder diffraction pattern obtained using Cu Kα radiation, having characteristic peaks expressed in degrees 2-theta (+/- 0.2) at 4.8, 5.4, 7.2, 9.7, 19.4, 24.3, 26.8, and 29.3. In some embodiments, Polymorph B of trimesate of MC3 exhibits an X-ray powder diffraction pattern obtained using Cu Kα radiation having at least seven characteristic peaks expressed in degrees

2-theta (+/- 0.2), selected from the group consisting of 4.8, 5.4, 7.2, 9.7, 12.1, 19.4, 21.9, 24.3, 26.8, and 29.3. In some embodiments, Polymorph B of trimesate of MC3 exhibits an X-ray powder diffraction pattern obtained using Cu Kα radiation having at least nine characteristic peaks expressed in degrees 2-theta (+/- 0.4) at 4.8, 5.4, 7.2, 9.7, 12.1, 14.5, 17.0, 19.4, 21.9, 24.3, 26.8, 29.3, or 31.8. In one embodiment, Polymorph B exhibits an X-ray powder diffraction pattern obtained using Cu Kα radiation, having peaks with 2-theta values substantially in accordance with Figure 59. In another embodiment, Polymorph B exhibits an X-ray powder diffraction pattern obtained using Cu Kα radiation, having peaks with 2-theta values substantially in accordance with Table XIV.

[0038] Polymorph B of MC3 trimesate can also be defined according to its differential scanning calorimetry thermogram. In one embodiment, the polymorph exhibits a differential scanning calorimetry thermogram showing a primary endotherm expressed in units of °C at a temperature of 187 +/- 2 °C. In another embodiment, the polymorph exhibits a differential scanning calorimetry thermogram substantially in accordance with Figure 60.

[0039] Also described herein is the preparation of the salt or cocrystal of heptadecan-9-yl 8-((2-hydroxyethyl)amino)octanoate ("Compound 1") and a compound selected from the group consisting of 4-hydroxybenzoic acid, oxalic acid, trimellitic acid, orotic acid, trimesic acid, and sulfuric acid.

[0040] Also described herein is a method for preparing the salt or cocrystal of heptadecan-9-yl 8-((2-hydroxyethyl)(6-oxo-6-(undecyloxy)hexyl)amino)octanoate ("Compound 2") and a compound selected from the group consisting of trimesic acid, (-)-2,3-dibenzoyl-L-tartaric acid, 4-acetamido benzoic acid, (+)-L-tartaric acid, and methanesulfonic acid.

[0041] This disclosure also provides a method of preparing the salt or cocrystal of heptadecan-9-yl 8-((2-hydroxyethyl)(8-(nonyloxy)-8-oxooctyl)amino)octanoate ("Compound 3") and trimesic acid.

[0042] This disclosure also provides a method of preparing the salt or cocrystal of . (6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl 4-(dimethylamino)butanoate ("MC3") ("MC3") and trimesic acid.

[0043] Also disclosed herein is a process of synthesizing Compound 2, Compound 3, or an analog thereof by reacting a salt or cocrystal of Compound 1 disclosed herein with a suitable electrophile, such as an ester substituted with a halogen (e.g., Br or I).

[0044] Also disclosed herein is a process of purifying Compound 1, 2, or 3 by forming a salt or cocrystal thereof disclosed herein to separate the salt or cocrystal thereof from the impurities. The method may further comprise neutralizing the salt or cocrystal to convert to Compound 1, 2, or 3 (i.e., a free base).

[0045] The process of the present disclosure is advantageous as compared to other processes in that the process of the disclosure produces Compound 1, 2, or 3 or a salt or cocrystal thereof

at a large scale and/or at a high purity, e.g., such that cumbersome purification (e.g., column chromatography, extraction, phase separation, distillation and solvent evaporation) is not needed. The process of the present disclosure is able to process at least 100 g, 200 g, 500 g, or more (e.g., 1 kg, 2 kg, 5 kg, 10 kg, 20 kg, 50 kg, 100 kg, 200 kg, 500 kg, or 1000 kg or more) Compound 1, 2, or 3 or a salt or cocrystal thereof. The process of the present disclosure is able to produce Compound 1, 2, or 3 or a salt or cocrystal thereof at least at a purity of at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 99.5%, or higher. The process of the present disclosure is able to produce Compound 1, 2, or 3 or a salt or cocrystal thereof with little or no impurity The impurity produced in the process of the present disclosure, even if produced, may be easily separated from Compound 1, 2, or 3 or a salt or cocrystal thereof, without cumbersome purification (e.g., column chromatography, extraction, phase separation, distillation and solvent evaporation).

[0046] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. In the specification, the singular forms also include the plural unless the context clearly dictates otherwise. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. In the case of conflict, the present specification, including definitions, will control. In addition, the materials, methods and examples are illustrative only and are not intended to be limiting.

[0047] Other features and advantages of the invention will be apparent from the following drawings, detailed description and claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0048]

Figure 1 depicts a representative X-ray powder diffraction (XRPD) pattern overlay of heptadecan-9-yl 8-((2-hydroxyethyl)amino)octanoate 4-hydroxybenzoate Polymorph A batches, i.e., 100 mg and 10 mg batches or batches Nos. 1 and 2.

Figure 2 depicts a ^{1}H NMR spectrum of heptadecan-9-yl 8-((2-hydroxyethyl)amino)octanoate 4-hydroxybenzoate Polymorph A, batch No. 2.

Figure 3 depicts thermo-gravimetric analysis (TGA) and differential scanning calorimetry (DSC) data for heptadecan-9-yl 8-((2-hydroxyethyl)amino)octanoate 4-hydroxybenzoate Polymorph A, batch No. 2.

Figure 4 depicts cyclic DSC data for heptadecan-9-yl 8-((2-hydroxyethyl)amino)octanoate 4-hydroxybenzoate Polymorph A, batch No. 2.

Figure 5 depicts a representative XRPD pattern overlay of heptadecan-9-yl 8-((2-hydroxyethyl)amino)octanoate 4-hydroxybenzoate Polymorph A (i.e., Type A in the figure), batch

No. 2, before and after heating.

Figure 6 depicts TGA and DSC data for heptadecan-9-yl 8-((2-hydroxyethyl)amino)octanoate 4-hydroxybenzoate Polymorph A, batch No. 1.

Figure 7 depicts variable temperature X-ray powder diffraction (VT-XRPD) pattern overlay of heptadecan-9-yl 8-((2-hydroxyethyl)amino)octanoate 4-hydroxybenzoate Polymorph A batch No. 1, before and after heating. Type A ref. in this figure is heptadecan-9-yl 8-((2-hydroxyethyl)amino)octanoate 4-hydroxybenzoate Polymorph A, batch No. 2.

Figure 8 depicts dynamic vapor sorption (DVS) data at 25 °C for heptadecan-9-yl 8-((2-hydroxyethyl)amino)octanoate 4-hydroxybenzoate Polymorph A, batch No. 1.

Figure 9 depicts an XRPD pattern overlay of heptadecan-9-yl 8-((2-hydroxyethyl)amino)octanoate 4-hydroxybenzoate Polymorph A, batch No. 1, before and after DVS.

Figure 10 depicts a polarized light microscopy (PLM) image for heptadecan-9-yl 8-((2-hydroxyethyl)amino)octanoate 4-hydroxybenzoate Polymorph A, batch No. 1.

Figure 11 depicts a representative XRPD pattern overlay of heptadecan-9-yl 8-((2-hydroxyethyl)amino)octanoate trimellitate Polymorph A batches, i.e., 100 mg and 10 mg batches or batches Nos. 1 and 2.

Figure 12 depicts an ^{1}H NMR spectrum of heptadecan-9-yl 8-((2-hydroxyethyl)amino)octanoate trimellitate Polymorph A, batch No. 2.

Figure 13 depicts TGA and DSC data for heptadecan-9-yl 8-((2-hydroxyethyl)amino)octanoate trimellitate Polymorph A, batch No. 1.

Figure 14 depicts a VT-XRPD pattern overlay of heptadecan-9-yl 8-((2-hydroxyethyl)amino)octanoate trimellitate Polymorph A batch No. 1, before and after heating.

Figure 15 depicts DVS data at 25 °C for heptadecan-9-yl 8-((2-hydroxyethyl)amino)octanoate trimellitate Polymorph A, batch No. 1.

Figure 16 depicts an XRPD pattern overlay of heptadecan-9-yl 8-((2-hydroxyethyl)amino)octanoate trimellitate Polymorph A, batch No. 1, before and after DVS.

Figure 17 depicts a polarized light microscopy (PLM) image for heptadecan-9-yl 8-((2-hydroxyethyl)amino)octanoate trimellitate Polymorph A, batch No. 1.

Figure 18 depicts a representative XRPD pattern overlay of heptadecan-9-yl 8-((2-hydroxyethyl)amino)octanoate orotate Polymorphs A and B.

Figure 19 depicts an ^{1}H NMR spectrum of heptadecan-9-yl 8-((2-hydroxyethyl)amino)octanoate orotate Polymorph A.

Figure 20 depicts TGA and DSC data for heptadecan-9-yl 8-((2-hydroxyethyl)amino)octanoate

orotate Polymorph A.

Figure 21 depicts a VT-XRPD pattern overlay of heptadecan-9-yl 8-((2-hydroxyethyl)amino)octanoate orotate Polymorph A, before and after heating.

Figure 22 depicts heating-cooling DSC curve for heptadecan-9-yl 8-((2-hydroxyethyl)amino)octanoate orotate Polymorph A.

Figure 23 depicts TGA and DSC data for heptadecan-9-yl 8-((2-hydroxyethyl)amino)octanoate orotate Polymorphs B.

Figure 24 depicts cyclic DSC data for heptadecan-9-yl 8-((2-hydroxyethyl)amino)octanoate orotate Polymorphs B.

Figure 25 depicts an XRPD pattern overlay of heptadecan-9-yl 8-((2-hydroxyethyl)amino)octanoate orotate Polymorph B, before and after cyclic DSC.

Figure 26 depicts DVS data at 25 °C for heptadecan-9-yl 8-((2-hydroxyethyl)amino)octanoate orotate Polymorphs B.

Figure 27 depicts an XRPD pattern overlay of heptadecan-9-yl 8-((2-hydroxyethyl)amino)octanoate orotate Polymorph B, before and after DVS.

Figure 28 depicts a PLM image of heptadecan-9-yl 8-((2-hydroxyethyl)amino)octanoate orotate Polymorph B.

Figure 29 depicts a PLM image of heptadecan-9-yl 8-((2-hydroxyethyl)amino)octanoate sulfate Polymorph A.

Figure 30 depicts an XRPD pattern of heptadecan-9-yl 8-((2-hydroxyethyl)amino)octanoate sulfate Polymorph A.

Figure 31 depicts TGA and DSC data of heptadecan-9-yl 8-((2-hydroxyethyl)amino)octanoate sulfate Polymorph A.

Figure 32 depicts an XRPD pattern of heptadecan-9-yl 8-((2-hydroxyethyl)amino)octanoate trimesate Polymorph A.

Figure 33 depicts an ^{1}H NMR overlay of heptadecan-9-yl 8-((2-hydroxyethyl)amino)octanoate trimesate and freebase.

Figure 34 depicts TGA data of heptadecan-9-yl 8-((2-hydroxyethyl)amino)octanoate.

Figure 35 depicts cyclic DSC data of heptadecan-9-yl 8-((2-hydroxyethyl)amino)octanoate (heating/cooling rate: 10 °C/min).

Figure 36 depicts an XRPD pattern overlay of heptadecan-9-yl 8-((2-hydroxyethyl)(6-oxo-6-(undecyloxy)hexyl)amino)octanoate dibenzoyl-L-tartrate Polymorph A and the corresponding acid, dibenzoyl-L-tartaric acid.

Figure 37 depicts TGA and DSC data for heptadecan-9-yl 8-((2-hydroxyethyl)(6-oxo-6-(undecyloxy)hexyl)amino)octanoate dibenzoyl-L-tartrate Polymorph A.

Figure 38 depicts an XRPD pattern overlay of heptadecan-9-yl 8-((2-hydroxyethyl)(6-oxo-6-(undecyloxy)hexyl)amino)octanoate trimesate Polymorph A and the corresponding acid, trimesic acid.

Figure 39 depicts TGA and DSC data for heptadecan-9-yl 8-((2-hydroxyethyl)(6-oxo-6-(undecyloxy)hexyl)amino)octanoate trimesate Polymorph A.

Figure 40 depicts an XRPD pattern overlay of heptadecan-9-yl 8-((2-hydroxyethyl)(6-oxo-6-(undecyloxy)hexyl)amino)octanoate L-tartrate Polymorph A and the corresponding acid, L-tartaric acid.

Figure 41 depicts TGA and DSC data for heptadecan-9-yl 8-((2-hydroxyethyl)(6-oxo-6-(undecyloxy)hexyl)amino)octanoate L-tartrate Polymorph A.

Figure 42 depicts an XRPD pattern of heptadecan-9-yl 8-((2-hydroxyethyl)(6-oxo-6-(undecyloxy)hexyl)amino)octanoate mesylate Polymorph A.

Figure 43 depicts TGA and DSC data for heptadecan-9-yl 8-((2-hydroxyethyl)(6-oxo-6-(undecyloxy)hexyl)amino)octanoate mesylate Polymorph A.

Figure 44 depicts an XRPD pattern overlay of heptadecan-9-yl 8-((2-hydroxyethyl)(6-oxo-6-(undecyloxy)hexyl)amino)octanoate 4-acetamido benzoate Polymorph A and the corresponding acid, 4-acetamido benzoic acid.

Figure 45 depicts TGA and DSC data for heptadecan-9-yl 8-((2-hydroxyethyl)(6-oxo-6-(undecyloxy)hexyl)amino)octanoate 4-acetamido benzoate Polymorph A.

Figure 46 depicts an XRPD pattern overlay of heptadecan-9-yl 8-((2-hydroxyethyl)(8-(nonyloxy)-8-oxooctyl)amino)octanoate trimesate Polymorph A and the corresponding acid, trimesic acid.

Figure 47 depicts TGA and DSC data for heptadecan-9-yl 8-((2-hydroxyethyl)(8-(nonyloxy)-8-oxooctyl)amino)octanoate trimesate Polymorph A.

Figure 48 depicts an XRPD pattern of heptadecan-9-yl 8-((2-hydroxyethyl)(8-(nonyloxy)-8-oxooctyl)amino)octanoate trimesate Polymorph B.

Figure 49 depicts TGA and DSC data for heptadecan-9-yl 8-((2-hydroxyethyl)(8-(nonyloxy)-8-oxooctyl)amino)octanoate trimesate Polymorph B.

Figure 50 depicts an ^{1}H NMR overlay of heptadecan-9-yl 8-((2-hydroxyethyl)(8-(nonyloxy)-8-oxooctyl)amino)octanoate trimesate Polymorph B and freebase.

Figure 51 is a polarized light microscopy (PLM) image of heptadecan-9-yl 8-((2-hydroxyethyl)(8-(nonyloxy)-8-oxooctyl)amino)octanoate trimesate Polymorph B.

Figure 52 is an XRPD pattern of (6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl 4-

(dimethylamino)butanoate trimesate Type A polymorph.

Figure 53 depicts TGA and DSC data for (6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl 4-(dimethylamino)butanoate trimesate Type A polymorph prepared with cyclohexane.

Figure 54 depicts TGA and DSC data for (6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl 4-(dimethylamino)butanoate trimesate Type A polymorph prepared with EtOAc.

Figure 55 is a polarized light microscopy (PLM) image of (6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl 4-(dimethylamino)butanoate trimesate Type A polymorph prepared with cyclohexane.

Figure 56 is a polarized light microscopy (PLM) image of (6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl 4-(dimethylamino)butanoate trimesate Type A polymorph prepared with EtOAc.

Figure 57 depicts DVS data at 25 °C for (6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl 4-(dimethylamino)butanoate trimesate Type A polymorphs before and after DVS.

Figure 58 is an XRPD pattern overlay of (6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl 4-(dimethylamino)butanoate trimesate Type A polymorphs before and after DVS.

Figure 59 is an XRPD pattern of (6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl 4-(dimethylamino)butanoate trimesate Type B polymorph.

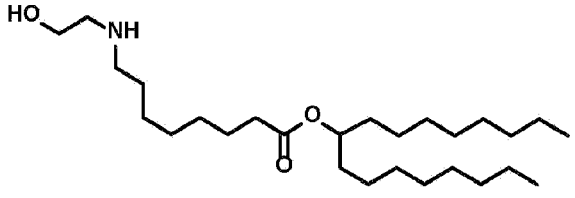
Figure 60 depicts TGA and DSC data for (6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl 4-(dimethylamino)butanoate trimesate Type B.

Figure 61 is a polarized light microscopy (PLM) image of (6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl 4-(dimethylamino)butanoate trimesate Type B polymorph.

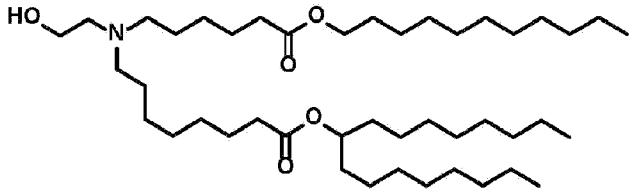
DETAILED DESCRIPTION

[0049] The solid form (e.g., crystal state) of a compound may be important when the compound is used for pharmaceutical purposes. Compared with an amorphous solid or viscous oil, the physical properties of a crystalline compound are generally enhanced. These properties change from one solid form to another, which may impact its suitability for pharmaceutical use. In addition, different solid forms of a crystalline compound may incorporate different types and/or different amounts of impurities. Different solid forms of a compound may also have different chemical stability upon exposure to heat, light and/or moisture (e.g., atmospheric moisture) over a period of time, or different rates of dissolution. Long-chain amino lipids are usually oils at room temperature. Solid forms of these lipids are desirable for e.g., improving handling, improving stability (such as storage stability), simplifying purification process, simplifying large-scale production process and/or increasing accuracy in measurements and characterization of lipids.

[0050] Provided herein are novel solid forms (e.g., crystalline forms) of each of Compound 1, Compound 2, and Compound 3, the structure of each of which is provided below:

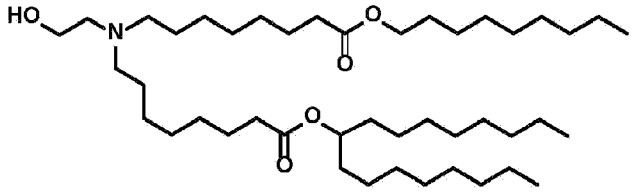


(Compound 1),



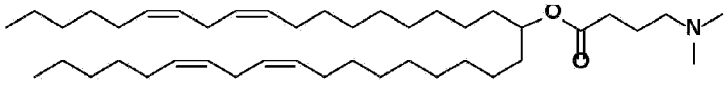
(Compound 2),

or



(Compound 3).

[0051] In another aspect, provided herein are novel solid forms (e.g., crystalline forms) of (6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl 4-(dimethylamino)butanoate ("MC3"), the structure of which is provided below:



("MC3").

[0052] Disclosed herein is salt or cocrystal of Compound 1, 2, or 3, which has a melting point of about 50 °C or greater (e.g., about 60 °C, about 70 °C or greater). For example, the salt or cocrystal of Compound 1, 2, or 3 is formed between Compound 1, 2, or 3 and a coformer compound (e.g., an acid). In another aspect, the salt or cocrystal of Compound 3 has a melting point of about 270 °C or greater (e.g., about 280 °C, about 290 °C or greater).

[0053] As used herein, "Compound 1" refers to heptadecan-9-yl 8-((2-hydroxyethyl)amino)octanoate; "Compound 2" refers to heptadecan-9-yl 8-((2-hydroxyethyl)(6-oxo-6-(undecyloxy)hexyl)amino)octanoate; and "Compound 3" refers to heptadecan-9-yl 8-((2-hydroxyethyl)(8-(nonyloxy)-8-oxooctyl)amino)octanoate. Compound 1 can be used as a starting material for the synthesis of Compound 2 or 3.

[0054] As used herein, "MC 3" refers to (6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl 4-(dimethylamino)butanoate.

[0055] Described herein is a salt or cocrystal of Compound 1 and a compound selected from the group consisting of 4-hydroxybenzoic acid, oxalic acid, trimellitic acid, orotic acid, trimesic acid,

and sulfuric acid. For example, the compound is 4-hydroxybenzoic acid. For example, the compound is oxalic acid.

[0056] In one aspect, the present invention relates to Polymorph A of 4-hydroxybenzoate of Compound 1. Also described herein are Polymorph B of 4-hydroxybenzoate of Compound 1, and Polymorphs A and B of orotate of Compound 1.

[0057] In one aspect, this disclosure is directed to a salt or cocrystal of (6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl 4-(dimethylamino)butanoate ("MC3"). In another aspect, the salt or cocrystal of MC3 has a melting point of about 150 °C or greater (e.g., about 160 °C, about 170 °C, about 180 °C or greater, about 190 °C or greater). In another aspect, the salt or cocrystal of MC3 has a melting point of about 50 °C or greater (e.g., about 60 °C, about 70 °C, about 80 °C or greater). For example, the salt or cocrystal of MC3 is formed between MC3 and a coformer compound (e.g., an acid).

[0058] The ability of a substance to exist in more than one crystal form is defined as polymorphism; the different crystal forms of a particular substance are referred to as "polymorphs" of one another. In general, polymorphism is affected by the ability of a molecule of a substance (or its salt, cocrystal, or hydrate) to change its conformation or to form different intermolecular or intra-molecular interactions, (e.g., different hydrogen bond configurations), which is reflected in different atomic arrangements in the crystal lattices of different polymorphs. In contrast, the overall external form of a substance is known as "morphology," which refers to the external shape of the crystal and the planes present, without reference to the internal structure. A particular crystalline polymorph can display different morphology based on different conditions, such as, for example, growth rate, stirring, and the presence of impurities.

[0059] The different polymorphs of a substance may possess different energies of the crystal lattice and, thus, in solid state they can show different physical properties such as form, density, melting point, color, stability, solubility, dissolution rate, etc., which can, in turn, effect the stability, dissolution rate and/or bioavailability of a given polymorph and its suitability for use as a pharmaceutical and in pharmaceutical compositions.

[0060] Polymorph A of 4-hydroxybenzoate of Compound 1 has a number of advantageous physical properties over its free base form, as well as other salts of the free base. In particular, Polymorph A of 4-hydroxybenzoate of Compound 1 has low hygroscopicity compared to other salt forms of Compound 1. More particularly, Polymorph A of 4-hydroxybenzoate of Compound 1 has low hygroscopicity compared to Polymorph A of Compound 1 trimellitate and Polymorph B of Compound 1 orotate (see, e.g., Table 1-2). Crystal forms that are highly hygroscopic may also be unstable, as the compound's dissolution rate (and other physicochemical properties) may change as it is stored in settings with varying humidity. Also, hygroscopicity can impact large-scale handling and manufacturing of a compound, as it can be difficult to determine the true weight of a hygroscopic agent when using it for reactions or when preparing a pharmaceutical composition comprising that agent. For example, in large scale medicinal formulating preparations, highly hygroscopic compounds can result in batch manufacturing inconsistency creating clinical and/or prescribing difficulties. For example, when Compound 1 is used as a

starting material for the synthesis of Compound 2 or 3, Polymorph A of 4-hydroxybenzoate of Compound 1 has a low hygoscopicity compared to other salt forms of Compound 1, and as such, it may be stored over appreciable periods or conditions (e.g., relative humidity conditions), and not suffer from weight changes that would be detrimental for consistent production of Compound 2 or 3.

[0061] Polymorph A of 4-hydroxybenzoate of Compound 1 is identifiable on the basis of characteristic peaks in an X-ray powder diffraction analysis. X-ray powder diffraction pattern, also referred to as XRPD pattern, is a scientific technique involving the scattering of x-rays by crystal atoms, producing a diffraction pattern that yields information about the structure of the crystal. Polymorph A of 4-hydroxybenzoate of Compound 1 exhibits an X-ray powder diffraction (XRPD) pattern obtained using Cu Kα radiation, having two, three, four or more characteristic peaks expressed in degrees 2-theta (+/- 0.2) selected from the group consisting of 4.5, 6.8, 9.1, 11.4, and 13.7. In certain embodiments, Polymorph A of 4-hydroxybenzoate of Compound 1 exhibits an X-ray powder diffraction (XRPD) pattern obtained using Cu Kα radiation, having from two (2) to seven (7) characteristic peaks expressed in degrees 2-theta at 4.5, 6.8, 9.1, 11.4, 13.7, 18.3, 20.1, and 20.6.

[0062] The skilled artisan recognizes that some variation is associated with 2-theta measurements in XRPD. Typically, 2-theta values may vary from ±0.1 to ± 0.2. Such slight variation can be caused, for example, by sample preparation, instrument configurations and other experimental factors. The skilled artisan appreciates that such variation in values are greatest with low 2-theta values, and least with high 2-theta values. The skilled artisan recognizes that different instruments may provide substantially the same XRPD pattern, even though the 2-theta values vary slightly. Moreover, the skilled artisan appreciates that the same instrument may provide substantially the same XRPD pattern for the same or different samples even though the XRPD of the respectively collected XRPD patterns vary slightly in the 2-theta values.

[0063] The skilled artisan also appreciates that XRPD patterns of the same sample (taken on the same or different instruments) may exhibit variations in peak intensity at the different 2-theta values. The skilled artisan also appreciates that XRPD patterns of different samples of the same polymorph (taken on the same or different instruments) may also exhibit variations in peak intensity at the different 2-theta values. XRPD patterns can be substantially the same pattern even though they have corresponding 2-theta signals that vary in their peak intensities.

[0064] In one embodiment, Polymorph A of 4-hydroxybenzoate of Compound 1 exhibits an X-ray powder diffraction pattern obtained using Cu Kα radiation, having three or more characteristic peaks expressed in degrees 2-theta (+/- 0.2) selected from the group consisting of 4.5, 6.8, 9.1, 11.4, and 13.7. In another embodiment, Polymorph A of 4-hydroxybenzoate of Compound 1 exhibits an X-ray powder diffraction pattern obtained using Cu Kα radiation, having four or more characteristic peaks expressed in degrees 2-theta (+/- 0.2) selected from the group consisting of 4.5, 6.8, 9.1, 11.4, and 13.7. In another embodiment, Polymorph A of 4-hydroxybenzoate of Compound 1 exhibits an X-ray powder diffraction pattern obtained using Cu Kα radiation, having characteristic peaks expressed in degrees 2-theta (+/- 0.2) at 4.5, 6.8, 9.1, 11.4, 13.7, 18.3,

20.1, and 20.6. In one embodiment, Polymorph A of 4-hydroxybenzoate of Compound 1 exhibits an X-ray powder diffraction pattern obtained using Cu Kα radiation, having two, three, four, or more characteristic peaks expressed in degrees 2-theta (+/- 0.2) selected from the group consisting of 4.5, 6.8, 9.1, 11.4, and 13.7.

[0065] In a particular embodiment, Polymorph A of 4-hydroxybenzoate of Compound 1 exhibits an X-ray powder diffraction pattern obtained using Cu Kα radiation, having at least eight characteristic peaks expressed in degrees 2-theta (+/- 0.2), selected from the group consisting of 4.5, 6.8, 9.1, 11.4, 13.7, 16.0, 18.3, 20.1, and 20.6. In another particular embodiment, Polymorph A of 4-hydroxybenzoate of Compound 1 exhibits an X-ray powder diffraction pattern obtained using Cu Kα radiation, having at least nine characteristic peaks expressed in degrees 2-theta (+/- 0.2), selected from the group consisting of 4.5, 6.8, 9.1, 11.4, 13.7, 16.0, 16.6, 18.3, 20.1, and 20.6. In a further embodiment, Polymorph A of 4-hydroxybenzoate of Compound 1 exhibits an X-ray powder diffraction pattern obtained using Cu Kα radiation, having at least ten characteristic peaks expressed in degrees 2-theta (+/- 0.2), selected from the group consisting of 4.5, 6.8, 9.1, 11.4, 13.7, 16.0, 16.6, 18.3, 20.1, 20.6, and 21.5. In one embodiment, Polymorph A exhibits an X-ray powder diffraction pattern obtained using Cu Kα radiation, having peaks with 2-theta values substantially in accordance with Figure 1. In another embodiment, Polymorph A exhibits an X-ray powder diffraction pattern obtained using Cu Kα radiation, having peaks with 2-theta values substantially in accordance with Table I below.

Table I

Peak		Position [°2Th.]
	1.	4.5
	2.	6.8
	3.	9.1
	4.	11.4
	5.	13.7
	6.	16.0
	7.	16.6
	8.	18.3
	9.	20.1
	10.	20.6
	11.	21.5
	12.	23.8
	13.	24.9
	14.	25.8

[0066] In other embodiments, Polymorph A of 4-hydroxybenzoate of Compound 1 is identifiable on the basis of a characteristic peak observed in a differential scanning calorimetry thermogram. Differential scanning calorimetry, or DSC, is a thermoanalytical technique in which the difference

in the amount of heat required to increase the temperature of a sample and reference is measured as a function of temperature. In one embodiment, Polymorph A of 4-hydroxybenzoate of Compound 1 exhibits a differential scanning calorimetry thermogram showing a characteristic primary endotherm peak expressed in units of °C with an onset temperature of about 103 +/- 2 °C. In another embodiment, Polymorph A of 4-hydroxybenzoate of Compound 1 exhibits a differential scanning calorimetry thermogram showing a characteristic second primary endotherm expressed in units of °C with an onset temperature of about 68 +/- 2 °C. In another embodiment, Polymorph A of 4-hydroxybenzoate of Compound 1 exhibits a differential scanning calorimetry thermogram substantially in accordance with the lower curve shown in Figure 3.

[0067] In another embodiment, provided herein is Polymorph A of 4-hydroxybenzoate of Compound 1, wherein the solid form undergoes a weight increase of less than 1.5% (e.g., less than 1%, or less than 0.6%) upon increasing relative humidity from 5.0% to 95.0% at e.g., 25 °C. In another embodiment, Polymorph A of 4-hydroxybenzoate of Compound 1 is characterized as having a dynamic vapor sorption profile that is substantially in accordance with Figure 8.

[0068] In one embodiment, Polymorph A of 4-hydroxybenzoate of Compound 1 is substantially free of impurities, meaning there is not a significant amount of impurities present in the sample of Polymorph A. In another embodiment, Polymorph A is a crystalline solid substantially free of amorphous Compound 1 (or any of its amorphous salt forms). In yet another embodiment, Polymorph A is a crystalline solid substantially free of other polymorphs of 4-hydroxybenzoate of Compound 1 and substantially free of amorphous Compound 1 (or any of its amorphous salt forms). For example, Polymorph A is a crystalline solid substantially free of Polymorph B of 4-hydroxybenzoate of Compound 1 and substantially free of amorphous Compound 1 (or any of its amorphous salt forms). The skilled artisan understands that a solid sample of Polymorph A may also include other polymorphs (e.g., Polymorph A), and/or amorphous Compound 1 (or any of its amorphous salt forms)

[0069] As used herein, the term "substantially free of amorphous Compound 1" means that the compound contains no significant amount of amorphous Compound 1 (or any of its amorphous salt forms). In another embodiment, a sample of a salt or cocrystal of Compound 1 comprises Polymorph A of 4-hydroxybenzoate of Compound 1 substantially free of other polymorphs (e.g., Polymorph B of 4-hydroxybenzoate of Compound 1). As used herein, the term "substantially free of other polymorphs" means that a sample of crystalline Compound 1 4-hydroxybenzoate contains no significant amount of other polymorphs (e.g., Polymorph B). In certain embodiments, at least about 90% by weight of a sample is Polymorph A, with only 10% being other polymorphs (e.g., Polymorph B) and/or amorphous Compound 1 (or any of its amorphous salt forms). In certain embodiments, at least about 95% by weight of a sample is Polymorph A, with only 5% being other polymorphs (e.g., Polymorph B) and/or amorphous Compound 1 (or any of its amorphous salt forms). In still other embodiments, at least about 98% by weight of a sample is Polymorph A, with only 2% by weight being other polymorphs (e.g., Polymorph B) and/or amorphous Compound 1 (or any of its amorphous salt forms). In still other embodiments, at least about 99% by weight of a sample is Polymorph A, with only 1% by weight being other polymorphs (e.g., Polymorph B) and/or amorphous Compound 1 (or any of its amorphous salt forms). In still other embodiments, at least about 99.5% by weight of a sample is Polymorph A,

with only 0.5% by weight being other polymorphs (e.g., Polymorph B) and/or amorphous Compound 1 (or any of its amorphous salt forms). In still other embodiments, at least about 99.9% by weight of a sample is Polymorph A, with only 0.1% by weight being other polymorphs (e.g., Polymorph B) and/or amorphous Compound 1(or any of its amorphous salt forms).

[0070] In certain embodiments, a sample of a salt or cocrystal of Compound 1 (e.g., Compound 1 4-hydroxybenzoate) may contain impurities. Non-limiting examples of impurities include other polymorph forms, or residual organic and inorganic molecules such as related impurities (e.g., intermediates used to make Compound 1 or by-products, e.g., heptadecan-9-yl 8-bromooctanoate and di(heptadecan-9-yl) 8,8'-((2-hydroxyethyl)azanediyl)dioctanoate), solvents, water or salts. In one embodiment, a sample of a salt or cocrystal of Compound 1 4-hydroxybenzoate Polymorph A is substantially free from impurities, meaning that no significant amount of impurities are present. In another embodiment, a sample of the salt or cocrystal of Compound 1 contains less than 10% weight by weight (wt/wt) total impurities. In another embodiment, a sample of the salt or cocrystal of Compound 1 contains less than 5% wt/wt total impurities. In another embodiment, a sample of the salt or cocrystal of Compound 1 contains less than 2% wt/wt total impurities. In another embodiment, a sample of the salt or cocrystal of Compound 1 contains less than 1% wt/wt total impurities. In yet another embodiment, a sample of the salt or cocrystal of Compound 1 contains less than 0.1% wt/wt total impurities. In yet another embodiment, a sample of the salt or cocrystal of Compound 1 does not contain a detectable amount of impurities.

[0071] Also disclosed herein are Polymorphs A and B of Compound 1 orotate. Polymorph A of Compound 1 orotate exhibits an X-ray powder diffraction pattern obtained using Cu Kα radiation, having two, three, four, or more characteristic peaks expressed in degrees 2-theta (+/-0.2) selected from the group consisting of 5.3, 10.7, 13.3, 16.1, and 18.7. Polymorph A may exhibit an X-ray powder diffraction pattern obtained using Cu Kα radiation, having peaks with 2-theta values substantially in accordance with Figure 18, lower profile. Polymorph A may exhibit an X-ray powder diffraction pattern obtained using Cu Kα radiation, having peaks with 2-theta values substantially in accordance with Table II below.

Table II

Peak	Position [°2Th.]
1.	5.3
2.	10.7
3.	13.3
4.	16.1
5.	18.7
6.	24.3
7.	26.9

[0072] Polymorph B of Compound 1 orotate can be defined according to its X-ray powder diffraction pattern. Accordingly, Polymorph B exhibits an X-ray powder diffraction pattern

obtained using Cu Kα radiation, having two, three, four, or more characteristic peaks expressed in degrees 2-theta (+/- 0.2) selected from the group consisting of 5.1, 7.5, 10.1, 12.7, 15.2, and 17.8. Polymorph B may exhibit an X-ray powder diffraction pattern obtained using Cu Kα radiation, having peaks with 2-theta values substantially in accordance with Figure 18, upper profile. Polymorph B may exhibit an X-ray powder diffraction pattern obtained using Cu Kα radiation, having peaks with 2-theta values substantially in accordance with Table III.

Table III

Peak	Position [°2Th.]
1.	5.1
2.	7.5
3.	10.1
4.	12.7
5.	15.2
6.	17.8
7.	20.2
8.	25.5
9.	28.2

[0073] Also disclosed herein is Polymorph A of Compound 1 trimesate. Polymorph A of Compound 1 trimesate exhibits an X-ray powder diffraction pattern obtained using Cu Kα radiation, having two, three, four, or more characteristic peaks expressed in degrees 2-theta (+/-0.2) selected from the group consisting of 3.3, 5.3, 6.7, 7.9, 10.5, 18.5, 21.3, 23.9, and 26.5. Polymorph A may exhibit an X-ray powder diffraction pattern obtained using Cu Kα radiation, having peaks with 2-theta values substantially in accordance with Figure 32. Polymorph A may exhibit an X-ray powder diffraction pattern obtained using Cu Kα radiation, having peaks with 2-theta values substantially in accordance with Table IV below.

Table IV

Peak		Position [°2Th.]
	1.	3.3
	2.	5.3
	3.	6.7
	4.	7.9
	5.	10.5
	6.	13.6
	7.	18.5
	8.	21.3
	9.	23.9
	10.	26.5
	11.	29.1

Peak	Position [°2Th.]

[0074] Also disclosed is Polymorph A of Compound 1 trimellitate. Polymorph A of Compound 1 trimellitate exhibits an X-ray powder diffraction pattern obtained using Cu Kα radiation, having two, three, four, or more characteristic peaks expressed in degrees 2-theta (+/- 0.2) selected from the group consisting of 4.6, 6.8, 9.2, 11.5, 23.1, and 25.4. Polymorph A may exhibit an X-ray powder diffraction pattern obtained using Cu Kα radiation, having peaks with 2-theta values substantially in accordance with Figure 11. Polymorph A may exhibit an X-ray powder diffraction pattern obtained using Cu Kα radiation, having peaks with 2-theta values substantially in accordance with Table V below.

Table V

Peak		Position [°2Th.]
	1.	4.6
	2.	6.8
	3.	9.2
	4.	11.5
	5.	23.1
	6.	25.4
	7.	27.7

[0075] Also disclosed is Polymorph A of Compound 1 sulfate. Polymorph A of Compound 1 sulfate exhibits an X-ray powder diffraction pattern obtained using Cu Kα radiation, having two, three, four, or more characteristic peaks expressed in degrees 2-theta (+/- 0.2) selected from the group consisting of 4.0, 11.8, 21.4, 21.8, and 22.8. Polymorph A may exhibit an X-ray powder diffraction pattern obtained using Cu Kα radiation, having peaks with 2-theta values substantially in accordance with Figure 30. Polymorph A may exhibit an X-ray powder diffraction pattern obtained using Cu Kα radiation, having peaks with 2-theta values substantially in accordance with Table VI below.

Table VI

Peak	Position [°2Th.]
1.	4.0
2.	11.4
3.	11.8
4.	19.8
5.	21.4
6.	21.8
7.	22.8

[0076] In another aspect, this disclosure is directed to a salt or cocrystal of heptadecan-9-yl 8-((2-hydroxyethyl)(6-oxo-6-(undecyloxy)hexyl)amino)octanoate ("Compound 2") and a compound selected from the group consisting of trimesic acid, (-)-2,3-dibenzoyl-L-tartaric acid, 4-acetamido benzoic acid, (+)-L-tartaric acid, and methanesulfonic acid.

[0077] The present invention provides Polymorph A of Compound 2 trimesate, which exhibits an X-ray powder diffraction pattern obtained using Cu Kα radiation, having four or more characteristic peaks expressed in degrees 2-theta (+/- 0.2) selected from the group consisting of 3.4, 6.8, 10.2, 20.5, and 23.8. In one embodiment, Polymorph A exhibits an X-ray powder diffraction pattern obtained using Cu Kα radiation, having peaks with 2-theta values substantially in accordance with Figure 38. In another embodiment, Polymorph A exhibits an X-ray powder diffraction pattern obtained using Cu Kα radiation, having peaks with 2-theta values substantially in accordance with Table VII below.

Table VII

Peak	Position [°2Th.]
1.	3.4
2.	6.8
3.	10.2
4.	20.5
5.	23.8

[0078] The present invention also provides Polymorph A of Compound 2 dibenzoyl-L-tartrate, which exhibits an X-ray powder diffraction pattern obtained using Cu Kα radiation, having two characteristic peaks expressed in degrees 2-theta (+/- 0.2) at 6.1 and 9.1 (in accordance with Table VIII below). In one embodiment, Polymorph A exhibits an X-ray powder diffraction pattern obtained using Cu Kα radiation, having peaks with 2-theta values substantially in accordance with Figure 36, upper profile.

Table VIII

Peak	Pos. [°2Th.]
1	6.1
2	9.1

[0079] In yet another embodiment, the present invention also provides Polymorph A of Compound 2 L-tartrate, which exhibits an X-ray powder diffraction pattern obtained using Cu Kα radiation, having two characteristic peaks expressed in degrees 2-theta (+/- 0.2) at 5.4 and 8.1 (in accordance with Table IX below). In one embodiment, Polymorph A exhibits an X-ray powder diffraction pattern obtained using Cu Kα radiation, having peaks with 2-theta values substantially in accordance with Figure 40, upper profile.

Table IX

Peak	Position [°2Th.]
1	5.4
2	8.1

[0080] In yet another embodiment, the present invention provides Polymorph A of Compound 2 mesylate, which exhibits an X-ray powder diffraction pattern obtained using Cu Kα radiation, having four characteristic peaks expressed in degrees 2-theta (+/- 0.2) selected from the group consisting of 4.0, 11.4, 11.8, and 19.8. In one embodiment, Polymorph A exhibits an X-ray powder diffraction pattern obtained using Cu Kα radiation, having peaks with 2-theta values substantially in accordance with Figure 42. In another embodiment, Polymorph A exhibits an X-ray powder diffraction pattern obtained using Cu Kα radiation, having peaks with 2-theta values substantially in accordance with Table X below.

Table X

Peak	Position [°2Th.]
1.	4.0
2.	11.4
3.	11.8
4.	19.8
5.	27.9
6.	36.0

[0081] Also disclosed herein is Polymorph A of Compound 3 trimesate. Polymorph A of Compound 3 trimesate exhibits an X-ray powder diffraction pattern obtained using Cu Kα radiation, having two, three, four or more characteristic peaks expressed in degrees 2-theta (+/-0.4) selected from the group consisting of 3.5, 6.8, 10.4, 18.9 and 20.9. Polymorph A may exhibit an X-ray powder diffraction pattern obtained using Cu Kα radiation, having peaks with 2-theta values substantially in accordance with Figure 46. Polymorph A may exhibit an X-ray powder diffraction pattern obtained using Cu Kα radiation, having peaks with 2-theta values substantially in accordance with Table XI below.

Table XI

Peak	Position [°2Th.]
1.	3.5
2.	6.8
3.	10.4
4.	18.9
5.	20.9
6.	24.3
7.	27.5

[0082] In one embodiment, the present invention also provides Polymorph B of Compound 3 trimesate, which exhibits an X-ray powder diffraction pattern obtained using Cu Kα radiation, having at least five characteristic peaks expressed in degrees 2-theta (+/- 0.2), selected from the group consisting of 6.2, 10.8, 12.4, 16.5, 18.7, 22.5, and 26.7. In one embodiment, Polymorph B of Compound 3 trimesate exhibits an X-ray powder diffraction obtained using Cu Kα radiation, pattern having at least six characteristic peaks expressed in degrees 2-theta (+/- 0.2), selected from the group consisting of 6.2, 10.8, 12.4, 16.5, 18.7, 22.5, and 26.7.

[0083] In one embodiment, Polymorph B exhibits an X-ray powder diffraction pattern obtained using Cu Kα radiation, having peaks with 2-theta values substantially in accordance with Figure 48. In another embodiment, Polymorph B exhibits an X-ray powder diffraction obtained using Cu Kα radiation, pattern having peaks with 2-theta values substantially in accordance with Table XII below.

Table XII

Peak	Position [°2Th.]
1.	6.2
2.	10.8
3.	12.4
4.	16.5
5.	18.7
6.	22.5
7.	26.7

[0084] In other embodiments, Polymorph B of trimesate of Compound 3 is identifiable on the basis of a characteristic peak observed in a differential scanning calorimetry thermogram. In one embodiment, Polymorph B of trimesate of Compound 3 exhibits a differential scanning calorimetry thermogram showing a characteristic melting endotherm peak expressed in units of °C with an onset temperature of about 305 +/- 2 °C. In another embodiment, Polymorph A of trimesate of Compound 3 exhibits a differential scanning calorimetry thermogram showing a second primary endotherm expressed in units of °C at a temperature of 240 +/- 2 °C. In another embodiment, Polymorph B of trimesate of Compound 3 exhibits a differential scanning calorimetry thermogram substantially in accordance with Figure 49.

[0085] Polymorph A of trimesate of Compound 3 may be substantially free of impurities, meaning there is not a significant amount of impurities present in the sample of Polymorph A. Polymorph A may be a crystalline solid substantially free of amorphous Compound 3 (or any of its amorphous salt forms). Polymorph A may be a crystalline solid substantially free of other polymorphs of 4-hydroxybenzoate of Compound 3 and substantially free of amorphous Compound 3 (or any of its amorphous salt forms). For example, Polymorph A may be a crystalline solid substantially free of Polymorph B of trimesate of Compound 3 and substantially

free of amorphous Compound 3 (or any of its amorphous salt forms). The skilled artisan understands that a solid sample of Polymorph B may also include other polymorphs (e.g., Polymorph A), and/or amorphous Compound 3 (or any of its amorphous salt forms).

[0086] A sample of a salt or cocrystal of Compound 3 may comprise Polymorph A of trimesate of Compound 3 substantially free of other polymorphs (e.g., Polymorph B of trimesate of Compound 3). As used herein, the term "substantially free of other polymorphs" means that a sample of crystalline Compound 3 trimesate contains no significant amount of other polymorphs (e.g., Polymorph B). In certain examples, at least about 90% by weight of a sample is Polymorph A, with only 10% being other polymorphs (e.g., Polymorph B) and/or amorphous Compound 3 (or any of its amorphous salt forms). In certain examples, at least about 95% by weight of a sample is Polymorph A, with only 5% being other polymorphs (e.g., Polymorph B) and/or amorphous Compound 3 (or any of its amorphous salt forms). In still other examples, at least about 98% by weight of a sample is Polymorph A, with only 2% by weight being other polymorphs (e.g., Polymorph B) and/or amorphous Compound 3 (or any of its amorphous salt forms). In still other examples, at least about 99% by weight of a sample is Polymorph A, with only 1% by weight being other polymorphs (e.g., Polymorph B) and/or amorphous Compound 3 (or any of its amorphous salt forms). In still other examples, at least about 99.5% by weight of a sample is Polymorph A, with only 0.5% by weight being other polymorphs (e.g., Polymorph B) and/or amorphous Compound 3 (or any of its amorphous salt forms). In still other examples, at least about 99.9% by weight of a sample is Polymorph A, with only 0.1% by weight being other polymorphs (e.g., Polymorph B) and/or amorphous Compound 3 (or any of its amorphous salt forms).

[0087] In certain embodiments, a sample of a salt or cocrystal of Compound 3 (e.g., Compound 3 trimesate) may contain impurities. Non-limiting examples of impurities include other polymorph forms, or residual organic and inorganic molecules such as related impurities (e.g., intermediates used to make Compound 3 or by-products), solvents, water or salts. In one embodiment, a sample of a salt or cocrystal of Compound 3, e.g., trimesate Polymorph A is substantially free from impurities, meaning that no significant amount of impurities are present. In another embodiment, a sample of the salt or cocrystal of Compound 3 contains less than 10% weight by weight (wt/wt) total impurities. In another embodiment, a sample of the salt or cocrystal of Compound 3 contains less than 5% wt/wt total impurities. In another embodiment, a sample of the salt or cocrystal of Compound 3 contains less than 2% wt/wt total impurities. In another embodiment, a sample of the salt or cocrystal of Compound 3 contains less than 1% wt/wt total impurities. In yet another embodiment, a sample of the salt or cocrystal of Compound 3 contains less than 0.1% wt/wt total impurities. In yet another embodiment, a sample of the salt or cocrystal of Compound 3 does not contain a detectable amount of impurities.

[0088] In one embodiment, the present invention also provides Polymorph A of MC3 trimesate, which exhibits an X-ray powder diffraction pattern obtained using Cu Kα radiation, having characteristic peaks expressed in degrees 2-theta (+/- 0.2) at 5.2, 7.8, 10.4, 18.3, 20.9, 23.6, and 26.2.

[0089] In one embodiment, Polymorph A of MC3 trimesate exhibits an X-ray powder diffraction

pattern obtained using Cu Kα radiation, having at least seven characteristic peaks expressed in degrees 2-theta (+/- 0.2), selected from the group consisting of 5.2, 7.8, 9.7, 10.4, 18.3, 20.9, 23.6, and 26.2. In another embodiment, Polymorph A of MC3 trimesate exhibits an X-ray powder diffraction pattern obtained using Cu Kα radiation, having at least nine characteristic peaks expressed in degrees 2-theta (+/- 0.2), selected from the group consisting of 5.2, 7.8, 9.7, 10.4, 11.5, 13.0, 18.3, 20.9, 23.6, and 26.2.

[0090] In one embodiment, Polymorph A exhibits an X-ray powder diffraction pattern obtained using Cu Kα radiation, having peaks with 2-theta values substantially in accordance with Figure 52. In another embodiment, Polymorph A exhibits an X-ray powder diffraction pattern obtained using Cu Kα radiation, having peaks with 2-theta values substantially in accordance with Table XIII below.

Table XIII

Peak	Position [°2Th.]
1.	5.2
2.	7.8
3.	9.7
4.	10.4
5.	11.5
6.	13.0
7.	18.3
8.	20.9
9.	23.6
10.	26.2

[0091] In other embodiments, Polymorph A of trimesate of MC3 is identifiable on the basis of a characteristic peak observed in a differential scanning calorimetry thermogram. In one embodiment, Polymorph A of trimesate of MC3 exhibits a differential scanning calorimetry thermogram showing a characteristic melting endotherm peak expressed in units of °C with an onset temperature of about 184 +/- 2 °C. In another embodiment, Polymorph A of trimesate of MC3 exhibits a differential scanning calorimetry thermogram substantially in accordance with the lower curve shown in Figure 53. In another embodiment, Polymorph A of trimesate of MC3 exhibits a differential scanning calorimetry thermogram showing a characteristic melting endotherm peak expressed in units of °C with an onset temperature of about 186 +/- 2 °C. In another embodiment, Polymorph A of trimesate of MC3 exhibits a differential scanning calorimetry thermogram showing a second primary endotherm expressed in units of °C at a temperature of 90 +/- 2 °C. In another embodiment, Polymorph A of trimesate of MC3 exhibits a differential scanning calorimetry thermogram substantially in accordance with Figure 54.

[0092] In another embodiment, provided herein is Polymorph A of trimesate of MC3, wherein the solid form undergoes a weight increase of less than 1.0% (e.g., less than 0.5%, or less than

0.3%) upon increasing relative humidity from 5.0% to 95.0% at e.g., 25 °C. In another embodiment, Polymorph A of trimesate of MC3 is characterized as having a dynamic vapor sorption profile that is substantially in accordance with Figure 57.

[0093] In one embodiment, Polymorph A of trimesate of MC3 is substantially free of impurities, meaning there is not a significant amount of impurities present in the sample of Polymorph A. In another embodiment, Polymorph A is a crystalline solid substantially free of amorphous MC3 (or any of its amorphous salt forms). In yet another embodiment, Polymorph A is a crystalline solid substantially free of other polymorphs of trimesate of MC3 and substantially free of amorphous MC3 (or any of its amorphous salt forms). For example, Polymorph A is a crystalline solid substantially free of Polymorph B of trimesate of MC3 and substantially free of amorphous MC3 (or any of its amorphous salt forms). The skilled artisan understands that a solid sample of Polymorph A may also include other polymorphs (e.g., Polymorph B), and/or amorphous MC3 (or any of its amorphous salt forms).

[0094] As used herein, the term "substantially free of amorphous MC3" means that the compound contains no significant amount of amorphous MC3 (or any of its amorphous salt forms). In another embodiment, a sample of a salt or cocrystal of MC3 comprises Polymorph A of trimesate of MC3 substantially free of other polymorphs (e.g., Polymorph B of trimesate of MC3). As used herein, the term "substantially free of other polymorphs" means that a sample of crystalline MC3 trimesate contains no significant amount of other polymorphs (e.g., Polymorph B). In certain embodiments, at least about 90% by weight of a sample is Polymorph A, with only 10% being other polymorphs (e.g., Polymorph B) and/or amorphous MC3 (or any of its amorphous salt forms). In certain embodiments, at least about 95% by weight of a sample is Polymorph A, with only 5% being other polymorphs (e.g., Polymorph B) and/or amorphous MC3 (or any of its amorphous salt forms). In still other embodiments, at least about 98% by weight of a sample is Polymorph A, with only 2% by weight being other polymorphs (e.g., Polymorph B) and/or amorphous MC3 (or any of its amorphous salt forms). In still other embodiments, at least about 99% by weight of a sample is Polymorph A, with only 1% by weight being other polymorphs (e.g., Polymorph B) and/or amorphous MC3 (or any of its amorphous salt forms). In still other embodiments, at least about 99.5% by weight of a sample is Polymorph A, with only 0.5% by weight being other polymorphs (e.g., Polymorph B) and/or amorphous MC3 (or any of its amorphous salt forms). In still other embodiments, at least about 99.9% by weight of a sample is Polymorph A, with only 0.1% by weight being other polymorphs (e.g., Polymorph B) and/or amorphous MC3 (or any of its amorphous salt forms).

[0095] In certain embodiments, a sample of a salt or cocrystal of MC3 (e.g., MC3 trimesate) may contain impurities. Non-limiting examples of impurities include other polymorph forms, or residual organic and inorganic molecules such as related impurities (e.g., intermediates used to make MC3 or by-products), solvents, water or salts. In one embodiment, a sample of a salt or cocrystal of MC3, e.g., trimesate Polymorph A is substantially free from impurities, meaning that no significant amount of impurities are present. In another embodiment, a sample of the salt or cocrystal of MC3 contains less than 10% weight by weight (wt/wt) total impurities. In another embodiment, a sample of the salt or cocrystal of MC3 contains less than 5% wt/wt total impurities. In another embodiment, a sample of the salt or cocrystal of MC3 contains less than

2% wt/wt total impurities. In another embodiment, a sample of the salt or cocrystal of MC3 contains less than 1% wt/wt total impurities. In yet another embodiment, a sample of the salt or cocrystal of MC3 contains less than 0.1% wt/wt total impurities. In yet another embodiment, a sample of the salt or cocrystal of MC3 does not contain a detectable amount of impurities.

[0096] In one embodiment, the present invention also provides Polymorph B of MC3 trimesate, whichexhibits an X-ray powder diffraction pattern obtained using Cu Kα radiation, having characteristic peaks expressed in degrees 2-theta (+/- 0.2) at 4.8, 5.4, 7.2, 9.7, 19.4, 24.3, 26.8, and 29.3.

[0097] In one embodiment, Polymorph B of MC3 trimesate exhibits an X-ray powder diffraction pattern obtained using Cu Kα radiation, having at least seven characteristic peaks expressed in degrees 2-theta (+/- 0.2), selected from the group consisting of 4.8, 5.4, 7.2, 9.7, 12.1, 19.4, 21.9, 24.3, 26.8, 29.3, and 31.8. In another embodiment, Polymorph B of MC3 trimesate exhibits an X-ray powder diffraction pattern obtained using Cu Kα radiation, having at least nine characteristic peaks expressed in degrees 2-theta (+/- 0.2), selected from the group consisting 4.8, 5.4, 7.2, 9.7, 12.1, 14.5, 17.0, 19.4, 21.9, 24.3, 26.8, and 29.3.

[0098] In one embodiment, Polymorph B exhibits an X-ray powder diffraction pattern obtained using Cu Kα radiation, having peaks with 2-theta values substantially in accordance with Figure 59. In another embodiment, Polymorph B exhibits an X-ray powder diffraction pattern obtained using Cu Kα radiation, having peaks with 2-theta values substantially in accordance with Table XIV below.

Table XIV

Peak	Position [°2Th.]
1.	4.8
2.	5.4
3.	7.2
4.	9.7
5.	12.1
6.	14.5
7.	17.0
8.	19.4
9.	21.9
10.	24.3
11.	26.8
12.	29.3
13.	31.8

[0099] In other embodiments, Polymorph B of trimesate of MC3 is identifiable on the basis of a characteristic peak observed in a differential scanning calorimetry thermogram. In one

embodiment, Polymorph B of trimesate of MC3 exhibits a differential scanning calorimetry thermogram showing a characteristic melting endotherm peak expressed in units of °C with an onset temperature of about 187 +/- 2 °C. In another embodiment, Polymorph B of trimesate of MC3 exhibits a differential scanning calorimetry thermogram substantially in accordance with Figure 60.

[0100] In one embodiment, Polymorph B of trimesate of MC3 is substantially free of impurities, meaning there is not a significant amount of impurities present in the sample of Polymorph B. In another embodiment, Polymorph B is a crystalline solid substantially free of amorphous MC3 (or any of its amorphous salt forms). In yet another embodiment, Polymorph B is a crystalline solid substantially free of other polymorphs of trimesate of MC3 and substantially free of amorphous trimesate of MC3 (or any of its amorphous salt forms). For example, Polymorph B is a crystalline solid substantially free of Polymorph A of trimesate of MC3 and substantially free of amorphous trimesate of MC3 (or any of its amorphous salt forms). The skilled artisan understands that a solid sample of Polymorph B may also include other polymorphs (e.g., Polymorph A), and/or amorphous MC3 (or any of its amorphous salt forms). As used herein, the term "substantially free of amorphous MC3" means that the compound contains no significant amount of amorphous MC3 (or any of its amorphous salt forms).

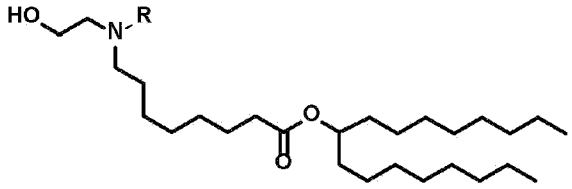
[0101] In another embodiment, a sample of a salt or cocrystal of MC3 comprises Polymorph B of trimesate of MC3 substantially free of other polymorphs (e.g., Polymorph A of trimesate of MC3).

[0102] As used herein, the term "substantially free of other polymorphs" means that a sample of crystalline MC3 trimesate contains no significant amount of other polymorphs (e.g., Polymorph A). In certain embodiments, at least about 90% by weight of a sample is Polymorph B, with only 10% being other polymorphs (e.g., Polymorph A) and/or amorphous MC3 (or any of its amorphous salt forms). In certain embodiments, at least about 95% by weight of a sample is Polymorph B, with only 5% being other polymorphs (e.g., Polymorph A) and/or amorphous MC3 (or any of its amorphous salt forms). In still other embodiments, at least about 98% by weight of a sample is Polymorph B, with only 2% by weight being other polymorphs (e.g., Polymorph A) and/or amorphous MC3 (or any of its amorphous salt forms). In still other embodiments, at least about 99% by weight of a sample is Polymorph B, with only 1% by weight being other polymorphs (e.g., Polymorph A) and/or amorphous MC3 (or any of its amorphous salt forms). In still other embodiments, at least about 99.5% by weight of a sample is Polymorph B, with only 0.5% by weight being other polymorphs (e.g., Polymorph A) and/or amorphous MC3 (or any of its amorphous salt forms). In still other embodiments, at least about 99.9% by weight of a sample is Polymorph B, with only 0.1% by weight being other polymorphs (e.g., Polymorph A) and/or amorphous MC3 (or any of its amorphous salt forms).

[0103] In certain embodiments, a sample of a salt or cocrystal of MC3 (e.g., MC3 trimesate) may contain impurities. Non-limiting examples of impurities include other polymorph forms, or residual organic and inorganic molecules such as related impurities (e.g., intermediates used to make MC3 or by-products), solvents, water or salts. In one embodiment, a sample of a salt or cocrystal of MC3, e.g., trimesate Polymorph B is substantially free from impurities, meaning that no significant amount of impurities are present. In another embodiment, a sample of the salt or

cocrystal of MC3 contains less than 10% weight by weight (wt/wt) total impurities. In another embodiment, a sample of the salt or cocrystal of MC3 contains less than 5% wt/wt total impurities. In another embodiment, a sample of the salt or cocrystal of MC3 contains less than 2% wt/wt total impurities. In another embodiment, a sample of the salt or cocrystal of MC3 contains less than 1% wt/wt total impurities. In yet another embodiment, a sample of the salt or cocrystal of MC3 contains less than 0.1% wt/wt total impurities.

[0104] Also disclosed herein is a salt or cocrystal of an alkylated Compound 1 (structure of which is shown below, wherein R is an alkyl having, e.g., 1-20 carbon atoms) and a coformer compound such as those disclosed herein, e.g., 4-hydroxybenzoic acid, oxalic acid, trimellitic acid, orotic acid, trimesic acid, sulfuric acid, (-)-2,3-dibenzoyl-L-tartaric acid, 4-acetamido benzoic acid, (+)-L-tartaric acid, and methanesulfonic acid. For example, the salt or cocrystal of an alkylated Compound 1 has a melting point of about 50 °C or greater (e.g., about 60 °C, 70 °C, or greater).



("alkylated Compound 1").

[0105] The salts or cocrystals disclosed herein may comprise Compound 1 (or Compound 2 or 3) and the coformer compound (e.g., an acid), within a ratio from 1:0.2 mol/mol to 1:5 mol/mol or from about 1:0.5 mol/mol to 1:2 mol/mol, or from 1:0.4 mol/mol to 1:1.1 mol/mol. For example, the molar ratio is about 1:1 mol/mol.

[0106] The salts or cocrystals disclosed herein may comprise (6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl 4-(dimethylamino)butanoate ("MC3") and the coformer compound (e.g., an acid), within a ratio from 1:0.5 mol/mol (i.e., 2:1 mol/mol) to 1:2 mol/mol.

[0107] The salts or cocrystals disclosed herein may be anhydrous and/or essentially solvent-free form, or be in hydrate and/or solvate form. For example, 4-hydroxybenzoate of Compound 1 is anhydrous. For example, Compound 1 orotate may be anhydrous or in a hydrate or solvate form.

Preparation of Salts or Cocrystals and Polymorphs thereof

[0108] General techniques for making polymorphs are understood by the skilled artisan. Conventionally, a salt form or cocrystal is prepared by combining in solution the free base compound and a coformer (e.g., an acid coformer) containing the anion of the salt form desired, and then isolating the solid salt or cocrystal product from the reaction solution (e.g., by crystallization, precipitation, evaporation, etc.). Other salt-forming or cocrystallization techniques may be employed.

[0109] In one aspect, provided herein is a method of preparing a salt or cocrystal of Compound 1 by combining Compound 1 with a compound selected from the group consisting of 4-hydroxybenzoic acid, oxalic acid, trimellitic acid, orotic acid, trimesic acid, and sulfuric acid. The method may comprise the steps: a) dissolving Compound 1 in a solvent to obtain a solution; b) combining the coformer compound with the solution; c) precipitating or crystallizing the salt or cocrystal from the solution; and d) collecting the salt or cocrystal. In one embodiment, the solvent used in step a) is n-heptane, ethyl acetate, or cyclohexane.Step c) may be carried out substantively free of evaporation to obtain 4-hydroxybenzoate, trimellitate, orotate, and trimesate of Compound 1. In another example, step c) is carried out by slow evaporation, at e.g., 5 °C, to obtain, e.g., sulfate of Compound 1. In some examples, the molar ratio of Compound 1 and the compound is about 1:1.

[0110] Also provided herein is a method for preparing a salt or cocrystal of Compound 2 by combining Compound 2 with a compound selected from the group consisting of trimesic acid, (-)-2,3-dibenzoyl-L-tartaric acid, 4-acetamido benzoic acid, (+)-L-tartaric acid, and methanesulfonic acid. The method may comprise the steps: a) dissolving Compound 2 in a solvent to obtain a solution; b) combining the coformer compound with the solution; c) precipitating or crystallizing the salt or cocrystal from the solution; and d) collecting the salt or cocrystal. In one example, the solvent used in step a) is n-heptane, ethyl acetate, or cyclohexane. In one example, step c) is carried out substantively free of evaporation to obtain trimesate, dibenzoyl-L-tartrate, or 4-acetamido benzoate of Compound 2. In another example, step c) is carried out by slow evaporation, at e.g., 5 °C, to obtain, e.g., dibenzoyl-L-tartrate, L-tartrate, or mesylate of Compound 2. In some embodiments, the molar ratio of Compound 2 and the compound is about 1:1.

[0111] This disclosure also provides a method of preparing the salt or cocrystal of Compound 3 by combining Compound 3 and trimesic acid. The method may comprise the steps: a) dissolving Compound 3 in a solvent to obtain a solution; b) combining trimesic acid with the solution; c) precipitating or crystallizing the salt or cocrystal from the solution; and d) collecting the salt or cocrystal. In one example, the solvent used in step a) is n-heptane or toluene. In one embodiment, step c) is carried out substantively free of evaporation. In another example, step c) is carried out by slow evaporation. In some embodiments, the molar ratio of Compound 3 and the compound is about 1:1.

[0112] This disclosure also provides a method of preparing the salt or cocrystal of MC3 by combining MC3 and a compound selected from (+)-O,O-di-pivaloyl-D-tartaric acid (DPDT), (-)-O,O-di-pivaloyl-L-tartaric acid (DPLT), (+)-2,3-dibenzoyl-D-tartaric acid (DBDT), and trimesic acid. The method may comprise the steps: a) dissolving MC3 in a solvent to obtain a solution; b) combining the compound with the solution; c) precipitating or crystallizing the salt or cocrystal from the solution; and d) collecting the salt or cocrystal. In one example, the solvent used in step a) is ethyl acetate, toluene, or cyclohexane. In one example, step c) is carried out substantively free of evaporation. In another example, step c) is carried out by slow evaporation. In some embodiments, the molar ratio of MC3 and the compound is about 1:1.

[0113] This disclosure also provides a method of preparing the salt or cocrystal of MC3 by

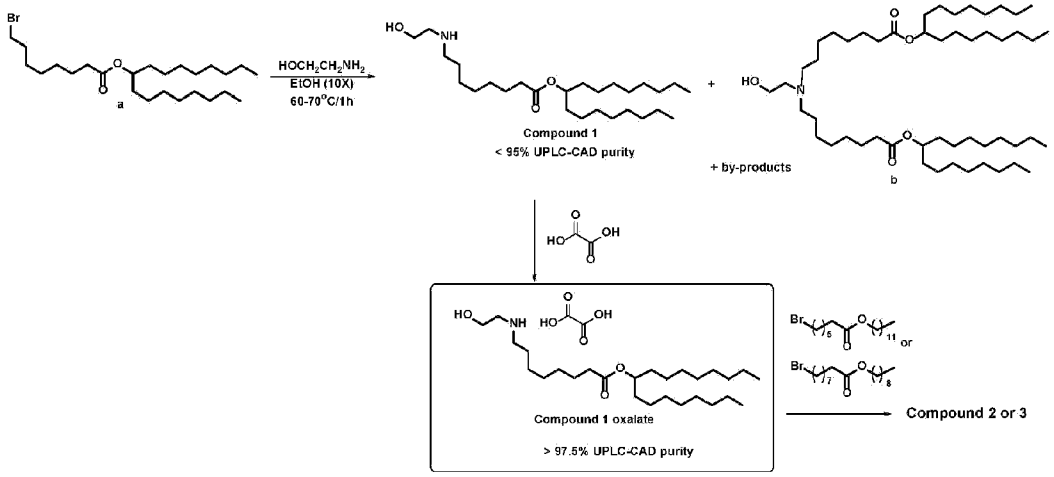
combining MC3 and a compound selected from (+)-O,O-di-pivaloyl-D-tartaric acid (DPDT), (-)-O,O-di-pivaloyl-L-tartaric acid (DPLT), (+)-2,3-dibenzoyl-D-tartaric acid (DBDT), and trimesic acid. The method may comprise the steps: a) combining MC3 and trimesic acid; b) dissolving the combination of MC3 and the compound to obtain a solution; c) precipitating or crystallizing the salt or cocrystal from the solution; and d) collecting the salt or cocrystal. In one example, the solvent used in step a) is ethyl acetate, toluene, or cyclohexane. In one example, step c) is carried out substantively free of evaporation. In another embodiment, step c) is carried out by slow evaporation. In some examples, the molar ratio of MC3 and the compound is about 1:1.

[0114] In one example of the method, the solvent comprises an aprotic solvent. In one example of the method, the solvent comprises a nonpolar aprotic solvent. In certain examples, one or more of the solutions of steps a) or b) is heated. For example, the solution from step b) is subject to temperature cycling, e.g., from about 50 °C to about 5 °C (for e.g., twice, three, or four times) before step c).

[0115] Also provided herein is a process of purifying Compound 1, 2, or 3 by forming a salt or cocrystal thereof disclosed herein to separate the salt or cocrystal thereof from the impurities. The method may further comprise neutralizing the salt or cocrystal to convert to Compound 1, 2, or 3 (i.e., a free base).

[0116] Also provided herein is a process of purifying MC3 by forming a salt or cocrystal thereof disclosed herein to separate the salt or cocrystal thereof from the impurities. The method may further comprise neutralizing the salt or cocrystal to convert to MC3 (i.e., a free base).

[0117] In still another aspect, provided herein is a process of synthesizing Compound 2, Compound 3, or an analog thereof by reacting a salt or cocrystal of Compound 1 disclosed herein with a suitable electrophile, such as an ester substituted with a halogen (e.g., Br or I). The scheme below illustrates one embodiment of the process.



[0118] In the scheme above, Compound 1 is oil and it is hard to purify it, e.g., by separating it from a and b, and other by-products. Compound 1 oxalate is a crystal, thus is easy to separate from a, b, and/or other by-products. Forming a salt or cocrystal of Compound 1, e.g., oxalate,

improves purification. Also, Compound 1 oxalate can be used to synthesize Compound 2 or 3 without converting back to Compound 1 (i.e., neutralization).

[0119] A process for synthesizing MC3 is described in Jayaraman, M.; Maximizing the Potency of siRNA Lipid Nanoparticles for Hepatic Gene Silencing In Vivo, Angew. Chem. Int. Ed. 2012, 51, 8529 -8533. MC3 corresponds to compound 16 in this article.

[0120] In one example, the process of the present disclosure is advantageous as compared to other processes in that the process of the disclosure produces Compound 1, 2, or 3 or a salt or cocrystal thereof at a large scale and/or at a high purity, e.g., such that cumbersome purification (*e.g.*, column chromatography, extraction, phase separation, distillation and solvent evaporation) is not needed. In one example, the process of the present disclosure is able to process at least 100 g, 200 g, 500 g or more (e.g., 1 kg, 2 kg, 5 kg, 10 kg, 20 kg, 50 kg, 100 kg, 200 kg, 500 kg, or 1000 kg or more) Compound 1, 2, or 3 or a salt or cocrystal thereof without the need to scale up. In one example, the process of the present disclosure is able to produce Compound 1, 2, or 3 or a salt or cocrystal thereof at least at a purity of at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 99.5%, or higher. In one example, the process of the present disclosure is able to produce Compound 1, 2, or 3 or a salt or cocrystal thereof with little or none impurity. In one example, the impurity produced in the process of the present disclosure, even if produced, is easy to be separated from Compound 1, 2, or 3 or a salt or cocrystal thereof, without cumbersome purification (e.g., column chromatography, extraction, phase separation, distillation and solvent evaporation).

[0121] All percentages and ratios used herein, unless otherwise indicated, are by weight (i.e., weight by weight or wt/wt). Other features and advantages of the present invention are apparent from the different examples. The provided examples illustrate different components and methodology useful in practicing the present invention. The examples do not limit the claimed invention. Based on the present disclosure the skilled artisan can identify and employ other components and methodology useful for practicing the present invention.

EXAMPLES

X-Ray Powder Diffraction

[0122] XRPD was performed with PANalytical Empyrean, X' Pert3, and Bruker D2 X-ray powder diffractometers. The parameters used are listed in the table below.

Parameters	**XRPD**		
Model	Empyrean	X' Pert3	**Bruker D2**
X-Ray wavelength	Cu, kα, Kα1 (Å): 1.540598, Kα2 (Å): 1.544426 Kα2/Kα1 intensity ratio: 0.50		
X-Ray tube setting	45 kV, 40 mA		30 kV, 10 mA

Parameters	**XRPD**		
Model	Empyrean	X' Pert3	**Bruker D2**
Divergence slit	Automatic	1/8°	0.6 mm
Scan mode	Continuous		
Scan range (°2-theta)	3-40		
Scan step time (s)	17.8	46.7	0.1
Step size (°2-theta)	0.0167	0.0263	0.0201
Scan speed (°/min)	5 min 30 s	5 min 04 s	3 min 27s

TGA/DSC

[0123] TGA data were collected using a TA Q500/Q5000 TGA from TA Instruments. DSC was performed using a TA Q200/Q2000 DSC from TA Instruments. Detailed parameters used are listed in the following table.

Parameters	**TGA**	**DSC**
Method	Ramp	Ramp
Sample pan	Aluminum or platinum, open	Aluminum or platinum, crimped
Temperature	RT - desired temperature; or RT-350 °C	-60 °C- desired temperature; or RT-300 °C
Heating rate	10 °C/min	
Purge gas	N_2	

HPLC

[0124] Agilent 1100 or Agilent 1100/1260 HPLC was utilized to analyze purity, with the detailed method listed in the table below.

HPLC	**Agilent 1100 with DAD Detector**		**Agilent 1100/1260**	
Column	Agilent Eclipse Plus C18, 150×4.6 mm, 5μm		Agilent ZORBAX SB-Phenyl, 150×4.6 mm, 3.5 μm	
Mobile phase	A: 0.1% TFA in H2O B: 0.1% TFA in Acetonitrile			
Gradient table	Time (min)	%B	Time (min)	%B
	0.0	30	0.0	10
	15.0	100	4.0	80
	22.0	100	6.0	80

HPLC	Agilent 1100 with DAD Detector		Agilent 1100/1260	
	22.1	30	6.10	10
	25.0	30	8.0	10
Run time	25.0 min		8.0 min	
Post time	0.0 min		0.0 min	
Flow rate	0.8 mL/min		1.0 mL/min	
Injection volume	5 µL		10 µL	
Column temperature	40 °C			
Sampler temperature	RT			
Diluent	MeOH		EtOH	
Detector	ELSD	Grace 3300	Detector wavelength	
	Temperature	50 °C	UV at 210 nm, reference 500 nm	
	Flow	2 L/min		
	Gain	1		

[0125] Agilent 1100/1260 HPLC with Halo C18 column was utilized for purity and concentration measurements of MC3 free base, with the detailed method listed in the table below.

Parameter	Condition	
Column	Halo C18, 100×4.6 mm, 2.7 µm	
Mobile phase	A: 20% NH_4HCO_3 (10 mM) + 40% MeOH + 40% THF	
	B: 20% IPA + 40% MeOH + 40% THF	
Gradient table	**Time (min)**	**%B**
	0.00	0
	30.00	40
	35.00	50
	35.01	0
	40.00	0
Parameter	**Condition**	
Run time	40.0 min	
Post time	0.0 min	
Flow rate	1.0 mL/min	
Injection volume	10 µL	
Detector wavelength	UV at 207 nm, reference 500 nm	
Column temperature	40 °C	

Parameter	Condition	
Sampler temperature	RT	
Diluent	EtOH	

Dynamic Vapor Sorption

[0126] DVS was measured on via a SMS (Surface Measurement Systems) DVS Intrinsic. The relative humidity at 25 °C were calibrated against deliquescence point of LiCl, $Mg(NO_3)_2$ and KCl. Actual parameters for DVS test are listed in the table below.

Parameters	DVS
Temperature	25 °C
Sample size	10 ~ 20 mg
Gas and flow rate	N2, 200 mL/min
dm/dt	0.002%/min
Min. dm/dt stability duration	10 min
Max. equilibrium time	180 min
RH range	0%RH-95%RH
RH step size	10% (0%RH-90%RH, 90%RH-0%RH)
	5% (90%RH-95%RH, 95%RH-90%RH)

[0127] ^1H NMR spectrum was collected on Bruker 400M NMR Spectrometer using DMSO-d6 as solvent.

[0128] Polarized light microscopic (PLM) images were captured on Axio Lab A1 upright microscope at room temperature.

Example 1: Salts or Cocrystals of Compound 1

Preparation

[0129] Compound 1 freebase is an oil at ambient conditions. As per the results in Figures 34 and 35, the freebase showed minor weight loss of 1.1% before 200 °C in TGA, and possible crystallization and melting signals in cyclic DSC, suggesting the existence of a crystalline form which melts around 17 °C (peak). Purity of the material was determined to be 99.95 area% by HPLC with ELSD detector.

[0130] To identify a crystalline salt form or cocrystal of Compound 1, screening was performed under 96 conditions using 32 acids and three solvent systems. Compound 1 freebase was dispersed in selected solvent with a 1.5-mL glass vial and corresponding salt former was added with a molar charge ratio of 1:1. The mixtures of freebase and the coformer compound (e.g., an acid) were first transferred to temperature cycling from 50 °C to 5 °C for two cycles (heating rate of 4.5 °C/min, cooling rate of 0.1 °C/min) and then stirred at 5 °C to induce precipitation. If the samples were still clear, they would be subjected to evaporation at different temperatures (5 °C or RT) to dryness. Resulted solids were isolated and analyzed.

[0131] Isolated crystal solids were characterized by X-ray powder diffraction (XRPD), thermo-gravimetric analysis (TGA) and differential scanning calorimetry (DSC), with proton nuclear magnetic resonance (^{1}H NMR) to confirm the freebase chemical structure and also potential coexistence with some organic acids. Exemplary data from the initial findings are summarized in Table 1.

Table 1

		n-Heptane	**EtOAc**	**Cyclohexane**
1	Hexanoic acid	Amorphous*	Amorphous*	Oil**
2	Fumaric acid	Acid + two extra peaks	Acid + two extra peaks*	Acid + two extra peaks
3	Adipic acid	Amorphous*	Amorphous*	Acid + one extra peak**
4	Suberic acid	Amorphous*	Acid*	Oil**
5	Cinnamic acid	Amorphous*	Amorphous*	Oil**
6	Benzoic acid, 4-acetamido	Acid	Two peaks*	Acid
7	(S)-Mandelic acid	Two peaks*	Two peaks*	Oil**
8	(-)-O,O-Di-pivaloyl-L-tartaric acid	Amorphous*	Amorphous*	Oil**
9	Terephthalic acid	Acid	Acid	Acid
10	Trimesic acid	Amorphous	Trimesate Polymorph A	Oil**
11	Citric acid	Two peaks*	Amorphous*	Two peaks**
12	Succinic acid	Two peaks*	Two peaks*	Two peaks**
13	Malonic acid	Amorphous*	Amorphous*	Oil**
14	(+)-Camphor-10-sulfonic acid	Amorphous*	Amorphous*	Oil**
15	Nicotinic acid	Amorphous*	Acid*	Oil**
16	(+)-L-tartaric acid	Two peaks	Two peaks*	Oil**

		n-Heptane	EtOAc	Cyclohexane
17	p-Toluenesulfonic acid	Amorphous*	Two peaks*	Oil**
18	Hydrochloric acid	Amorphous*	Amorphous*	Amorphous**
19	Sulfuric acid	Sulfate Polymorph A*	Amorphous*	Oil**
20	Phosphoric acid	Two peaks*	Amorphous*	Oil**
20	Acetic acid	Amorphous*	Amorphous*	Oil**
21	Methanesulfonic acid	Amorphous*	Amorphous*	Oil**
22	Sebacic acid	Sebacic acid	Sebacic acid*	Sebacic acid*
23	Benzoic acid	Amorphous*	Amorphous*	Amorphous*
24	1,2,4-Trimellitic acid	Trimellitate Polymorph A	Trimellitate Polymorph A	Trimellitate Polymorph A
25	Phthalic acid	Oil*	Oil*	Oil*
26	Isophthalic acid	Isophthalic acid	Isophthalic acid	Isophthalic acid
27	Orotic acid	Orotate Polymorph A	Orotate Polymorph A	Orotate Polymorph A
28	4-Hydroxybenzoic acid	4-Hydroxybenzoate Polymorph A	4-Hydroxybenzoate Polymorph A	4-Hydroxybenzoate Polymorph A
29	(-)-Dibenzoyl-L-tartaric acid	Weakly crystalline	Amorphous*	Weakly crystalline
30	2,5-Dihydroxybenzoic acid	Oil*	Oil*	2,5-Dihydroxybenzoic acid
31	2-Hydroxy benzoic acid	Oil**	Oil**	Oil**
32	3-Hydroxy benzoic acid	Oil**	Oil**	Oil**

*: clear solutions obtained after 5 °C stirring were transferred to 5 °C evaporation.
**: clear solutions obtained after 5 °C stirring were slow evaporated at RT.

[0132] Among them, five crystalline hits were discovered, including 4-hydroxybenzoate, trimellitate, orotate, trimesate and sulfate. Table 2 summarizes the properties of certain polymorphs of the salts or cocrystals.

Table 2

	4-Hydroxybenzoate Polymorph A	Trimellitate Polymorph A	Orotate	
			Polymorph A	Polymorph B
Appearance	White powder	Wax-like solid	Wax-like solid	
Solid form	Anhydrate	Hydrate	Anhydrate/Hydrate	Hydrate/solvate
Crystallinity	High	Medium	Medium	
Purity, area%	99.96	99.97	-	99.97
TGA weight loss, %	0.7-1.7	1.5-3.4	4.0	4.0
DSC endotherm, °C (onset)	66.8, 101.8 (batch 1) 68.2, 103.5 (batch 2)	78.3, 137.1 (batch 1) 80.0*, 137.1 (batch 2)	78.8*, 85.1*, 176.3*	83.5*
Hygroscopicity (form change after	Non-hygroscopic (no)	Slightly hygroscopic (no)	-	Hygroscopic (convert to orotate
DVS)				Polymorph A)
*: peak temperature. --: no data available.				

[0133] Three crystalline polymorphs of Compound 1 (4-hydroxybenzoate Polymorph A, trimellitate Polymorph A and orotate Polymorph B) were prepared to larger scale for further investigation, with the detailed procedure shown below:

1. 1. About 100 mg of freebase Compound 1 was added into a 3-mL glass vial;
2. 2. Add corresponding acids (molar charge ratio is 1:1) into the vial;
3. 3. Add 0.5 mL of solvent and transfer the suspension to temperature cycling from 50 °C to 5 °C (cooling rate of 0.1 °C/min, two cycles) with magnetic stirring.
4. 4. Centrifuge to isolate solids and vacuum dry at RT.

Characterization of 4-hydroxybenzoate

[0134] Two batches of 4-hydroxybenzoate Polymorph A (or Type A) (batch Nos. 1 and 2) were prepared by slurry in n-heptane and showed high crystallinity as characterized by XRPD in Figure 1. The ^{1}H NMR of sample (batch No. 2) was collected with spectrum shown in Figure 2. Besides freebase, a certain amount of 4-hydroxybenzic acid was detected in ^{1}H NMR (signals around 6.7 and 7.7 ppm), indicating the possibility of salt formation.

[0135] As indicated by the TGA and DSC data in Figure 3, sample (batch No. 2) showed a weight loss of 0.7% up to 140 °C and two sharp endothermic peaks at 68.2 °C and 103.5 °C (onset temperature) before decomposition. Based on the negligible weight loss in TGA, 4-hydroxybenzoate Polymorph A was considered to be an anhydrous form. In addition, the two sharp endothermic signals in DSC curve implied the possible existence of another anhydrous form at higher temperature.

[0136] As evidenced by heating experiments in Figure 5 and VT-XRPD results in Figures 6 and 7, form change (new form assigned as 4-hydroxybenzoate Polymorph B) was observed after heating sample (batch No. 1) to 83 °C (over the first endotherm in DSC) in VT-XRPD test and no form change was observed after heating sample (batch No. 2) over the first endotherm and cooling back to RT. Considering results of heating experiments and thermal signals in cyclic DSC (Figure 4), 4-hydroxybenzoate Polymorphs A and B are possibly enantiotropically related and Polymorph A is more stable at lower temperature (RT).

[0137] Further evaluation on hygroscopicity of 4-hydroxybenzoate Polymorph A was conducted via DVS isotherm collection at 25 °C. Results in Figures 8 and 9 showed that sample (batch No. 1) is non-hygroscopic with no form change before and after DVS test. Moreover, sample (batch No. 1) showed aggregation of small particles (< 10 μm) in PLM image (Figure 10) and a purity of 99.96 area% determined by HPLC (Table 3).

Table 3

# Peak	Time (min)	RRT	Area (mAU*S)	Area (%)
1	16.58	1.00	2070.9	**99.96**
2	16.99	1.02	0.8	0.04

Characterization of Trimellitate

[0138] Trimellitate Polymorph A samples (batch Nos. 1 and 2) were prepared by reactive crystallization in EtOAc with XRPD patterns shown in Figure 11. The ^{1}H NMR spectrum was collected for sample (batch No. 2) and is shown in Figure 12. Compared to freebase, a certain amount of trimellitic acid was detected (signals between 8.0 and 9.0 ppm), indicating the salt formation.

[0139] As per the TGA and DSC data in Figure 13, sample (batch No. 1) showed a weight loss of 3.4% up to 110 °C and two endothermic peaks at 78.3 °C and 137.1 °C (onset temperature) before decomposition. As demonstrated by VT-XRPD results in Figure 14, extra diffraction peaks appeared after 20 minutes of N_2 flow, and new form was observed at 90 °C, which converted back to trimellitate Polymorph A after being heated and exposed to ambient condition, suggesting that Polymorph A is a hydrated form.

[0140] Further evaluation on hygroscopicity of trimellitate Polymorph A was performed via DVS

isotherm collection at 25 °C. Results in Figures 15 and 16 showed that sample (batch No. 1) is slightly hygroscopic with no form change before and after DVS test. Platform observed in DVS plot (Figure 15) also indicated that Polymorph A is a hydrated form. Moreover, sample (batch No. 1) showed irregular particles (< 10 μm) in PLM image (Figure 17) and a purity of 99.97 area% determined by HPLC (Table 4).

Table 4

# Peak	Time (min)	RRT	Area (mAU*S)	Area (%)
1	16.62	1.00	1404.2	**99.97**
2	16.99	1.02	0.5	0.03

Characterization of Orotate

[0141] Orotate Polymorph A and Polymorph B were generated via reactive crystallization in EtOAc with XRPD patterns shown in Figure 18. The ^{1}H NMR spectrum of Polymorph A was collected and is shown in Figure 19. In addition to freebase, a certain amount of orotic acid was detected (signal at 5.7 ppm).

[0142] As per the TGA and DSC data in Figure 20, Polymorph A sample showed a weight loss of 4.0% up to 110 °C and endothermic peaks at 78.8, 85.1 and 176.3 °C (peak temperature) before decomposition. Results of heating experiments in Figure 21 showed that no form change was observed after heating Polymorph A sample over the first two endothermic signals and cooling back to RT, suggesting Polymorph A is anhydrous or a hydrated form which can rapidly absorb water at ambient conditions after de-hydration. In addition, as evidenced by the heating-cooling DSC curve of Polymorph A in Figure 22, endothermic and exothermic signals with similar enthalpy were observed at 170~175 °C and 80~90 °C, suggesting the possible form transition and the existence of anhydrate form at higher temperature.

[0143] TGA and DSC data of Polymorph B in Figure 23 showed a weight loss of 4.0% up to 110 °C and endothermic peak at 78.1 °C (onset) before decomposition. After cyclic DSC between 25 °C and 130 °C, Polymorph B converted to Polymorph A with data illustrated in Figure 24 and Figure 25, indicating Polymorph B is a hydrated or solvate form. DVS test of Polymorph B sample showed that it is slightly hygroscopic and converted to Polymorph A after DVS test, with data displayed in Figure 26 and Figure 27. Also, Polymorph B sample showed irregular particles in PLM image (Figure 28) and a purity of 99.97 area% detected by HPLC (Table 5).

Table 5

# Peak	Time (min)	RRT	Area (mAU*S)	Area (%)
1	16.62	1.00	1464.2	**99.97**
2	17.00	1.02	0.5	0.03

Characterization of Sulfate

[0144] Sulfate Polymorph A was generated by slow evaporation at 5 °C in n-heptane. Needle like crystals were observed during evaporation (Figure 29), which was further isolated for XRPD, TGA and DSC tests. Results in Figures 30 and 31 showed that the sample is crystalline with continuous weight loss and multiple endotherms.

Characterization of Trimesate

[0145] Trimesate Polymorph A was generated from reactive crystallization in EtOAc system and XRPD pattern is shown in Figure 32. ^{1}H NMR results in Figure 33 showed obvious signal of trimesic acid besides chemical shifts of freebase.

Characterization of Oxalate

[0146] Compound 1 Oxalate was generated from recrystallization. A purity of >97.5 area% detected by UPLC-CAD.

Example 2: Salts or Cocrystals of Compound 2

Preparation

[0147] Compound 2 freebase showed minor weight loss of 1.6% before reaching 200 °C in TGA. No obvious glass transition signal was observed and multiple endothermic peaks were observed with temperature elevated from -60 to 35 °C. Two endothermic signals at -47.7 and -34.0 °C (onset) were observed during temperature elevated from -60 to 35 °C.

[0148] Similar to the process described in Example 1, to identify a crystalline salt form or cocrystal of Compound 2, screening was performed under 93 conditions using 31 acids and three solvent systems. 0.3 mL stock solutions of Compound 2 freebase (~50 mg/mL) was dispersed in selected solvent and corresponding salt former was added with a molar charge ratio of 1:1. The mixtures of freebase and the coformer compound (e.g., an acid) were first transferred to temperature cycling from 50 °C to 5 °C for three cycles (heating rate of 4.5 °C/min, cooling rate of 0.1 °C/min) and then stored at 5 °C before analysis. If the samples were still clear, they would be subjected to slow evaporation at 5 °C to dryness. Resulted solids were isolated and analyzed.

[0149] Isolated crystal solids were characterized by X-ray powder diffraction (XRPD), thermo-gravimetric analysis (TGA) and differential scanning calorimetry (DSC), with proton nuclear

magnetic resonance (^{1}H NMR) to confirm the freebase chemical structure and also potential coexistence with some organic acids. Exemplary data from the initial findings are summarized in Table 6.

Table 6

#	**Acid**	**Solvent**		
		n-Heptane	Cyclohexane	EtOAc
1	Trimesic acid	Trimesate Polymorph A	Trimesate Polymorph A	Gel
2	Trimellitic acid	Amorphous + acid	Amorphous	Gel
3	(-)-2,3-Dibenzoyl-L-tartaric acid	Dibenzoyl-L-tartrate Polymorph A	Dibenzoyl-L-tartrate Polymorph A*	Dibenzoyl-L-tartrate Polymorph A*
4	Fumaric acid	Amorphous + two peaks	Acid	Gel
5	Terephthalic acid	Acid	Acid	Gel
6	Phthalic acid	Gel	Gel	Gel
7	Isophthalic acid	Acid	Acid	Gel
8	Benzoic acid	Gel	Gel	Gel
9	Cinnamic acid	Gel	Gel	Gel
10	4-Hydroxy benzoic acid	Amorphous	Gel	Gel
11	Salicylic acid	Gel	Gel	Gel
12	Adipic acid	Acid	Gel	Gel
13	Suberic acid	Acid	Acid	Gel
14	Sebacic acid	Gel	Acid	Acid
15	4-Acetamido benzoic acid	4-Acetamido benzoate Polymorph A + acid	Acid	Acid
16	S-(+)-Mandelic	Gel	Gel	Gel
17	Orotic acid	Gel	Acid	Acid
18	Hexanoic acid	Gel	Gel	Gel
19	Citric acid	Gel	Gel	Gel
20	Acetic acid	Gel	Gel	Gel
21	Succinic acid	Acid	Acid	Gel
22	Malonic acid	Gel	Gel	Gel
23	(+)-Camphor-10-sulfonic acid	Gel	Gel	Gel
24	Nicotinic acid	Acid	Acid	Acid
25	(+)-L-tartaric acid	L-Tartrate Polymorph	Gel	L-Tartrate

#	Acid	Solvent		
		n-Heptane	Cyclohexane	EtOAc
		A*		Polymorph A*
26	Hydrochloric acid	Gel	Gel	Gel
27	Sulfuric acid	Gel	Gel	Gel
28	Phosphoric acid	Gel	Gel	Gel
29	Methanesulfonic acid	Mesylate Polymorph A*	Mesylate Polymorph A*	Gel
30	p-Toluene sulfonic acid	Gel	Gel	Gel
31	2,5-Dihydroxybenzoic acid	Gel	Gel	Gel
*: solids obtained after 5 °C evaporation.				

Characterization of dibenzoyl-L-tartrate

[0150] Compound 2 dibenzoyl-L-tartrate Polymorph A was prepared by combining Compound 2 freebase with (-)-2,3-dibenzoyl-L-tartaric acid in n-heptane and showed crystallinity as characterized by XRPD in Figure 36. The TGA/DSC data as shown in Figure 37 indicate a weight loss of 30.5% up to 100 °C and broad endothermic signals before decomposition.

Characterization of Trimesate

[0151] Compound 2 trimesate Polymorph A was prepared by combining Compound 2 freebase with trimesic acid in n-heptane and showed crystallinity as characterized by XRPD in Figure 38. The TGA/DSC data as shown in Figure 39 indicate a weight loss of 0.8% up to 150 °C and multiple endothermic signals before decomposition.

Characterization of L-tartrate

[0152] Compound 2 L-tartrate Polymorph A was prepared by combining Compound 2 freebase with L-tartaric acid in n-heptane and showed crystallinity as characterized by XRPD in Figure 40. The TGA/DSC data as shown in Figure 41 indicate a weight loss of 4.0% up to 100 °C and multiple endothermic signals before decomposition.

Characterization of mesylate

[0153] Compound 2 mesylate Polymorph A was prepared by combining Compound 2 freebase with methanesulfonic acid in n-heptane and showed crystallinity as characterized by XRPD in Figure 42. The TGA/DSC data as shown in Figure 43 indicate a weight loss of 5.9% up to 100 °C and irregular signals in the DSC curve.

Characterization of 4-acetamido benzoate

[0154] Compound 2 4-acetamido benzoate Polymorph A was prepared by combining Compound 2 freebase with 4-acetamido benzoic acid in n-heptane and showed crystallinity as characterized by XRPD in Figure 44. The TGA/DSC data as shown in Figure 45 indicate a weight loss of 0.02% up to 150 °C and multiple endothermic signals before decomposition.

Example 3: Salts or Cocrystals of Compound 3

Preparation

[0155] Compound 3 freebase, as characterized via modulated DSC (mDSC), exhibits no glass transition signal. A weight loss of 1.2% was observed up to 200 °C, and endotherms were observed at -44.1 °C and -29.9 °C (peak).

[0156] Similar to the process described in Example 1 or 2, to identify a crystalline salt form or cocrystal of Compound 3, screening was performed under 93 conditions using 31 acids and three solvent systems. 0.5 mL stock solutions of Compound 3 freebase (~40 mg/mL) was dispersed in selected solvent and corresponding salt former was added with a molar charge ratio of 1:1. The mixtures of freebase and the coformer compound (e.g., an acid) were first transferred to temperature cycling from 50 °C to 5 °C for three cycles (heating rate of 4.5 °C/min, cooling rate of 0.1 °C/min) and then stored at 5 °C before analysis. If the samples were still clear, they would be subjected to slow evaporation at 5 °C to obtain gels. Resulting solids were isolated and analyzed.

[0157] Isolated crystal solids were characterized by X-ray powder diffraction (XRPD), thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC), with proton nuclear magnetic resonance (^{1}H NMR) to confirm the freebase chemical structure and also potential coexistence with some organic acids. Exemplary data from the initial findings are summarized in Table7.

Table 7

#	Acid	Solvent		
		n-Heptane	EtOAc	Toluene
1	Trimesic acid	Trimesate Type A	Acid	Trimesate Type A
2	Trimellitic acid	Acid	Acid	Acid
3	(-)-2,3 -Dibenzoyl-L-tartaric acid	Gel	Gel	Gel
4	Fumaric acid	Gel	Gel	Gel
5	Terephthalic acid	Gel	Gel	Gel
6	Phthalic acid	Gel	Gel	Gel
7	Isophthalic acid	Acid	Acid	Acid
8	Benzoic acid	Gel	Gel	Gel
9	Cinnamic acid	Gel	Gel	Gel
10	4-Hydroxy benzoic acid	Gel	Gel	Gel
11	Salicylic acid	Gel	Gel	Gel
12	Adipic acid	Acid	Acid	Acid
13	Suberic acid	Acid	Gel	Acid
14	Sebacic acid	Acid	Acid	Acid
15	4-Acetamido benzoic acid	Acid	Acid	Acid
16	S-(+)-Mandelic	Gel	Gel	Gel
17	Orotic acid	Acid	Acid	Acid
18	Hexanoic acid	Gel	Gel	Gel
19	Citric acid	Gel	Gel	Gel
20	Acetic acid	Gel	Gel	Gel
21	Succinic acid	Acid	Gel	Gel
22	Malonic acid	Gel	Gel	Gel
23	(+)-Camphor- 10-sulfonic acid	Gel	Gel	Gel
24	Nicotinic acid	Acid	Acid	Acid
25	(+)-L-tartaric acid	Gel	Gel	Gel
26	Hydrochloric acid	Gel	Gel	Gel
27	Sulfuric acid	Gel	Gel	Gel
28	Phosphoric acid	Gel	Gel	Gel
29	Methanesulfonic acid	Gel	Gel	Gel
30	p-Toluene sulfonic acid	Gel	Gel	Gel
31	2,5-Dihydroxybenzoic acid	Gel	Gel	Gel

Characterization of Trimesate

[0158] Compound 3 trimesate Polymorph A was prepared by combining Compound 3 freebase with trimesic acid in n-heptane and showed crystallinity as characterized by XRPD in Figure 46. The TGA/DSC data as shown in Figure 47 indicate a weight loss of 0.9% up to 200 °C and three endothermic peaks at 49.4 °C, 100.2 °C and 129.2 °C (peak temperature) before decomposition. Polymorph B was obtained via temperature cycling in EtOH/n-heptane (1:19, v/v) from 50 °C to 5 °C with molar charge ratio (compound 3: trimesic acid) at 1:1, and showed crystallinity as characterized by XRPD in Figure 48. The TGA/DSC data as shown in Figure 49 indicate a weight loss of 5.4% up to 200 °C and two endothermic peaks at 239.9 °C and 257.5 °C before decomposition at 304.6 °C. An ^{1}H NMR spectrum was collected using $(CD_3)_2SO$ as the test solvent, and signals of trimesic acid and compound 3 were observed. See Figure 50.

Example 4: Salts or Co-crystals of MC3

[0159] Only one crystalline salt of MC3 (O,O-Dibenzoyl-L-Tartrate, abbreviated as "DBLT" hereafter) has been previously identified, and only one polymorph, Type A, has been discovered for the DBLT salt. An onset temperature of 69.8 °C in DSC analysis indicated a low melting point, however, not as low as the free base which is oil-like at room temperature. The crude free base has an HPLC purity of 88.6 area% and was used in the synthesis of the DBLT salt. Impurities are not rejected by the salt formation and the purity of the crystallized salt was found to be the same as the crude free base. Additional salt screening experiments were performed to identify new crystalline salts.

[0160] An oil-like MC3 free base with an HPLC purity of 97.6 area% ("purified free base") was used in the salt screening. A total of 24 acids and three solvent systems were screened. Crystalline salt hits were obtained with (+)-O,O-di-pivaloyl-D-tartaric acid (DPDT), (-)-O,O-dipivaloyl-L-tartaric acid (DPLT), and trimesic acid.

Solvent screening

[0161] A solvent screening was performed by reaction of free base and DPDT, DPLT and trimesic acid in 17 selected solvents to improve crystallinity and facilitate salt isolation and re-preparation. The X-ray powder diffraction (XRPD) results showed that crystalline trimesate Type A and B were obtained in ketones, esters and some other selected solvents from slurry at room temperature. For DPDT and DPLT salts, no suitable anti-solvent was found, only clear solutions were obtained during the solvent screening.

[0162] Based on the screening results, attempts were made to re-prepare trimesate Type A and B, but only trimesate Type A was successfully prepared at a 100-mg scale. Both polymorphs were further characterized using thermogravimetric analysis (TGA), differential scanning calorimetry (DSC), polarizing microscopy (PLM), dynamic vapor sorption (DVS), and HPLC. The

characterization results of trimesate samples are summarized in Table 8. As the results show, trimesate Type A is anhydrous and non-hygroscopic.

Table 8

Salt form	Trimesate Tvpe A		Trimesate Type B
Prepared solvent	EtOAc	Cyclohexane	Toluene
Scale, mg	100	100	10
Molar ratio (acid/FB)[a]	1.2	1.1	1.5
Speculated form[b]	Anhydrate	Anhydrate	N/A
HPLC purity (area%)	98.3	99.4[c]	93.7
Weight loss (%)	1.9	0.3	8.0
Endotherm (°C, onset)	186.4	183.8	186.8
Hygroscopicity/purity decrease	Non-hygroscopic	N/A	N/A
Morphology	Aggregated of small particles (<20 μm)		
Appearance of solution in preparation	Suspension	Wax/emulsus	Wax/emulsus

N/A: not applicable or data not collected in this study.
[a]: the molar ratio (acid/FB) was determined by HPLC/IC.
[b]: results speculated based on the preliminary thermal analysis data.
[c]: average value of three sampling (100.0 area%, 99.34 area %, and 98.74 area%), suggesting the sample is inhomogeneous.
Hygroscopicity concluded using the water uptake up to 80%RH at 25 °C: <0.2% for non-hygroscopic.

Salt Screening

[0163] A total of 41 screening experiments were designed based on the free base pKa >8 and the solubility of MC3. Crystalline hits of trimesate (Type A), DPDT and DPLT salts were obtained.

[0164] In the 1st tier experiments, about 10 mg of MC3 free base and the corresponding acid were mixed, at a 1:1 molar ratio, into a 1.5-mL glass vial and 0.5 mL of n-heptane were then added. The mixtures were stirred at room temperature for about two days. If clear solutions were obtained, the samples were cooled at 5°C or left to evaporate to induce solid formation. All the obtained solids were isolated by centrifugation and vacuum dried at room temperature for about 5 hours before being analyzed by X-Ray Powder Diffraction (XRPD). As summarized in Table 9, amorphous salts or acids were found under most of the conditions while potential crystalline forms were obtained with DPDT, DPLT, and trimesic acid.

[0165] To enhance the chance of crystallization during the 2nd tier screening, the concentration

of free base was increased from 20 to 50 mg/mL when using the acids that yielded solutions in the 1st tier screening. Also, isopropyl alcohol/n-heptane (3:97, v/v) was used with those acids which yielded crystalline acid in the 1st tier screening. As summarized in Table 10, no new crystalline hit was obtained.

[0166] Six more acids with structures closely related to trimesic acid were screened. The free base and the acids were mixed, at a 1:1 molar ratio, in EtOAc (free base loading 50 mg/mL) and the suspensions were then shaken at room temperature for about three days. The results are summarized in Table 11.

Table 9

No.	Acid	Solid form	No.	Acid	Solid form
1	Hexanoic acid	Amorphous[a]	10	(R)-(-)-Mandelic acid	Amorphous[a]
2	Fumaric acid	Acid	11	Benzyloxy lactic acid	Amorphous[a]
3	Adipic acid	Amorphous	12	(+)-O,O-Di-pivaloyl-D-tartaric acid	DPDT salt Type A[a]
4	Suberic acid	Acid	13	(-)-O,O-Di-pivaloyl-L-tartaric acid	DPLT salt Type A[a]
5	Sebacic acid	Acid	14	Terephthalic acid	Acid
6	Alginic acid	Amorphous[a]	15	Trimesic acid	Acid+new peaks[c]
7	Cinnamic acid	Amorphous[a]	16	4-Hydroxy benzoic	Acid
8	Benzoic acid, 4-acetamido	Acid	17	2-(4-Hydroxybenzoyl)-benzoic acid	Amorphous[a]
9	(S)-(+)-Mandelic acid	Amorphous[a]	18	(+)-2,3-Dibenzoyl-D-tartaric acid	DBDT salt Type A[b]

[a]: clear solution was observed after slurry at room temperature (RT) and 5 °C, which was then transferred to slow evaporate at RT.
[b]: obtained in a previous experiment with no obvious purity improvement.
[c]: new peaks conformed to trimesate Type A.

Table 10

No.	Acid	Solvent	Solid form	No.	Acid	Solvent	Solid form
1	Hexanoic acid	n-Heptane	N/A	10	Fumaric acid	IPA/H_2O (3:97, v/v)	Acid
2	Alginic acid		N/A	11	Adipic acid		Amorphous
3	Cinnamic acid		N/A	12	Suberic acid		Acid
4	(S)-(+)-Mandelic acid		N/A	13	Sebacic acid		Acid
5	R)-(-)-Mandelic acid		N/A	14	Benzoic acid, 4-acetamido		Acid
6	Benzyloxy lactic		N/A	15	Terephthalic		Acid

No.	Acid	Solvent	Solid form	No.	Acid	Solvent	Solid form
	acid				acid		
7	(+)-O,O-Di-pivaloyl-D-tartaric acid		N/A	16	Trimesic acid		Acid
8	(-)-O,O-Di-pivaloyl-L-tartaric acid		N/A	17	4-Hydroxy benzoic		Acid
9	2-(4-Hydroxybenzoyl)-benzoic acid		N/A	-	-		-
N/A: clear solution was observed after slurry at RT and 5 °C.							

Table 11

No.	Acid	Solvent	Solid form
1	1,2,4-Trimellitic acid	EtOAc	Amorphous
2	Phthalic acid		Amorphous
3	Isophthalic acid		Amorphous
4	Terephthalic acid		Acid
5	Orotic acid		Acid + new peaks*
6	1,2,3-Benzene tricarboxylic acid		Amorphous
*: only amorphous was observed in the re-preparation experiment.			

Optimization of solvent systems

[0167] A solvent screening was performed to select an optimal solvent system for re-preparation of the salt hits and to improve crystallinity. The free base was mixed in a 1:1 molar ratio, with DPDT, DPLT, and trimesic acid in 17 selected solvents. Trimesate Type A and B polymorphs were isolated from slurries in several solvents (see Table 12). DPDT and DPLT salts were not obtained as solids from any solvent. In addition, the samples containing tetrahydrofuran (THF)/H_2O, THF, cyclohexane and 1,4-dioxane were freeze-dried, but no crystalline solid was obtained.

Table 12

Acid		DPDT	DPLT	Trimesic acid
Form	Solvent			
1	Acetone	N/A*	N/A*	Trimesate Type A
2	Methyl isobutyl ketone (MIBK)	N/A	N/A	Trimesate Type A
3	Methyl ethyl ketone (MEK)	N/A	N/A	Trimesate Type A

Acid		DPDT	DPLT	Trimesic acid
Form	Solvent			
4	CH_2Cl_2	N/A	N/A	Acid
5	Methyl tert-butyl ether (MTBE)	N/A	N/A	Trimesate Type A
6	2-Methyl tetrahydrofuran (2-MeTHF)	N/A	N/A	N/A
7	Tetrahydrofuran (THF)	N/A*	N/A*	N/A
8	Anisole	N/A	N/A	Trimesate Type A
9	1,4-Dioxane	N/A*	N/A*	N/A
10	EtOAc	N/A	N/A	Trimesate Type A
11	Isopropyl acetate (IPAc)	N/A	N/A	Trimesate Type A
12	Acetonitrile (CAN)	N/A*	N/A*	N/A
13	MeOH	N/A*	N/A*	N/A
14	Isopropyl alcohol (IPA)	N/A*	N/A*	N/A
15	Cyclohexane	N/A	N/A	Trimesate Type A
16	Xylene	N/A	N/A	N/A
17	Toluene	N/A	N/A	Trimesate Type B

N/A: clear solution was obtained after slurry at RT and 5 °C.
*: about 0.2~0.3 mL of H_2O was added into the clear solution to induce precipitation and emulsion was obtained.

Preparation of trimesate polymorphs (100 mg scale)

[0168] Heating and cooling experiments were carried out at 100-mg scale to improve crystal morphology and chemical purity. Trimesate Type A polymorph was successfully re-prepared in cyclohexane and EtOAc following the procedure detailed below.

Preparation of trimesate* Type *A polymorph:

[0169] A 5 mL vial was charged with 100.0 mg of the free base (97.6 area%) and 30 mg of trimesic acid and 2 mL of cyclohexane or EtOAc, were added. The suspension was stirred at room temperature for about 0.5 h. The solution was continued to be stirred while being heated and cooled between 5 °C and 50 °C for two cycles with a 4.5 °C/min heating rate and a 0.1 °C/min cooling rate. The resulting solid was isolated by centrifugation and dried under vacuum at room temperature for 2 hours before characterization.

Preparation of trimesate* Type *B polymorph:

[0170] About 10 mg of free base and trimesic acid were mixed, at a 1:1 molar ratio, in a 1.5-mL glass vial. n-Heptane (0.5 mL) was added. The mixtures were magnetically stirred at RT for about two days. If clear solutions were obtained, the samples were cooled at 5°C or left to evaporate to induce solid formation. All the obtained solids were isolated by centrifugation and vacuum dried at RT for about 5 hours before being analyzed by XRPD.

Characterization of trimesate polymorphs

[0171] Both trimesate Type A (100-mg scale) and Type B (10-mg scale) were characterized, and results are summarized in Table 8.

[0172] The XRPD pattern of polymorph A is shown in Figure 52. TGA/DSC curves of trimesate Type A polymorph prepared with cyclohexane, displayed in Figure 53, shows a weight loss of 0.3% before 120 °C and a sharp melting endotherm at 183.8 °C (onset temperature). The TGA/DSC curves of trimesate Type A polymorph prepared with EtOAc displayed in Figure 54, shows a weight loss of 1.9% before 120 °C and a sharp melting endotherm at 186.4 °C (onset temperature). Agglomerate and small particles (<20 μm) were observed in the trimesate Type A polymorphs. See Figures 55 and 56. The XRPD pattern of trimesate Type B polymorph is shown in Figure 59. TGA/DSC curves displayed in Figure 60 show a weight loss of 8.0% before 150 °C and a sharp melting endotherm at 186.8 °C (onset temperature). As shown in Figure 61, agglomerate particles with small size (<20 μm) are observed in trimesate Type B sample.

[0173] As the DVS result shows, the trimesate Type A polymorph is non-hygroscopic. See Figure 57. The hygroscopicity of free base (crude and pure) was determined as well. The crude free base was slightly hygroscopic (0.27 and 0.24 % water uptake at 80% relative humidity for the desorption and adsorption isotherms, respectively), but the pure free base was non-hygroscopic (0.17 and 0.14 % water uptake at 80% relative humidity for the desorption and adsorption isotherms, respectively).

HPLC Purity of Trimesate Type A

[0174] Trimesate Type A samples were prepared according to the procedure described in the foregoing, using the crude free base (HPLC purity of 88.5 area%) or purified free base (HPLC purity of 97.6 area%) as starting material, and analyzed by HPLC. The results of the HPLC purity analysis for the samples prepared with crude and purified free base are summarized in Tables 13 and 14, respectively. No significant HPLC purity change was observed for both samples after the DVS experiment.

Table 13

Sample	Solvent /scale (mg)	Imp 1 (RRT 0.08)	Imp 2 (RRT 0.50)	Imp 3 (RRT 0.51)	Imp 4 (RRT 0.52)	Imp 5 (RRT 0.53)	Imp 6 (RRT 0.90)
Free base	N/A	0.11	0.22	< 0.05	0.34	0.44	1.74
Trimesate Type A	EtOAc/100	< 0.05	4.18	1.38	< 0.05	< 0.05	1.96
	Cyclohexane /100	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05	1.91
Sample	**Solvent /scale (mg)**	**Imp 7 (RRT 0.91)**	**Imp 8 (RRT 0.99)**	**Imp 9 (RRT 1.04)**	**Imp 10 (RRT 1.06)**	**Imp 11 (RRT 1.14)**	**Area (%)**
Free base	N/A	0.16	0.36	5.02	0.28	2.74	88.6
Trimesate Type A	EtOAc/100	< 0.05	< 0.05	3.78	< 0.05	3.31	85.38
	Cyclohexane /100	< 0.05	< 0.05	4.45	< 0.05	3.97	89.66

Table 14

Sample	Solvent /scale (mg)	Imp 1 (RRT 0.58)	Imp 2 (RRT 1.04)	Imp 3 (RRT 1.14)	Area(%)	
Free base	N/A	0.99	1.41	< 0.05	97.60	
Trimesate Type A	EtOAc/100	< 0.05	1.04	0.68	98.28	
	Cyclohexane /100	< 0.05	< 0.05	< 0.05	100.00	99.36 (av.)
		< 0.05	1.26	< 0.05	98.74	
		< 0.05	0.66	< 0.05	99.34	

[0175] The invention can be embodied in other specific forms without departing from the essential characteristics thereof. The foregoing embodiments are therefore to be considered in all respects illustrative rather than limiting on the invention described herein. The scope of the invention is defined by the appended claims.

REFERENCES CITED IN THE DESCRIPTION

Cited references

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Patent documents cited in the description

- US62471908 [0001]
- WO2016176330A1 [0005]
- WO2012000104A1 [0005]
- WO2012054365A2 [0005]
- WO2015011633A1 [0005]

Non-patent literature cited in the description

- **MUTHUSAMY JAYARAMAN et al.**ANGEWANDTE CHEMIE INTERNATIONAL EDITION20120000vol. 51, 8529-8533 [0005]
- **JAYARAMAN, M.**Maximizing the Potency of siRNA Lipid Nanoparticles for Hepatic Gene Silencing In VivoAngew. Chem. Int. Ed., 2012, vol. 51, 8529-8533 [0119]

Patentkrav

1. Salt eller co-krystal, der er 4-hydroxybenzoat af heptadecan-9-yl-8-((2-hydroxyethyl)amino)octanoat ("forbindelse 1"), og som har et smeltepunkt på 50 °C eller derover, hvor saltet eller co-krystallet udviser et røntgenpulverdiffraktionsmønster, der er opnået under anvendelse af Cu Kα-stråling, med to, tre, fire eller flere karakteristiske toppe, som er udtrykt i grader 2-theta (+/- 0,2), valgt fra gruppen bestående af 4,5, 6,8, 9,1, 11,4 og 13,7.

2. Salt eller co-krystal ifølge krav 1, hvor støkiometrien for forbindelse 1 og 4-hydroxybenzoesyre er inden for området fra 1:0,2 til 1:5; fra 1:0,5 til 1:2; eller er 1:1.

3. Salt eller co-krystal ifølge et hvilket som helst af de foregående krav, hvor saltet eller co-krystallet udviser et røntgenpulverdiffraktionsmønster, der er opnået under anvendelse af Cu-Kα-stråling, med:

(a) karakteristiske toppe, som er udtrykt i grader 2-theta (+/- 0,2) ved 4,5, 6,8, 9,1, 11,4, 13,7, 18,3, 20,1 og 20,6; eller

(b) mindst otte karakteristiske toppe, som er udtrykt i grader 2-theta (+/- 0,2), valgt fra gruppen bestående af 4,5, 6,8, 9,1, 11,4, 13,7, 16,0, 18,3, 20,1 og 20,6; eller

(c) mindst ni karakteristiske toppe, som er udtrykt i grader 2-theta (+/- 0,2), valgt fra gruppen bestående af 4,5, 6,8, 9,1, 11,4, 13,7, 16,0, 16,6, 18,3, 20,1 og 20,6; eller

(d) mindst ti karakteristiske toppe, som er udtrykt i grader 2-theta (+/- 0,2), valgt fra gruppen bestående af 4,5, 6,8, 9,1, 11,4, 13,7, 16,0, 16,6, 18,3, 20,1, 20,6 og 21,5; eller

(e) toppe med 2-theta-værdier i overensstemmelse med tabellen nedenfor.

Top	Pos. [° 2 Th.]
1	4,6
2	6,8

Top	Pos. [° 2 Th.]
3	9,1
4	11,4
5	13,7
6	16,0
7	16,6
8	18,3
9	20,1
10	20,6
11	21,5
12	23,8

4. Salt eller co-krystal ifølge et hvilket som helst af de foregående krav, hvor saltet eller co-krystallet udviser et termogram for differentiel scanningskalorimetri, der viser en primær endoterm, udtrykt i °C-enheder, ved en temperatur på 103 +/- 2 °C;
og som eventuelt viser en anden primær endoterm, udtrykt i °C-enheder, ved en temperatur på 68 +/- 2 °C.

5. Salt eller co-krystal, der er trimesat af heptadecan-9-yl-8-((2-hydroxyethyl)(8-(nonyloxy)-8-oxooctyl)amino)octanoat ("forbindelse 3"), hvor saltet eller co-krystallet udviser et røntgenpulverdiffraktionsmønster, der er opnået under anvendelse af Cu Kα-stråling, med mindst fem karakteristiske toppe, som er udtrykt i grader 2-theta (+/- 0,2), valgt fra gruppen bestående af 6,2, 10,8, 12,4, 16,5, 18,7, 22,5 og 26,7.

6. Salt eller co-krystal ifølge krav 5, hvor støkiometrien for forbindelse 3 og trimesinsyre er inden for området fra 1:0,2 mol/mol til 1:5 mol/mol; fra 1:0,5 mol/mol til 1:2 mol/mol; eller er 1:1 mol/mol

7. Salt eller co-krystal ifølge et hvilket som helst af kravene 5-6, hvor saltet eller co-krystallet udviser:

(a) et røntgenpulverdiffraktionsmønster, der er opnået under anvendelse af Cu Kα-stråling, med mindst seks karakteristiske toppe, som er udtrykt i grader 2-theta (+/- 0,2), valgt fra gruppen bestående af 6,2, 10,8, 12,4, 16,5, 18,7, 22,5 og 26,7;

(b) et røntgenpulverdiffraktionsmønster, der er opnået under anvendelse af Cu Kα-stråling, med toppe med 2-theta-værdier i overensstemmelse med tabellen nedenfor

Top	Pos. [° 2 Th.]
1	6,2
2	10,8
3	12,4
4	16,5
5	18,7
6	22,5
7	26,7

og/eller

(c) et termogram for differentiel scanningskalorimetri, der viser en primær endoterm, udtrykt i °C-enheder, ved en temperatur på 305 +/- 2 °C; og eventuelt en anden primær endoterm, udtrykt i °C-enheder, ved en temperatur på 240 +/- 2 °C.

8. Salt eller co-krystal, der er trimesat af (6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl-4-(dimethylamino)butanoat ("MC3"), hvor saltet eller co-krystallet udviser et røntgenpulverdiffraktionsmønster med karakteristiske toppe, som er udtrykt i grader 2-theta (+/- 0,2) ved 5,2, 7,8, 10,4, 18,3, 20,9, 23,6 og 26,2.

9. Salt eller co-krystal ifølge krav 8, hvor støkiometrien for MC3 og trimesinsyre er inden for området fra 1:0,5 mol/mol til 1:2 mol/mol, eller
hvor støkiometrien for MC3 og trimesinsyre er 1:1,2 mol/mol, 1:1,1 mol/mol eller 1:1,5 mol/mol.

10. Salt eller co-krystal ifølge et hvilket som helst af kravene 8-9, hvor saltet eller co-krystallet udviser et røntgenpulverdiffraktionsmønster, der er opnået under anvendelse af Cu Kα-stråling, med

(a) mindst syv karakteristiske toppe, som er udtrykt i grader 2-theta (+/- 0,2), valgt fra gruppen bestående af 5,2, 7,8, 9,7, 10,4, 18,3, 20,9, 23,6 og 26,2;

(b) mindst ni karakteristiske toppe, som er udtrykt i grader 2-theta (+/- 0,2), valgt fra gruppen bestående af 5,2, 7,8, 9,7, 10,4, 11,5, 13,0, 18,3, 20,9, 23,6 og 26,2; eller

(c) toppe med 2-theta-værdier i overensstemmelse med tabellen nedenfor.

Top	Position [° 2 Th.]
1	5,2
2	7,8
3	9,7
4	10,4
5	11,5
6	13,0
7	18,3
8	20,9
9	23,6
10	26,2

11. Salt eller co-krystal ifølge et hvilket som helst af kravene 8-10, hvor saltet eller co-krystallet udviser et termogram for differentiel scanningskalorimetri, der viser:

(a) en primær endoterm, udtrykt i °C-enheder, ved en temperatur på 184 +/- 2 °C; eller

(b) en primær endoterm, udtrykt i °C-enheder, ved en temperatur på 186 +/- 2 °C; og eventuelt en anden primær endoterm, udtrykt i °C-enheder, ved en temperatur på 90 +/- 2 °C.

12. Salt eller co-krystal, der er trimesat af (6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl-4-(dimethylamino)butanoat ("MC3"), hvor saltet eller co-krystallet

udviser et røntgenpulverdiffraktionsmønster, der er opnået under anvendelse af Cu Kα-stråling, med karakteristiske toppe, som er udtrykt i grader 2-theta (+/- 0,2) ved 4,8, 5,4, 7,2, 9,7, 19,4, 24,3, 26,8 og 29,3.

13. Salt eller co-krystal ifølge krav 12, hvor saltet eller co-krystallet udviser et røntgenpulverdiffraktionsmønster, der er opnået under anvendelse af Cu Kα-stråling, med:

(a) mindst syv karakteristiske toppe, som er udtrykt i grader 2-theta (+/- 0,2), valgt fra gruppen bestående af 4,8, 5,4, 7,2, 9,7, 12,1, 19,4, 21,9, 24,3, 26,8 og 29,3;

(b) mindst ni karakteristiske toppe, som er udtrykt i grader 2-theta (+/- 0,2), valgt fra gruppen bestående af 4,8, 5,4, 7,2, 9,7, 12,1, 14,5, 17,0, 19,4, 21,9, 24,3, 26,8, 29,3 og 31,8; eller

(c) toppe med 2-theta-værdier i overensstemmelse med tabellen nedenfor.

Top	Position [° 2 Th.]
1	4,8
2	5,4
3	7,2
4	9,7
5	12,1
6	14,5
7	17,0
8	19,4
9	21,9
10	24,3
11	26,8
12	29,3
13	31,8

14. Salt eller co-krystal ifølge et hvilket som helst af de foregående krav, hvor:

(a) saltet eller co-krystallet er et anhydrat, et solvat eller et hydrat; (b) saltet eller co-krystallet er fri for urenheder; og/eller

(c) saltet eller co-krystallet er et krystallinsk faststof, der er fri for andre krystallinske former af saltet eller co-krystallet.

15. Salt eller co-krystal, der er

(a) dibenzoyl-L-tartrat af heptadecan-9-yl-8-((2-hydroxyethyl)(6-oxo-6-(undecyloxy)hexyl)amino)octanoat ("forbindelse 2"), hvor saltet eller co-krystallet udviser et røntgenpulverdiffraktionsmønster, der er opnået under anvendelse af Cu Kα-stråling, med to karakteristiske toppe, som er udtrykt i grader 2-theta (+/- 0,2) ved 6,1 og 9,1;

(b) trimesat af forbindelse 2, hvor saltet eller co-krystallet udviser et røntgenpulverdiffraktionsmønster, der er opnået under anvendelse af Cu Kα-stråling, med fire eller flere karakteristiske toppe, som er udtrykt i grader 2-theta (+/- 0,2), valgt fra gruppen bestående af 3,4, 6,8, 10,2, 20,5 og 23,8;

(c) L-tartrat af forbindelse 2, hvor saltet eller co-krystallet udviser et røntgenpulverdiffraktionsmønster, der er opnået under anvendelse af Cu Kα-stråling, med to karakteristiske toppe, som er udtrykt i grader 2-theta (+/- 0,2) ved 5,4 og 8,1; eller

(d) mesylat af forbindelse 2, hvor saltet eller co-krystallet udviser et røntgenpulverdiffraktionsmønster, der er opnået under anvendelse af Cu Kα-stråling, med fire karakteristiske toppe, som er udtrykt i grader 2-theta (+/- 0,2), valgt fra gruppen bestående af 4,0, 11,4, 11,8 og 19,8.

DRAWINGS

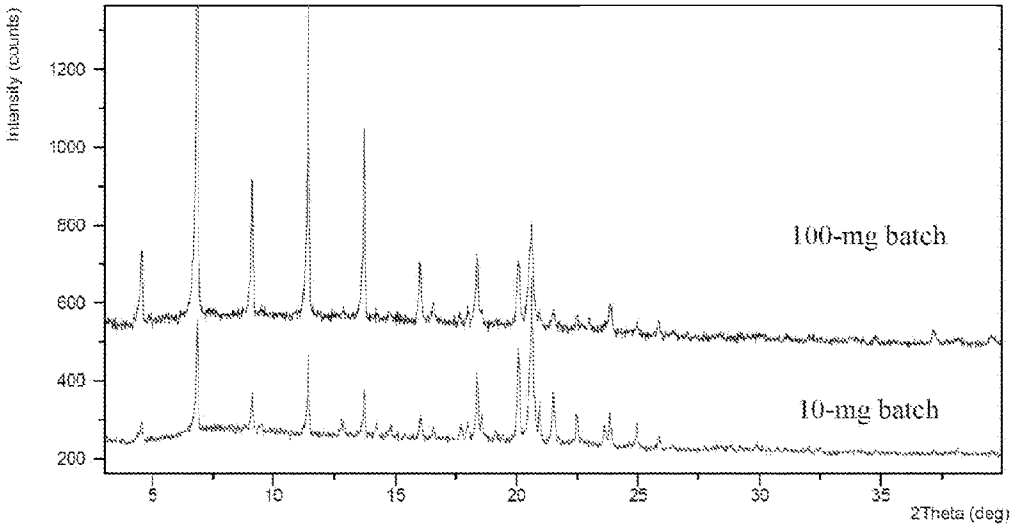


Figure 1

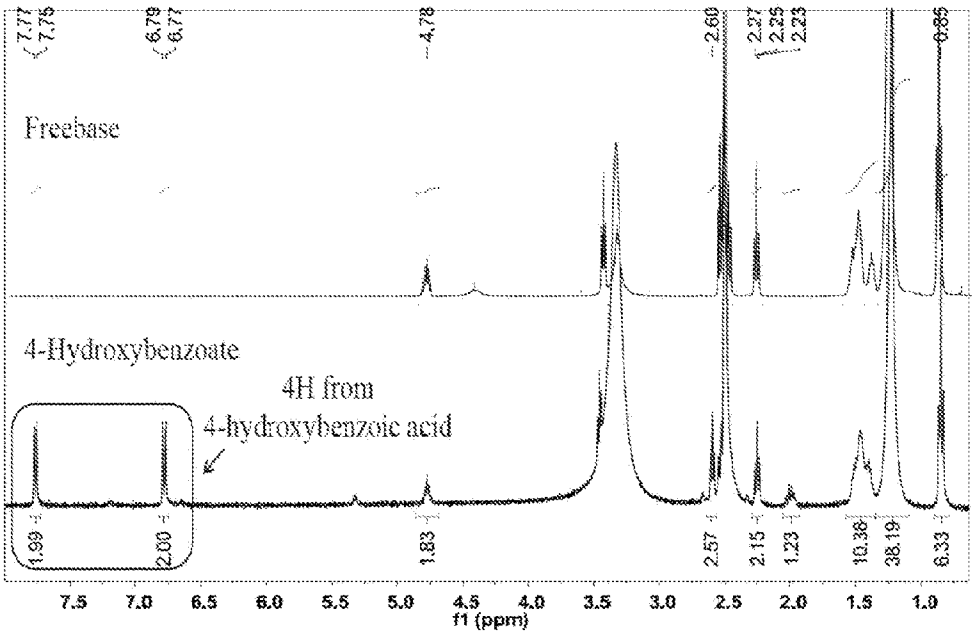
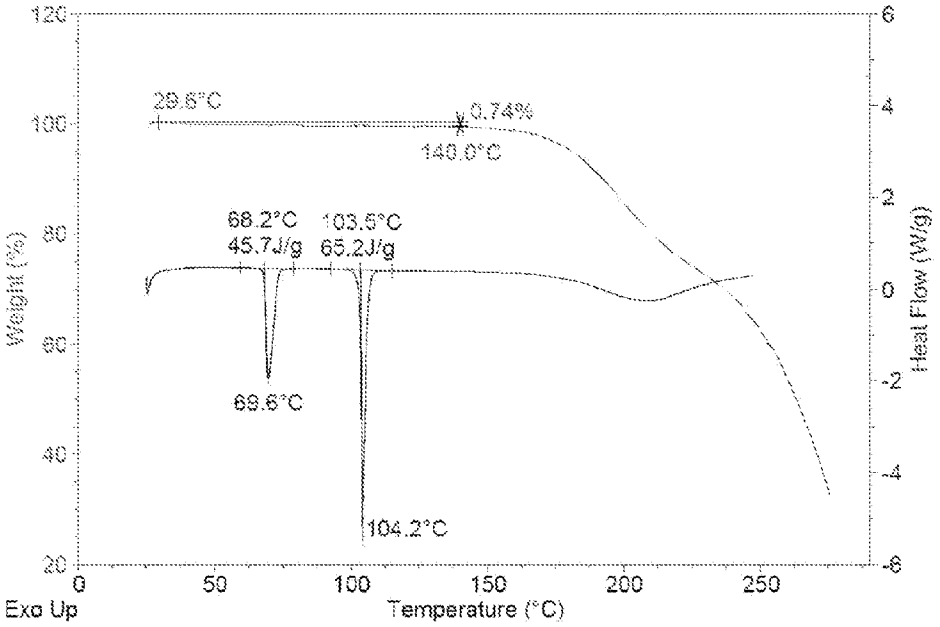


Figure 2



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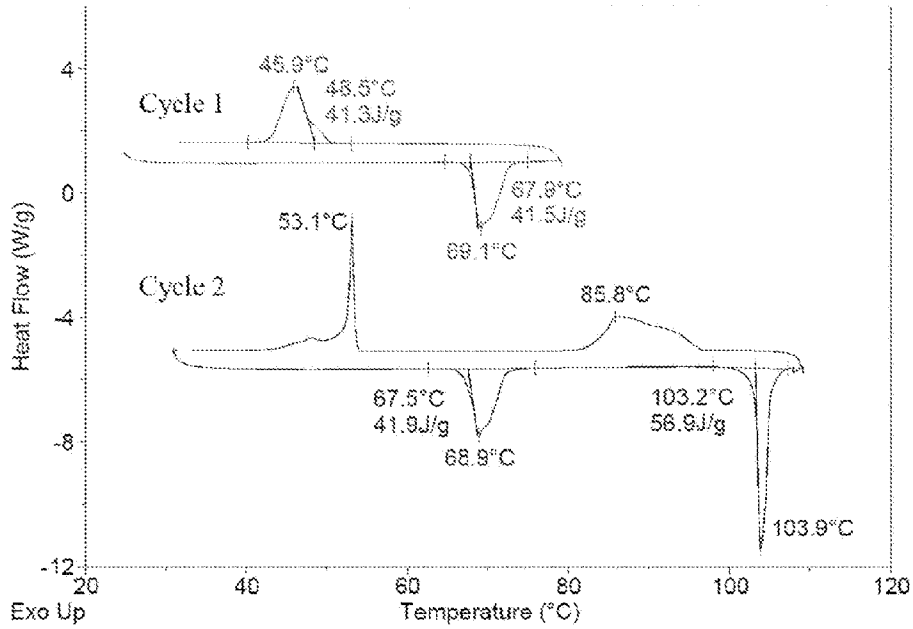

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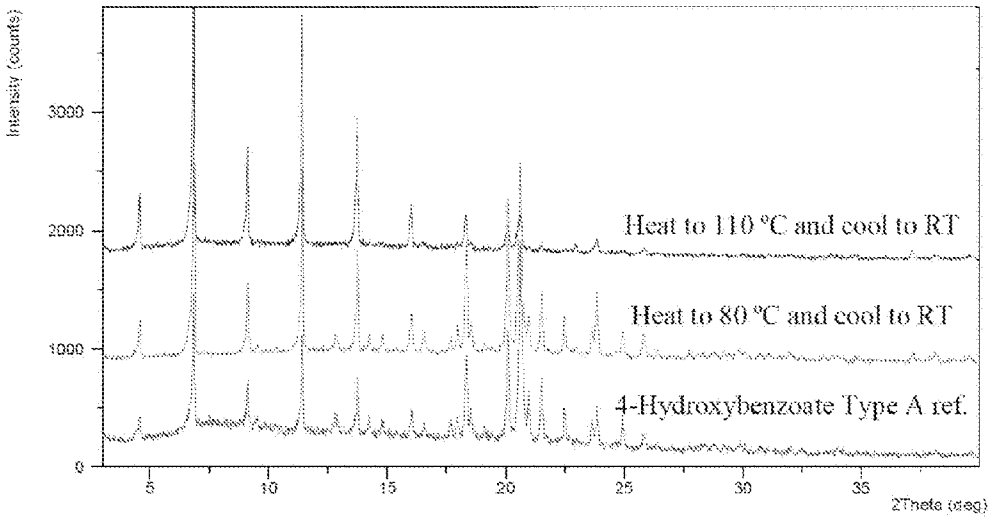

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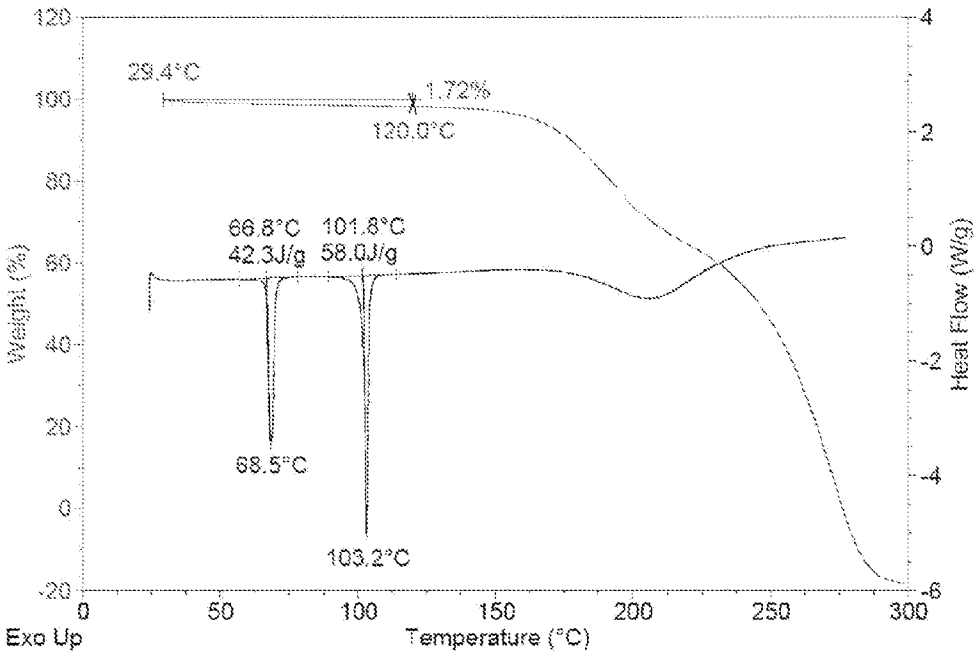

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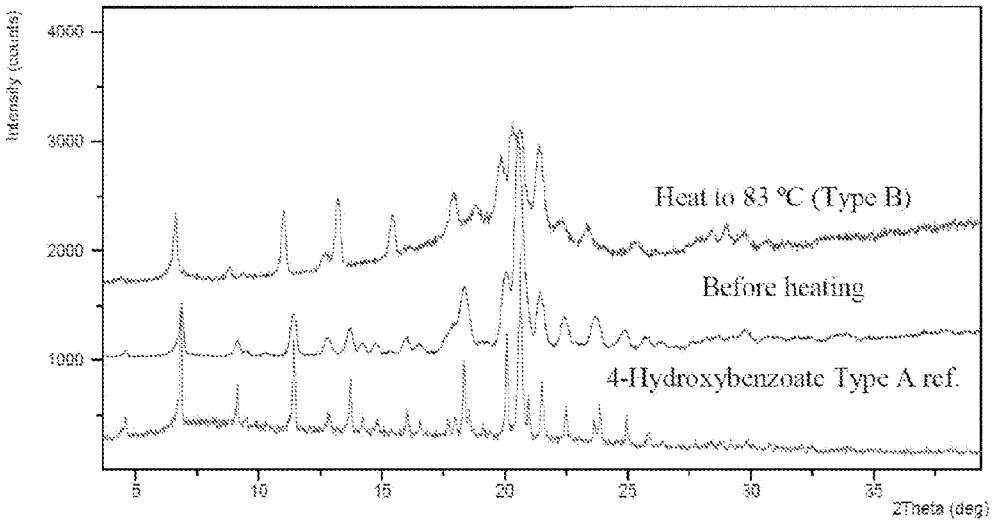

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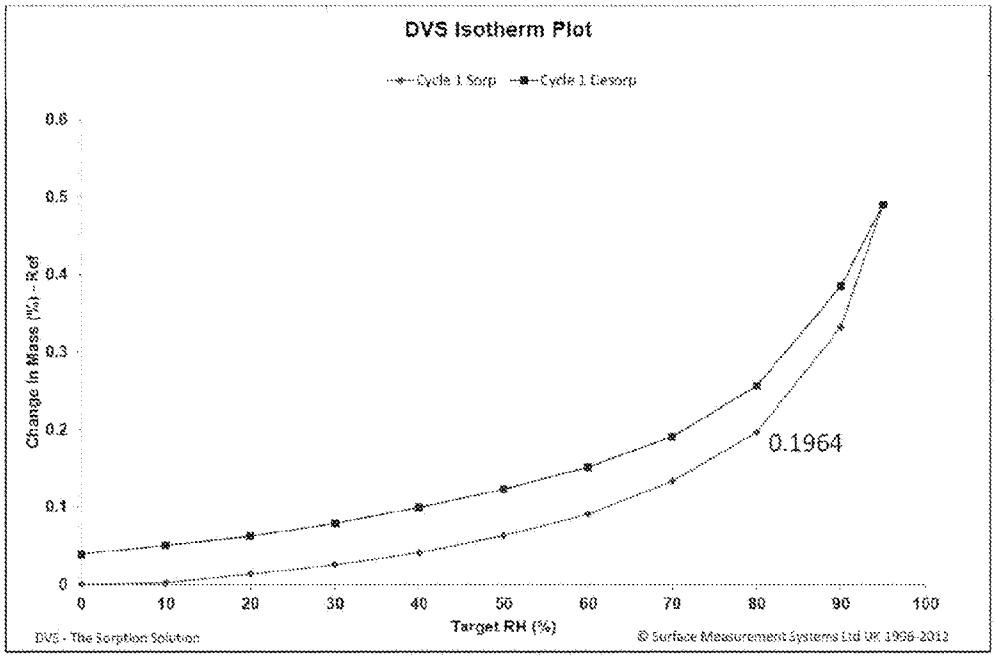

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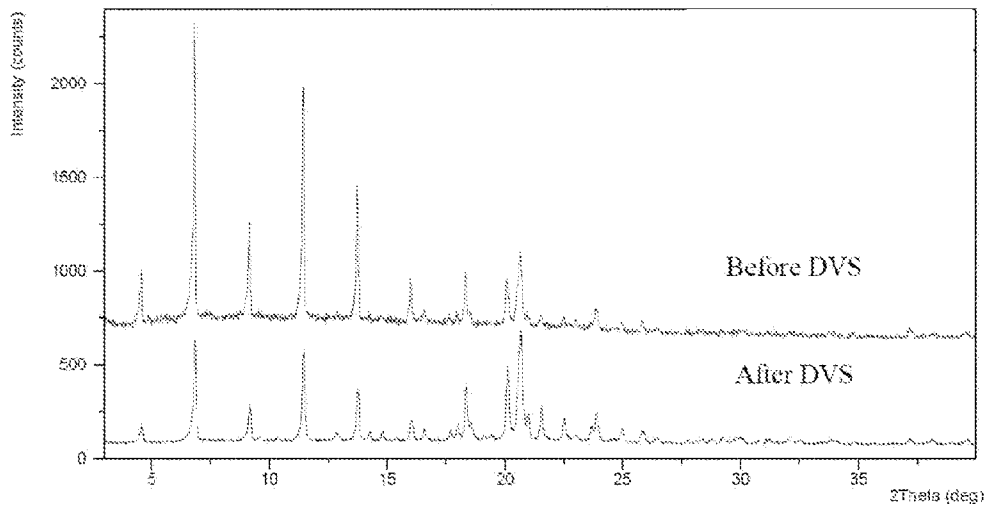

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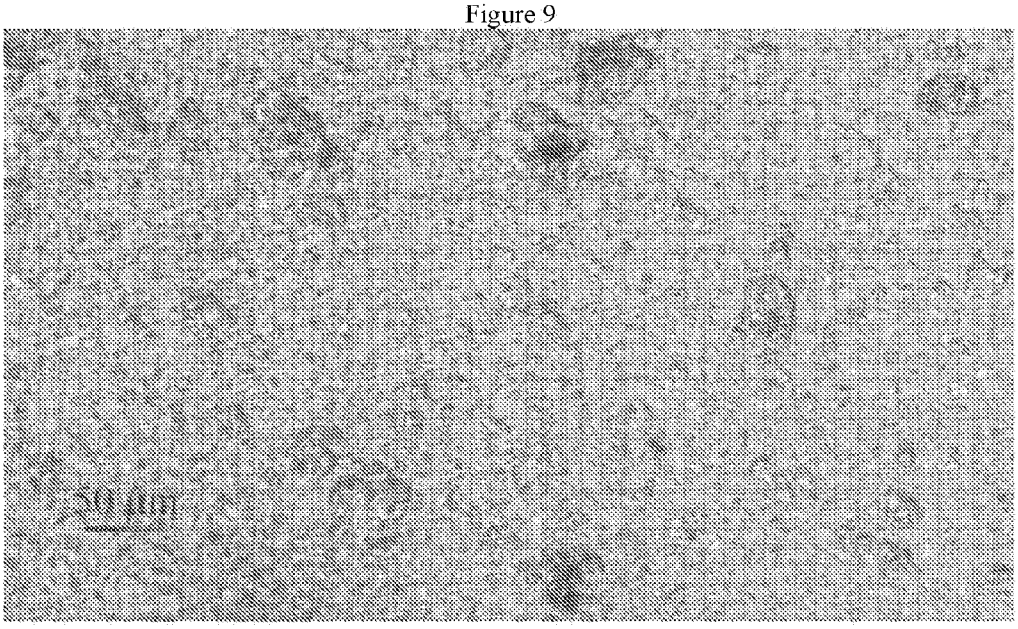


Figure 10

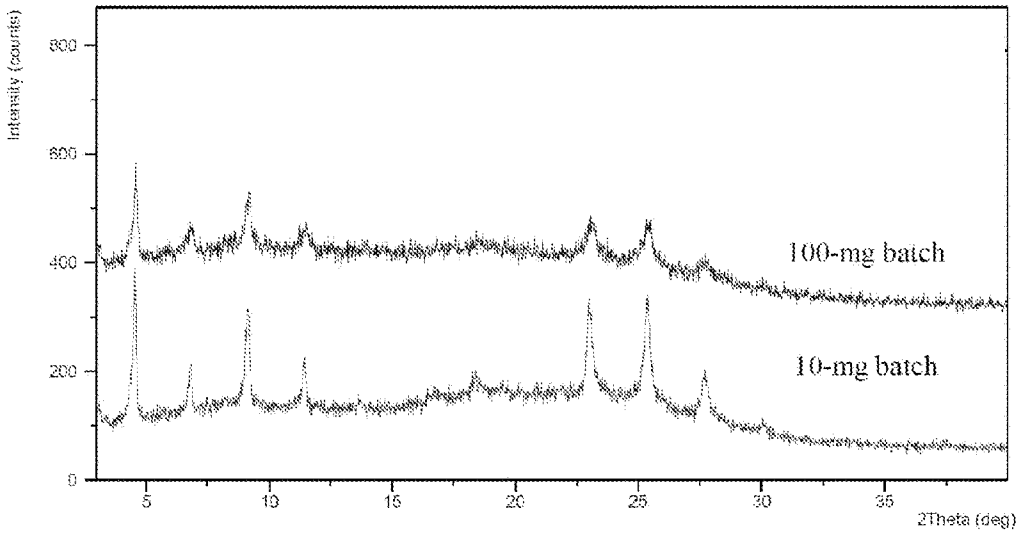


Figure 11

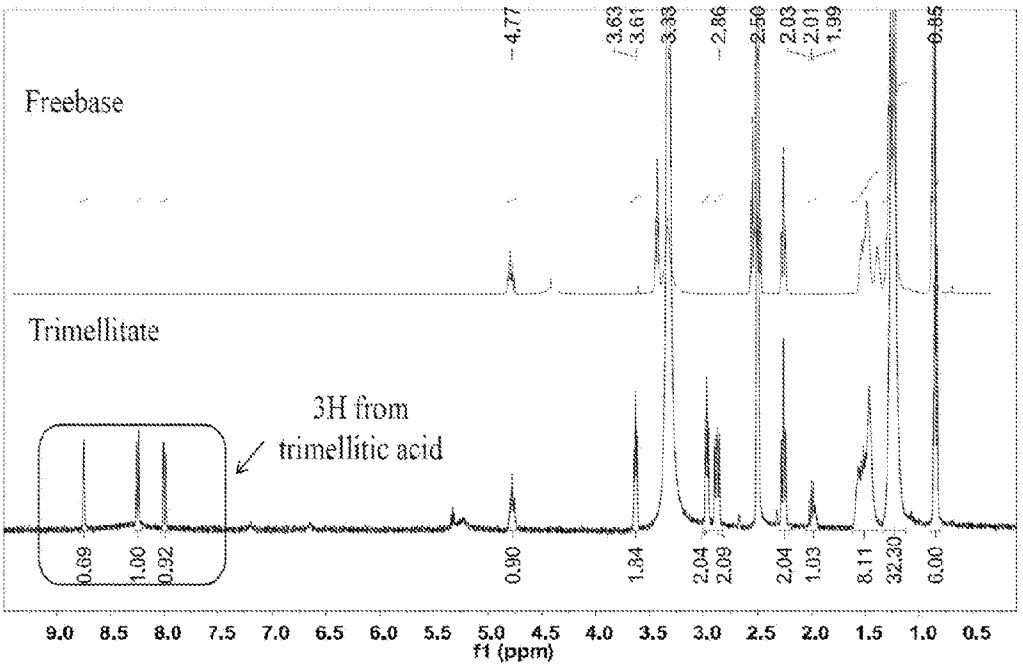


Figure 12

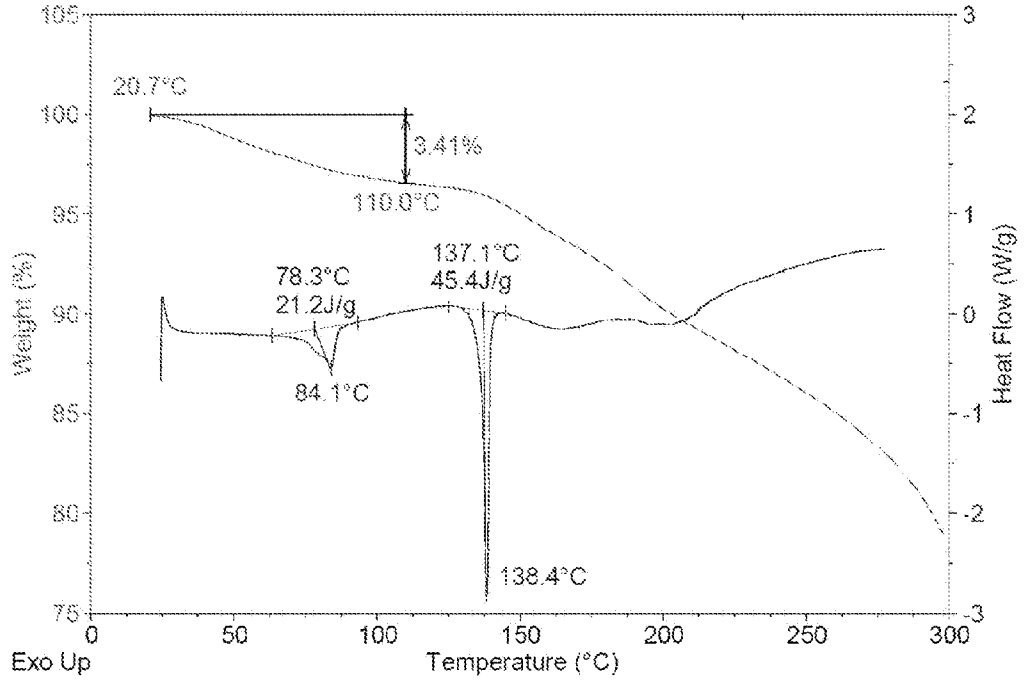
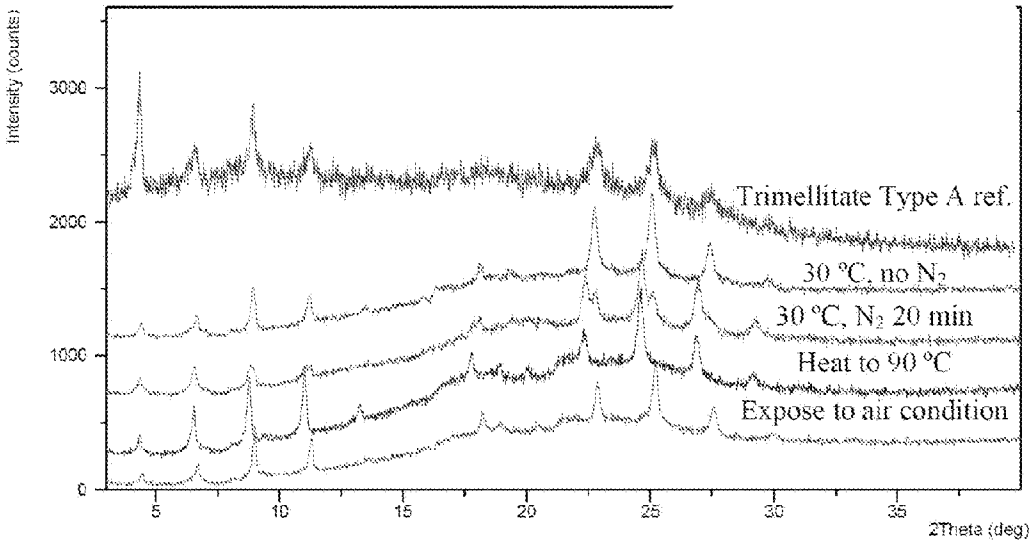


Figure 13



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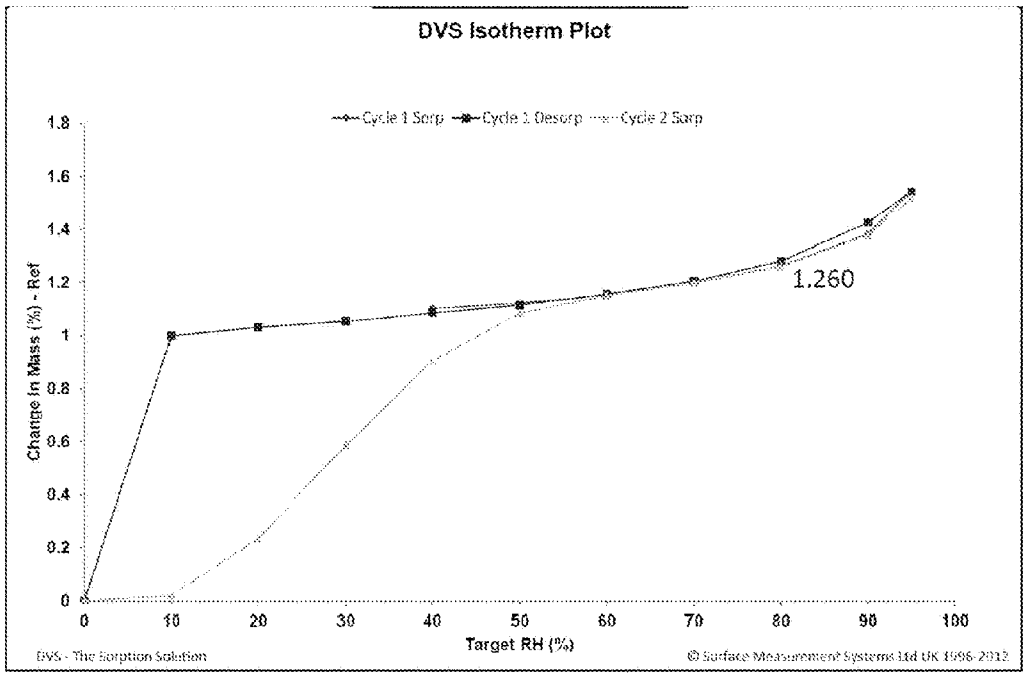


Figure 15

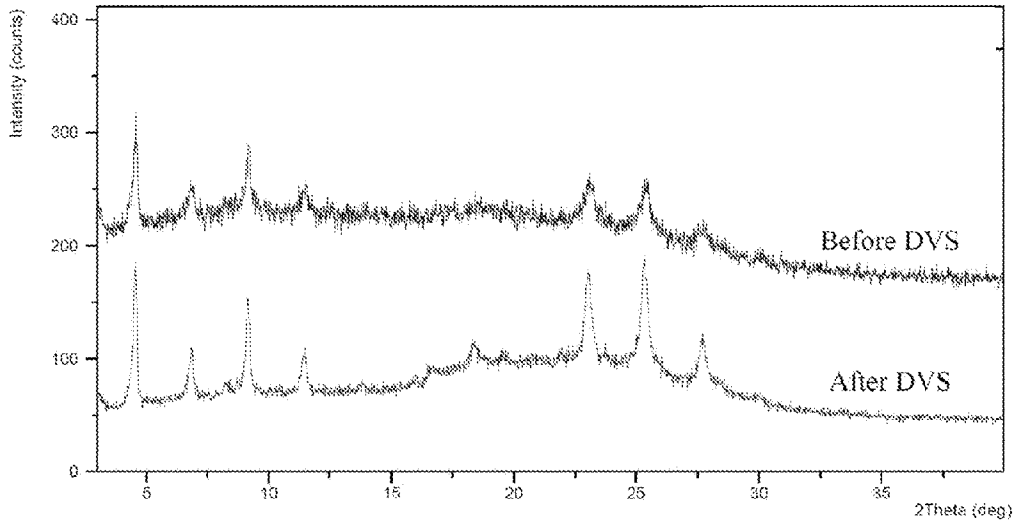
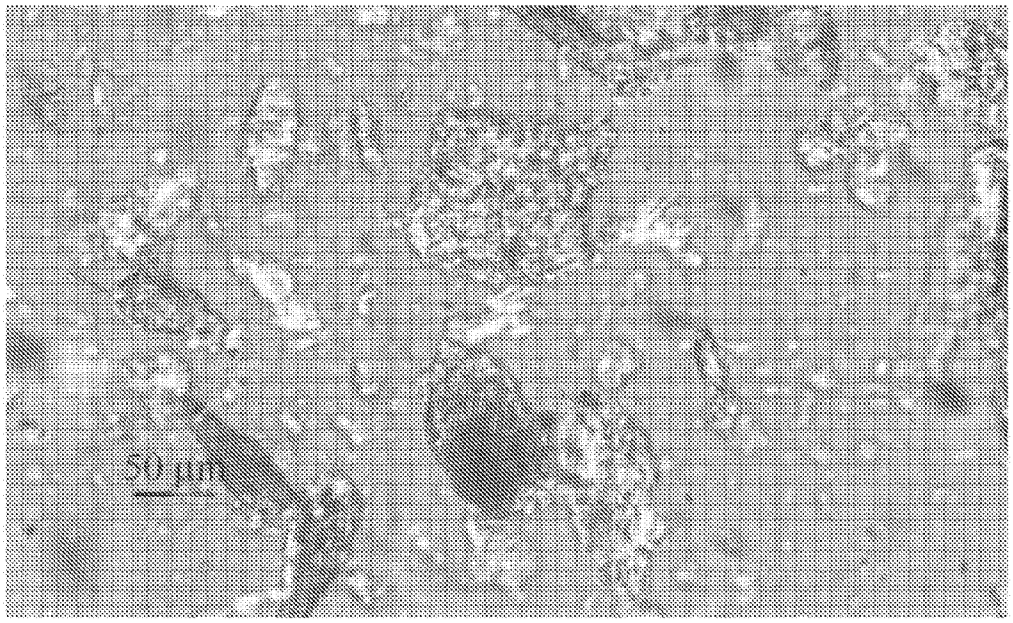


Figure 16



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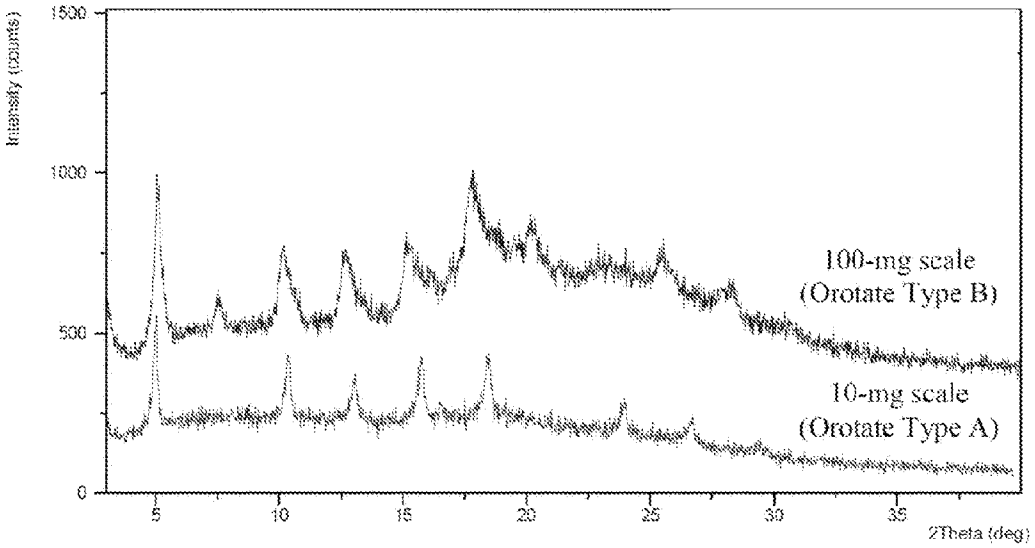

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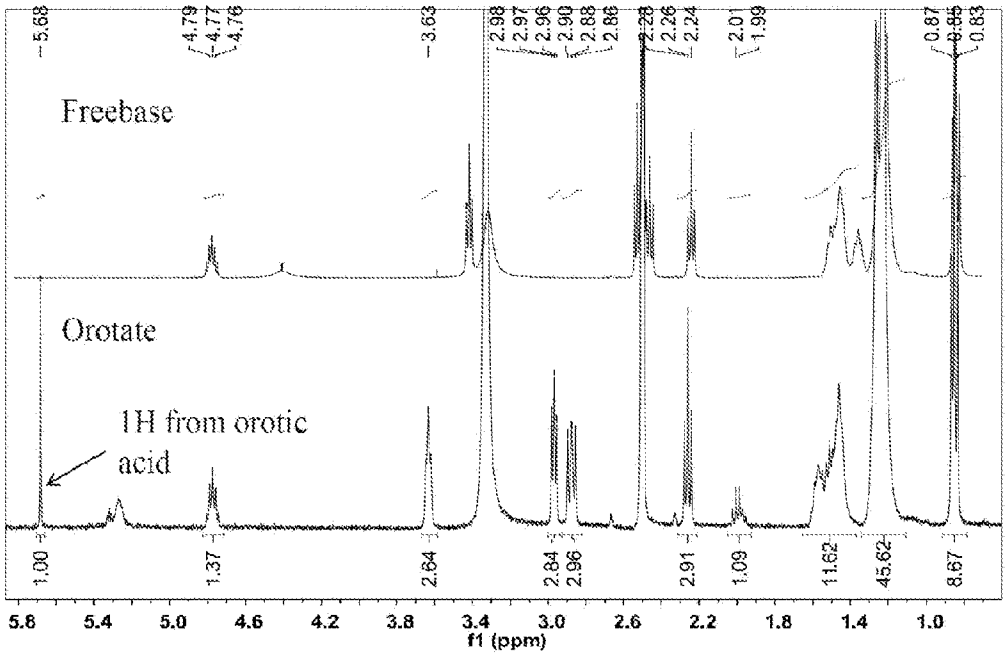
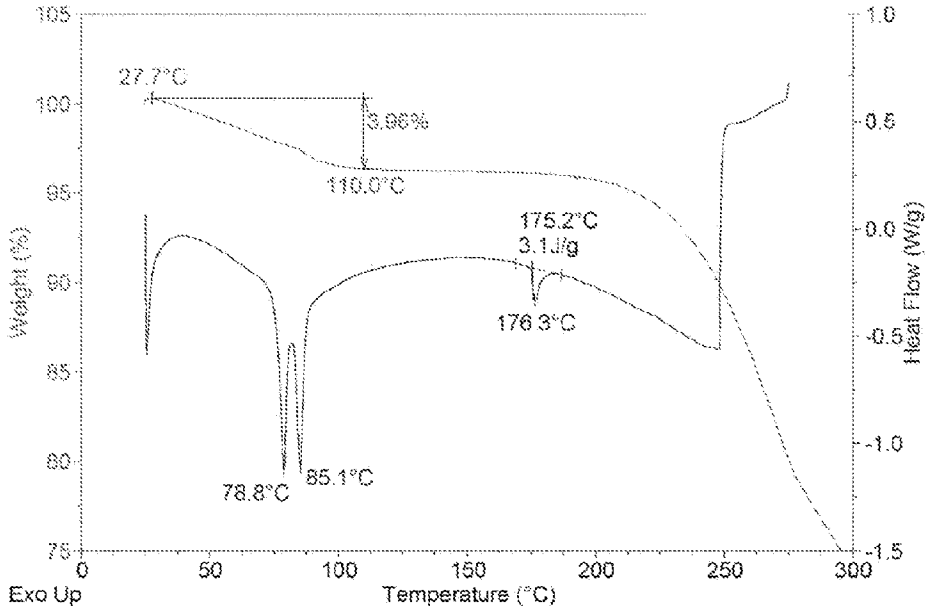


Figure 19



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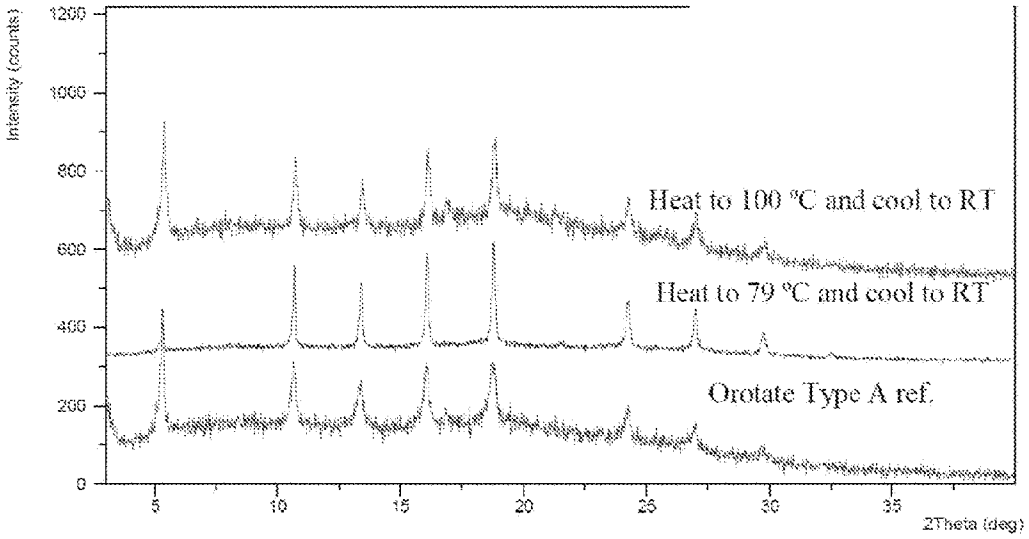

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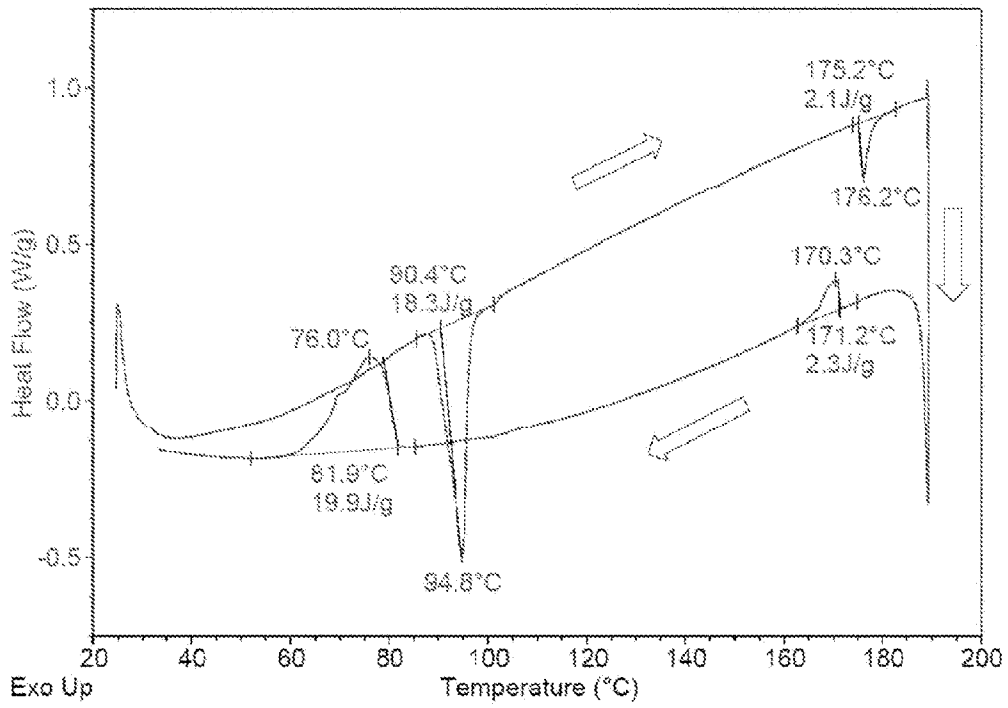

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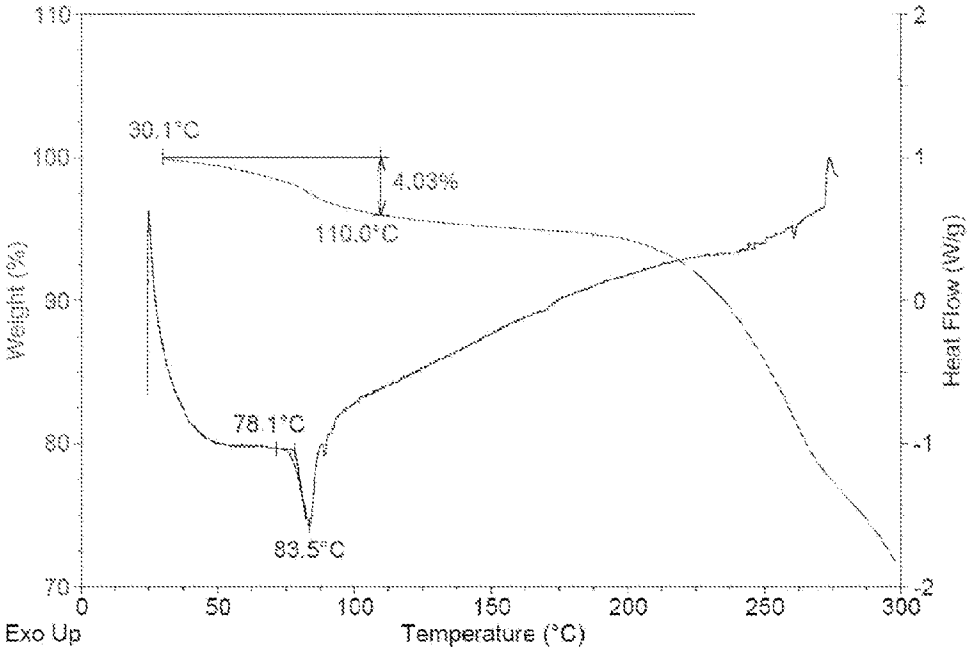

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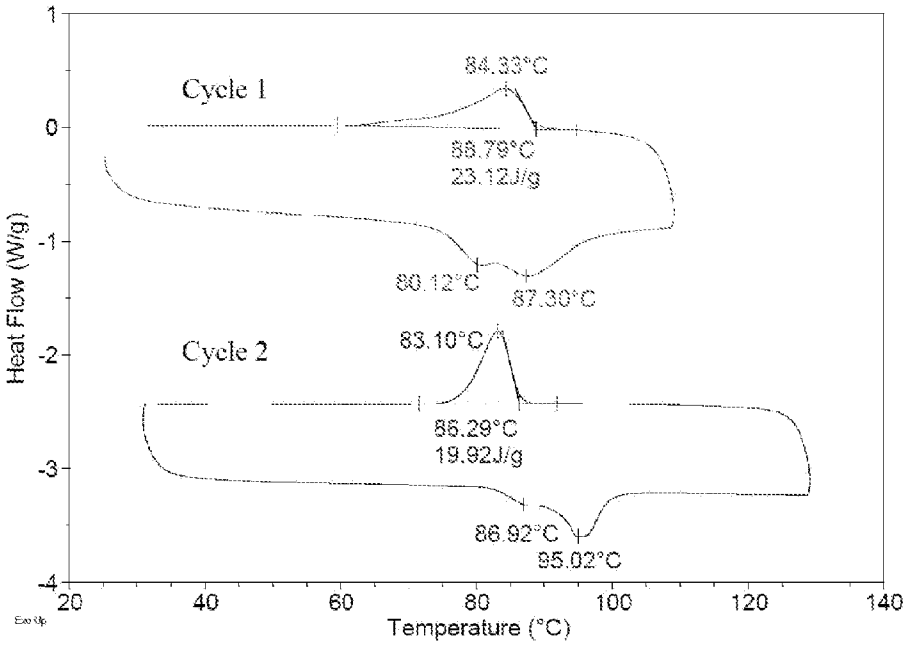

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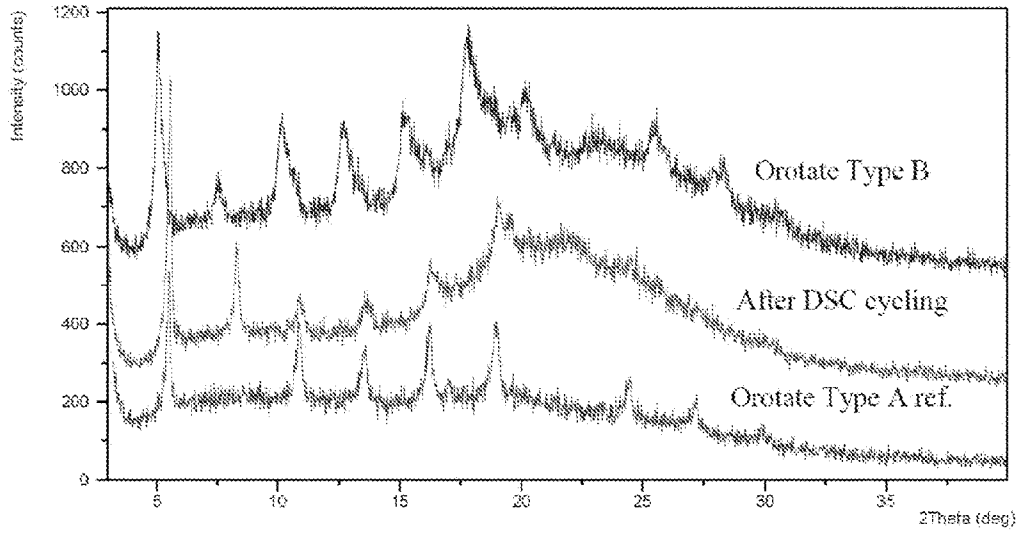

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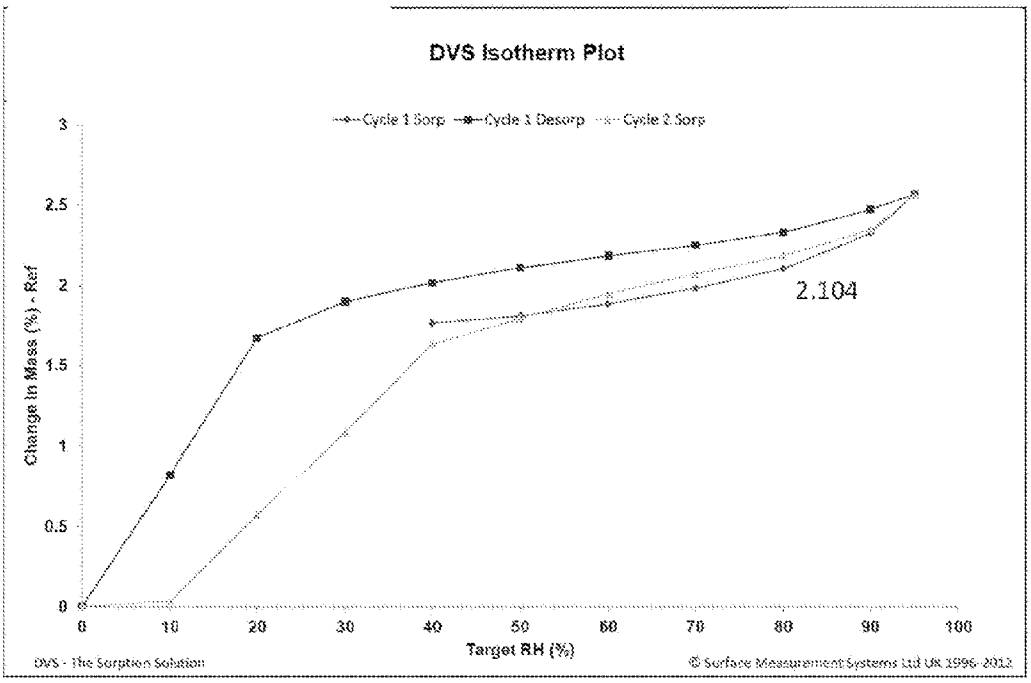

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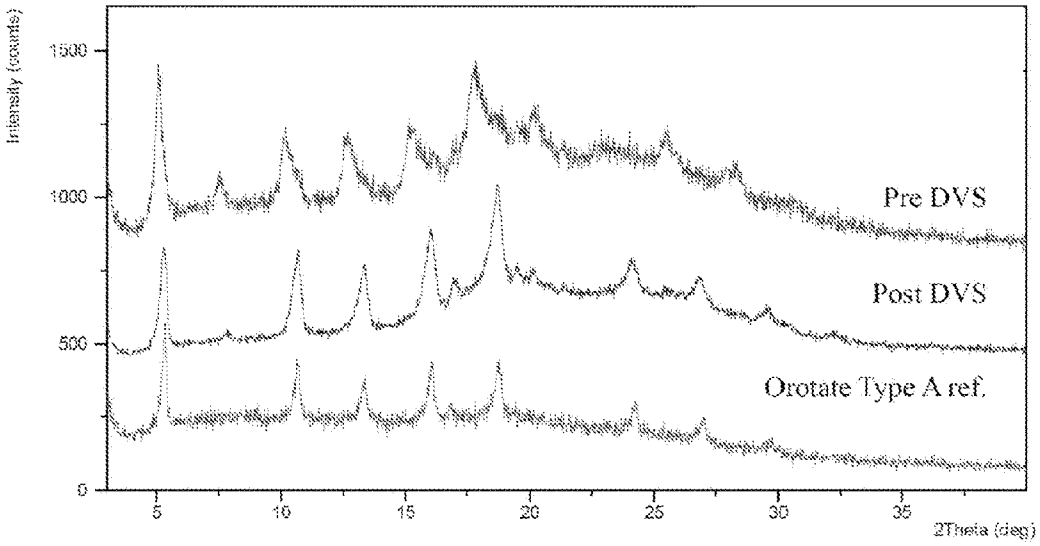

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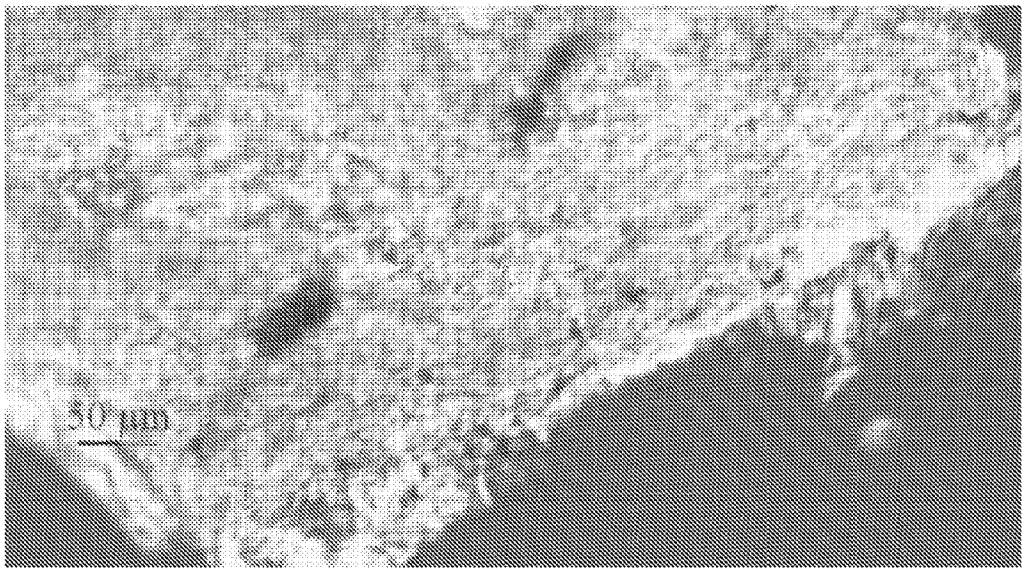

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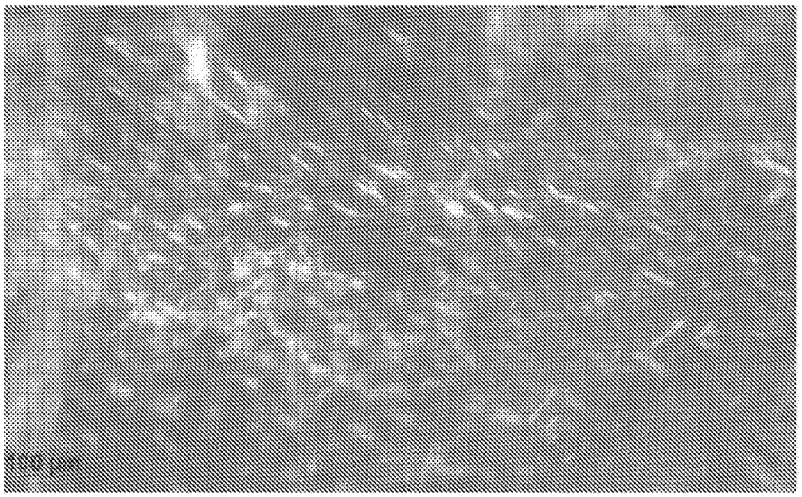

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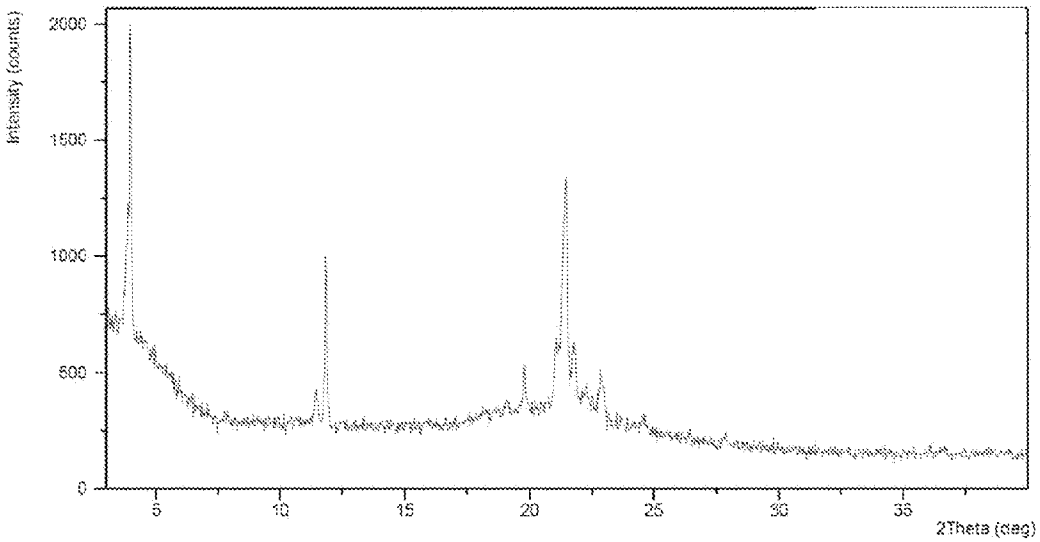

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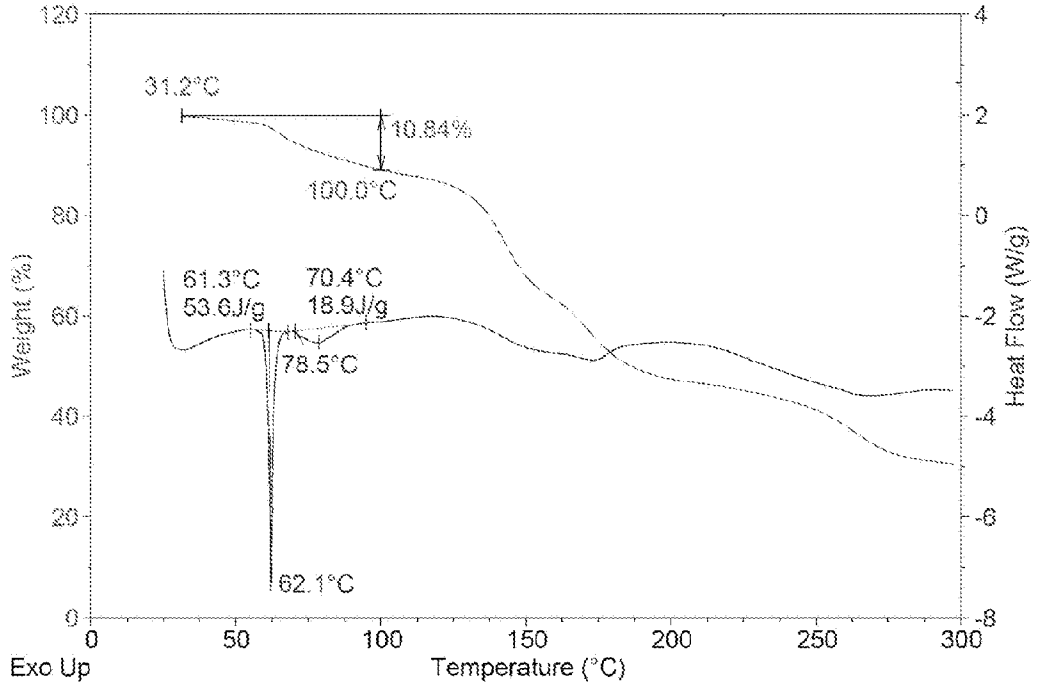

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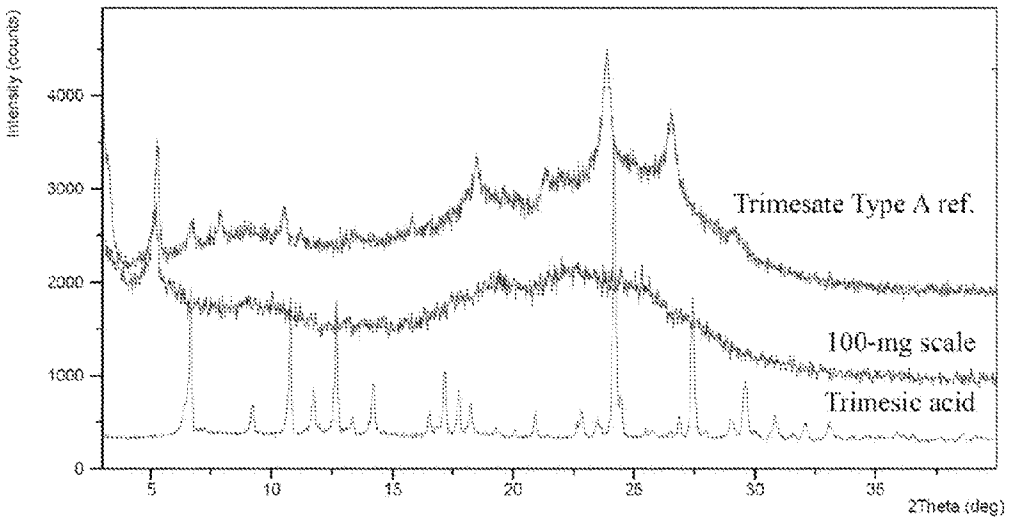
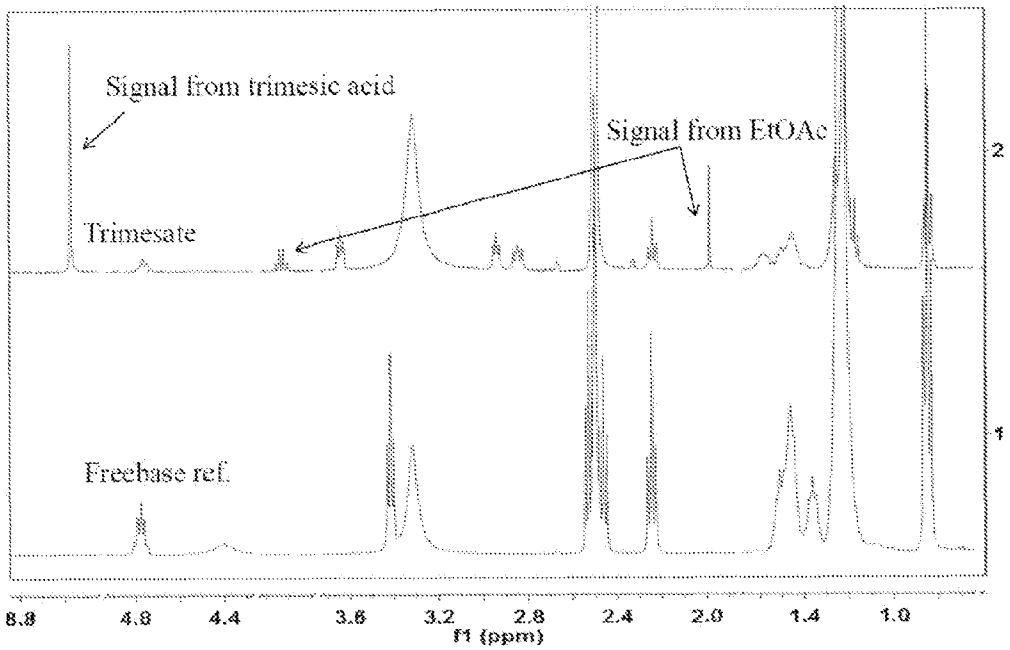


Figure 32



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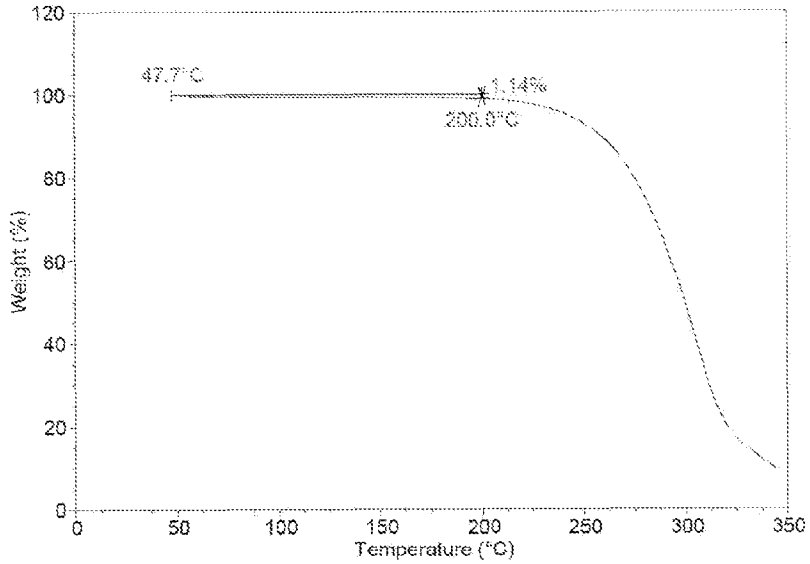
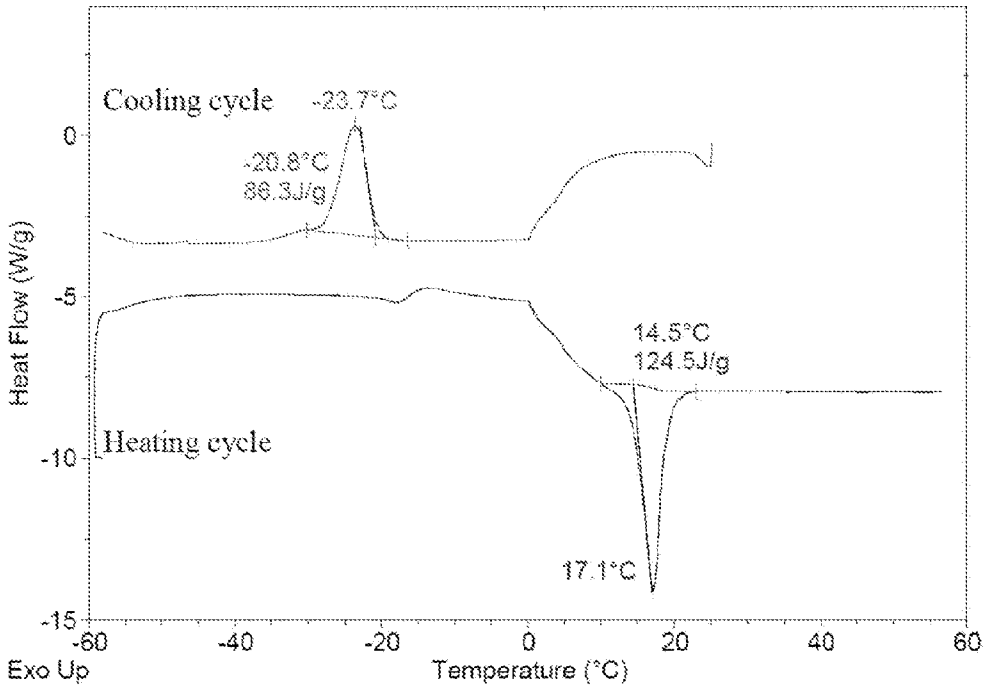


Figure 34



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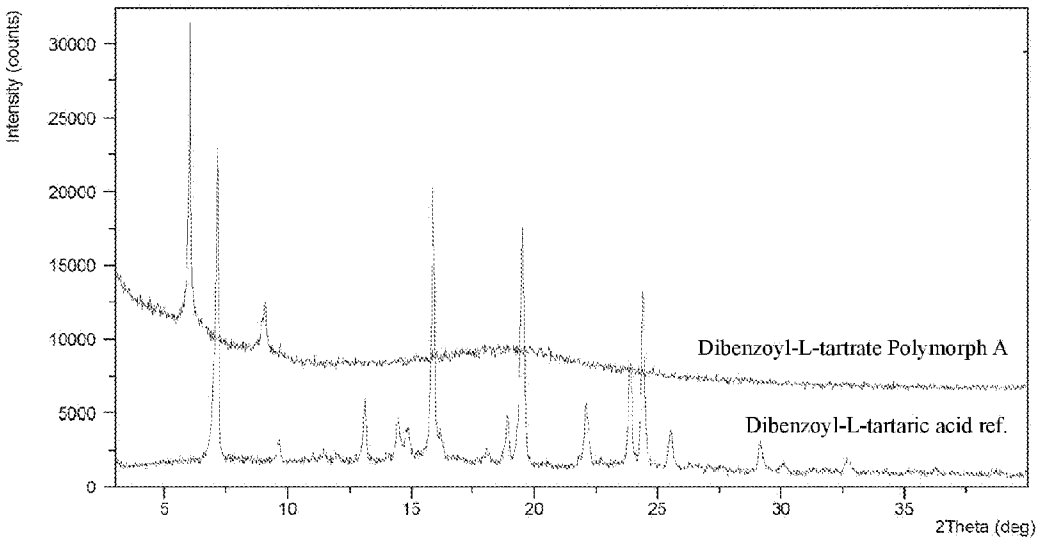

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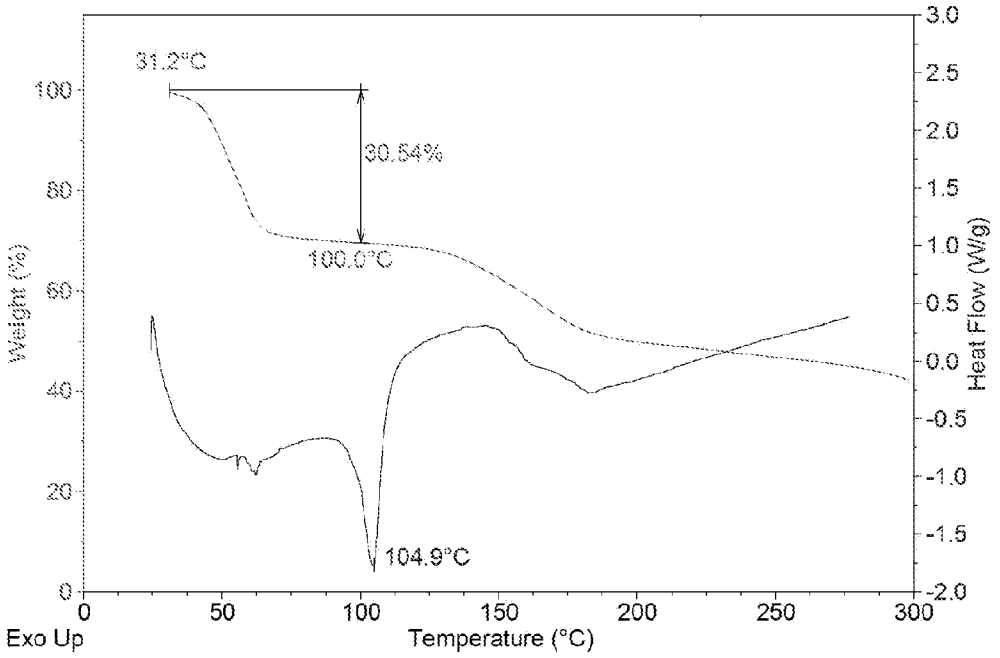

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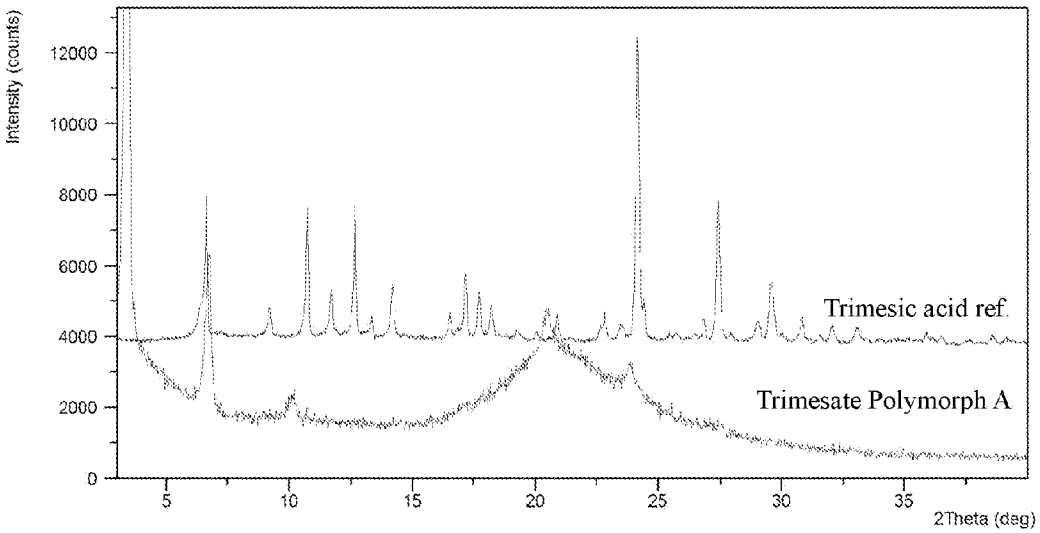

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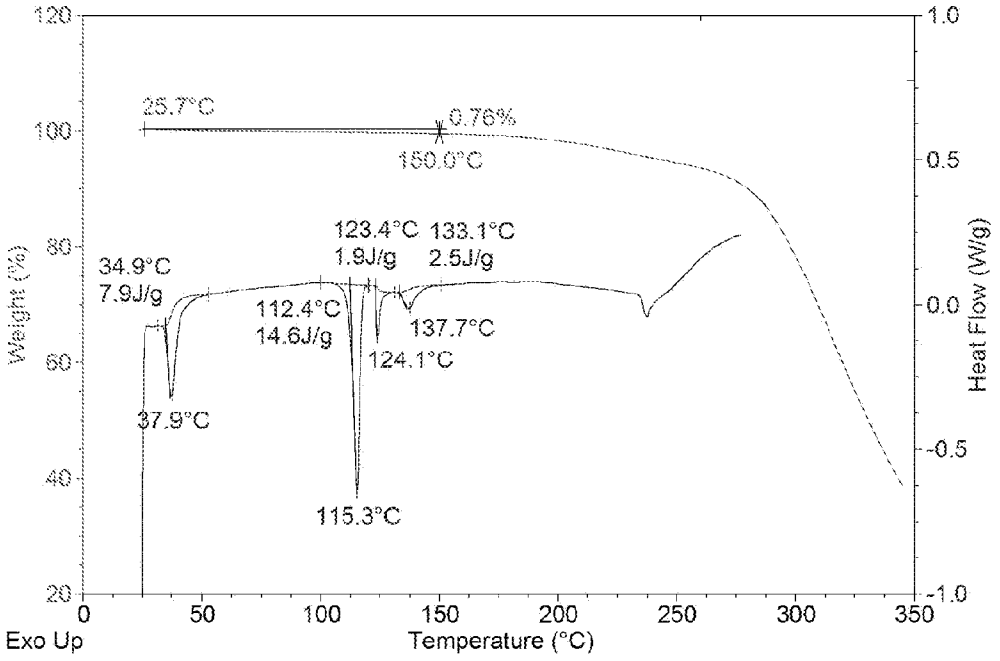

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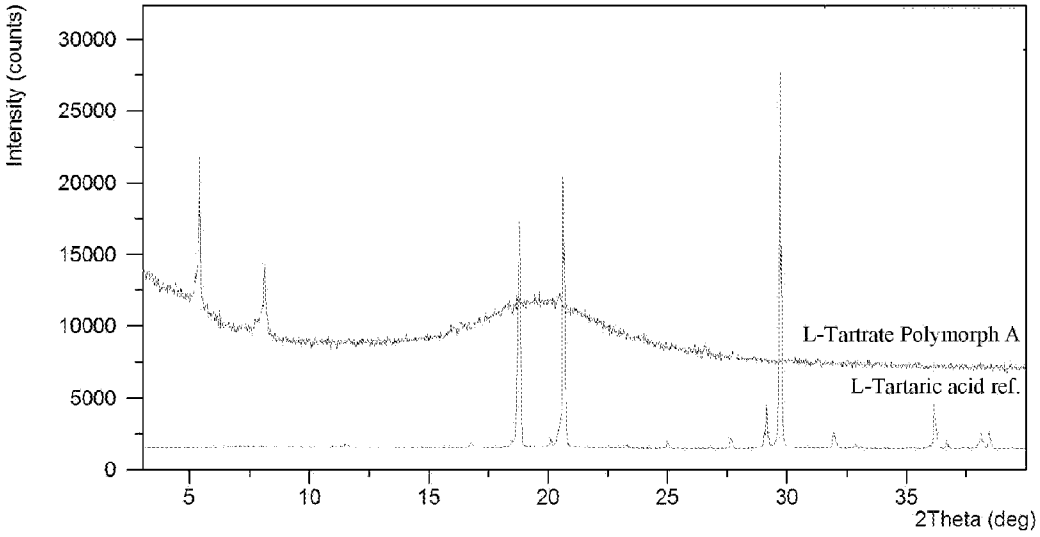

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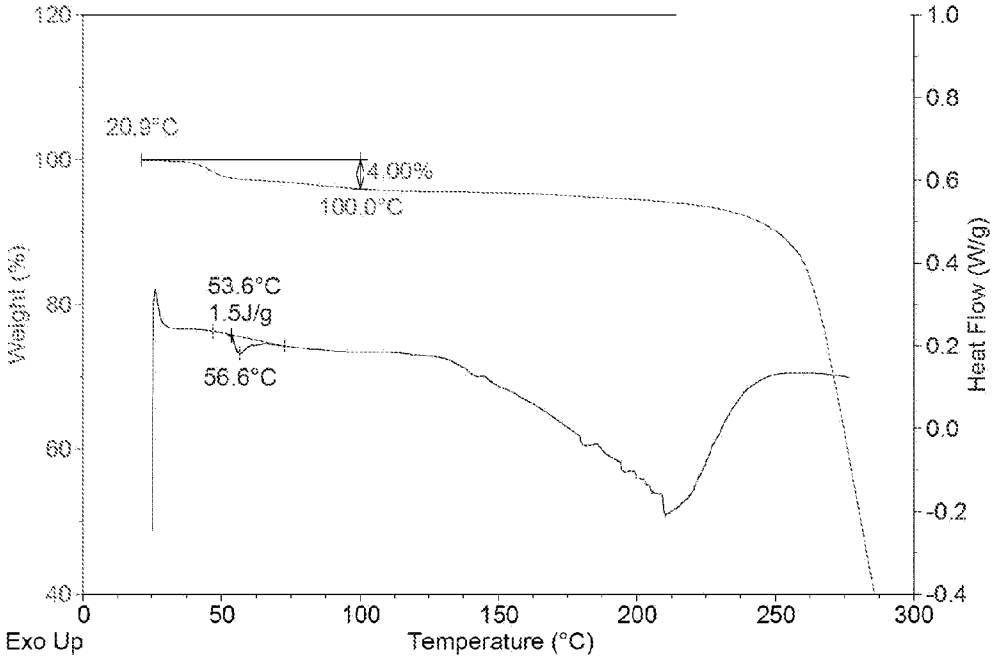

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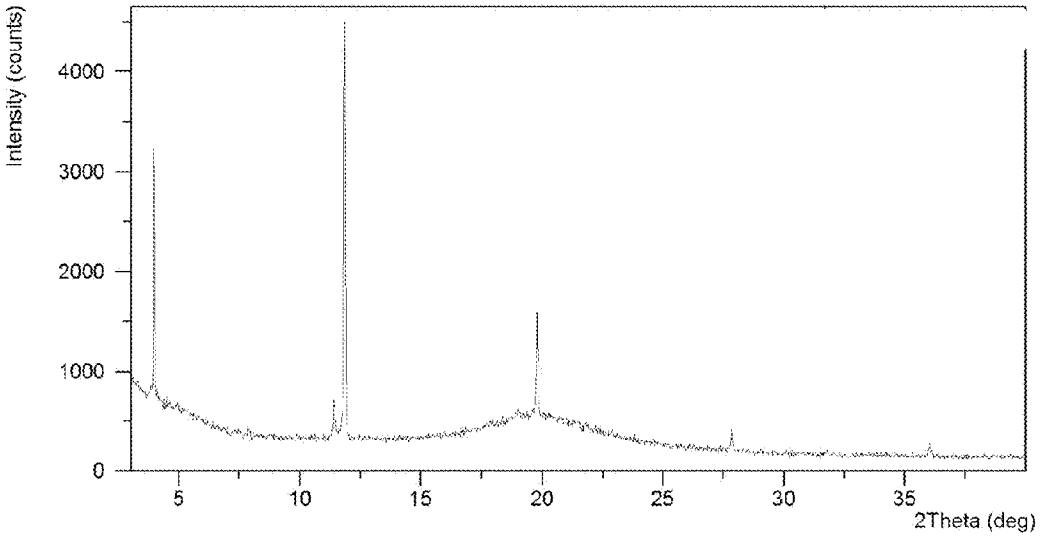

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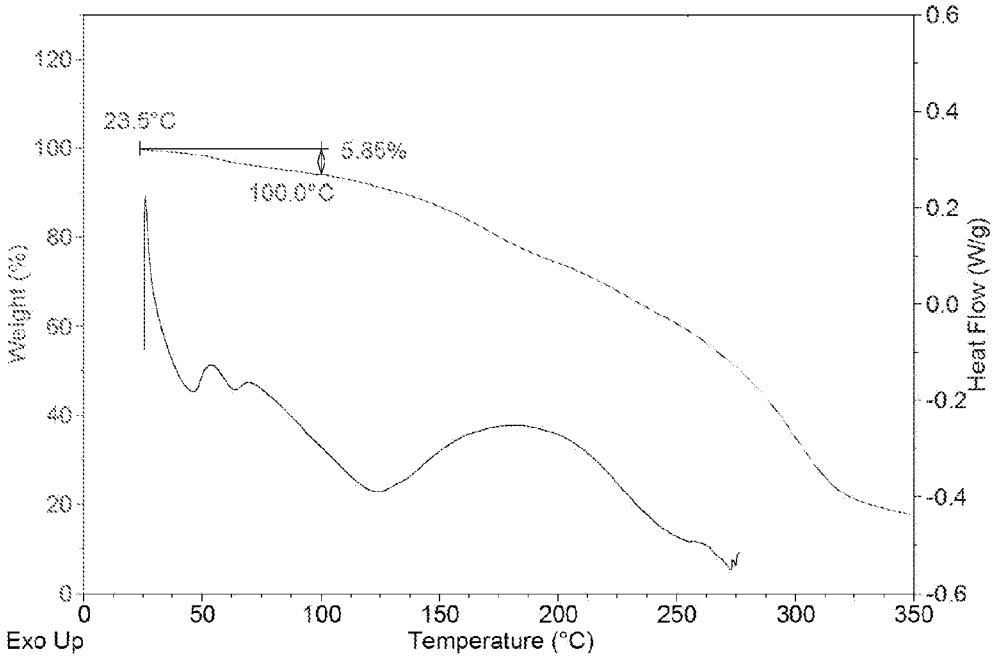
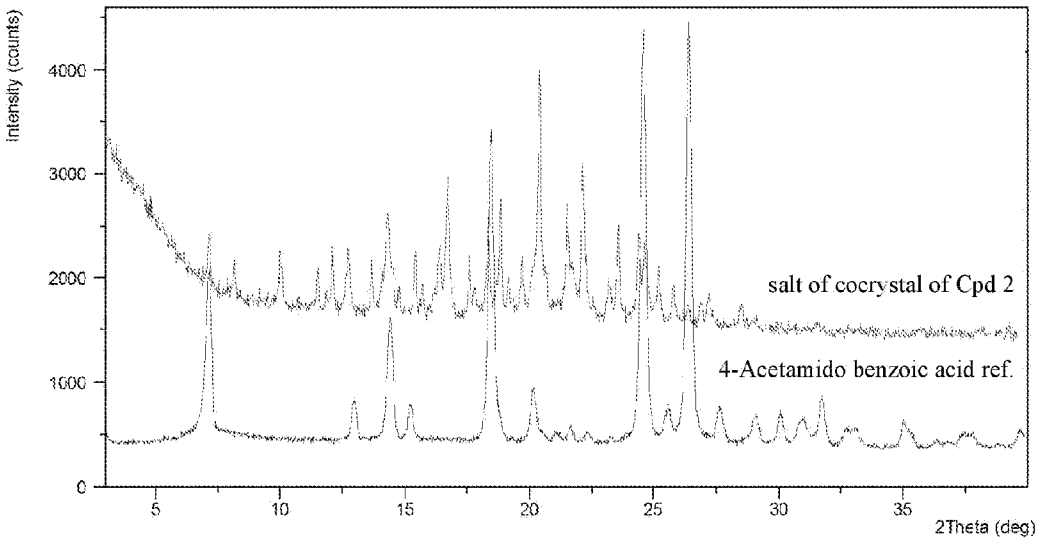


Figure 43



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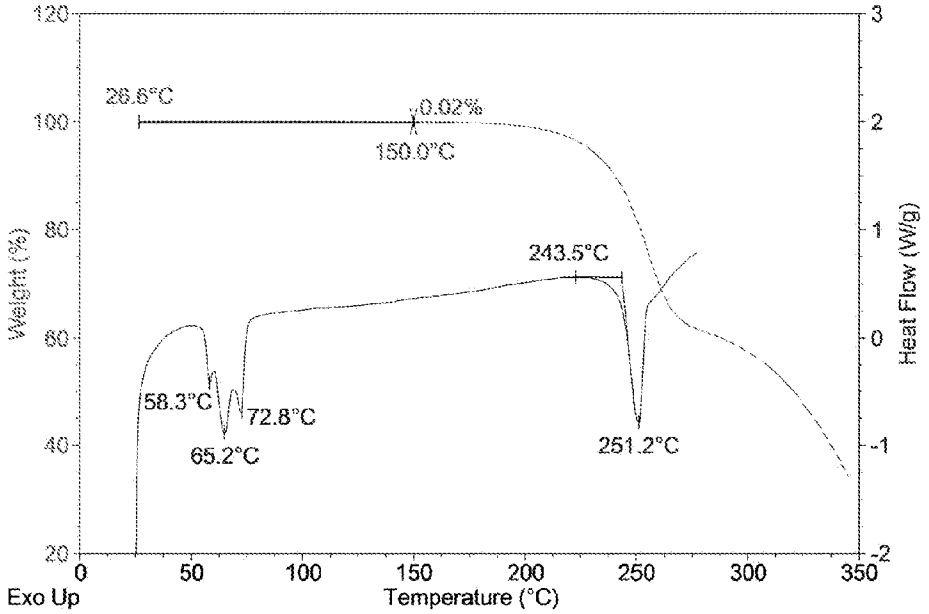

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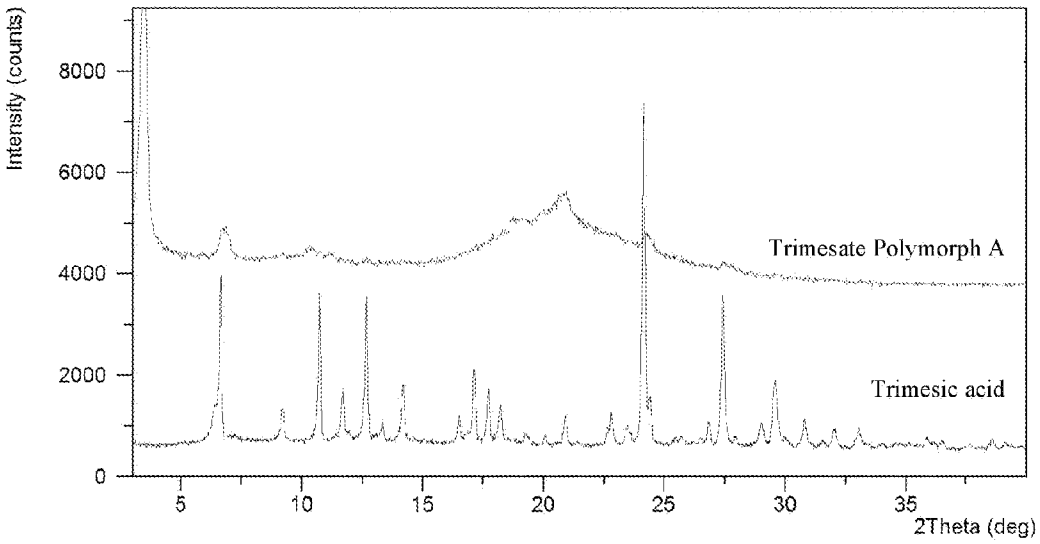

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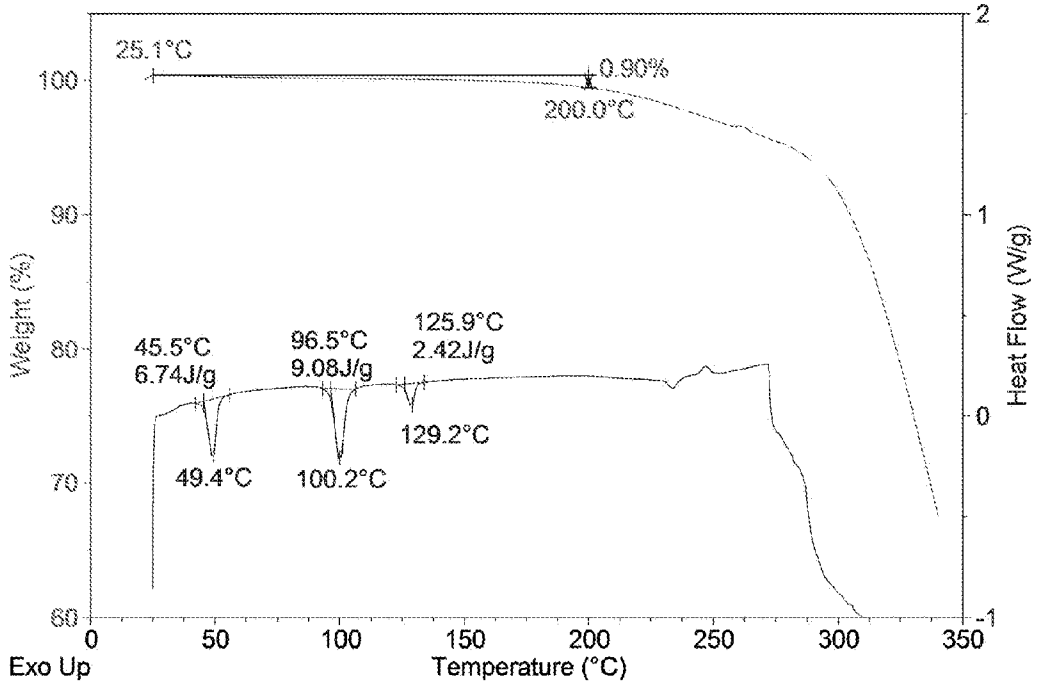

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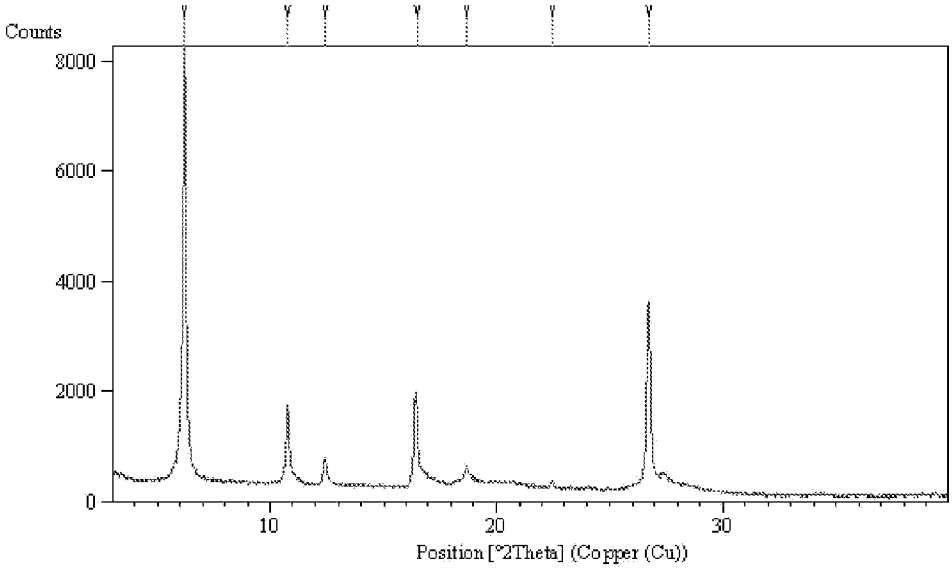

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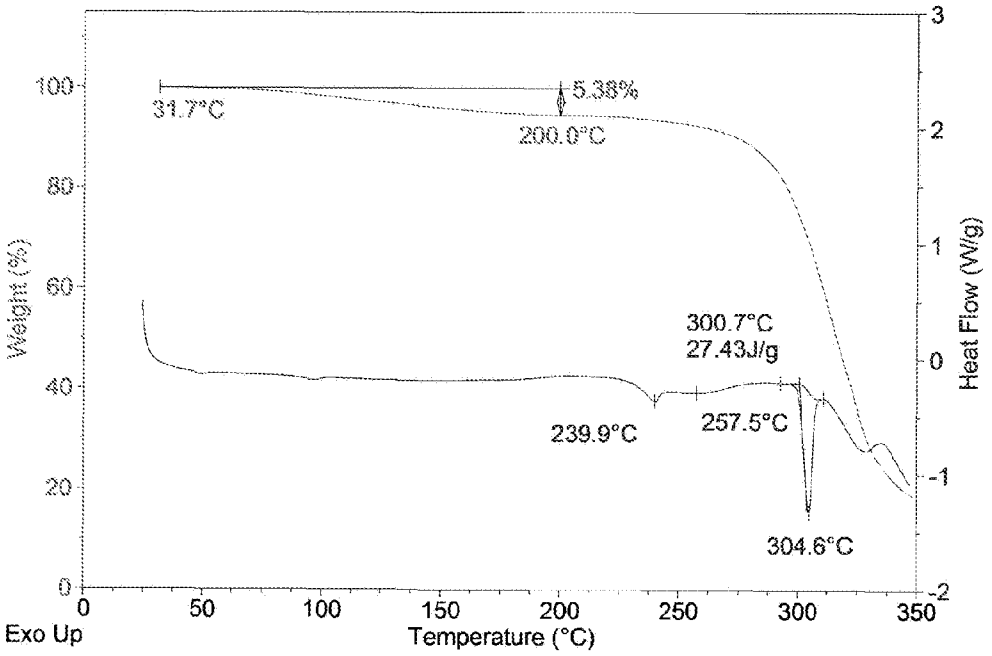

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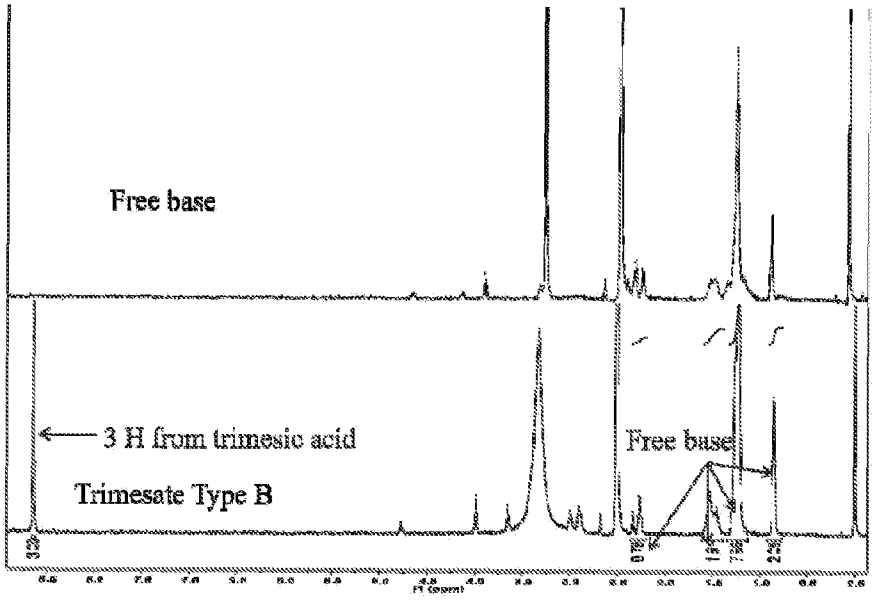

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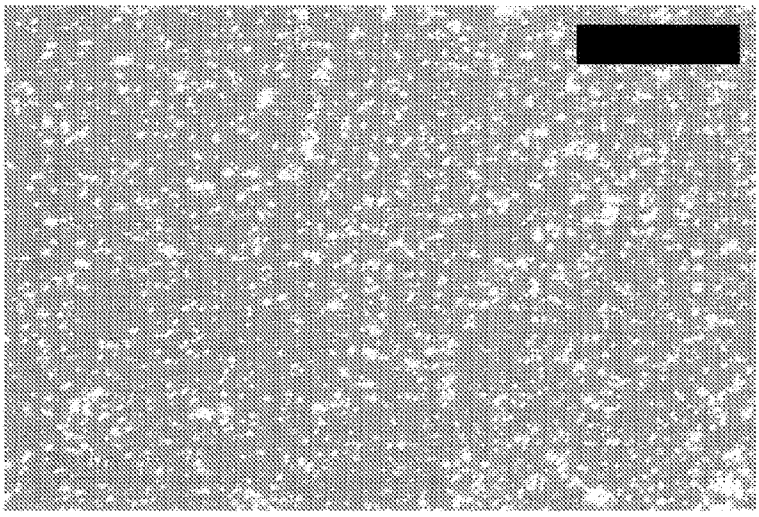

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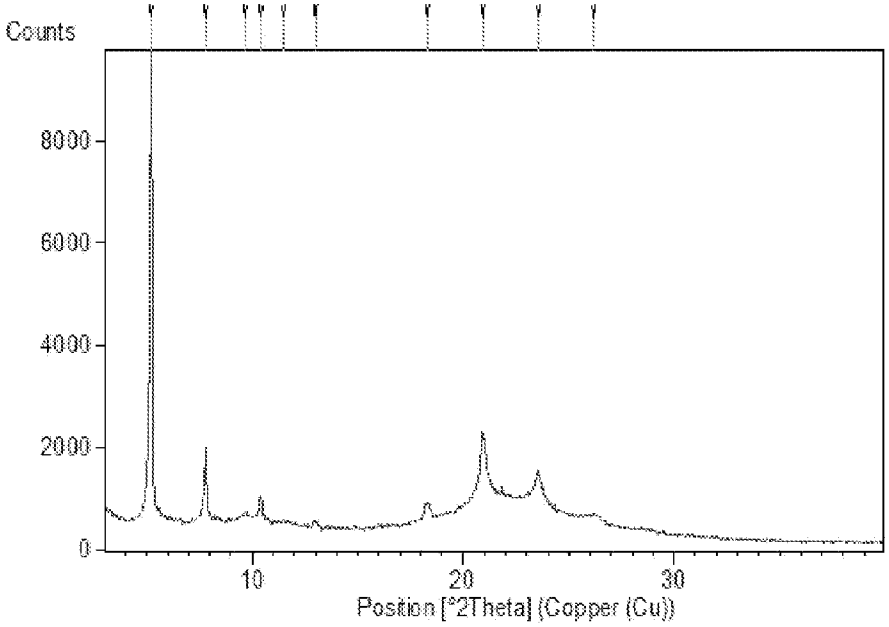

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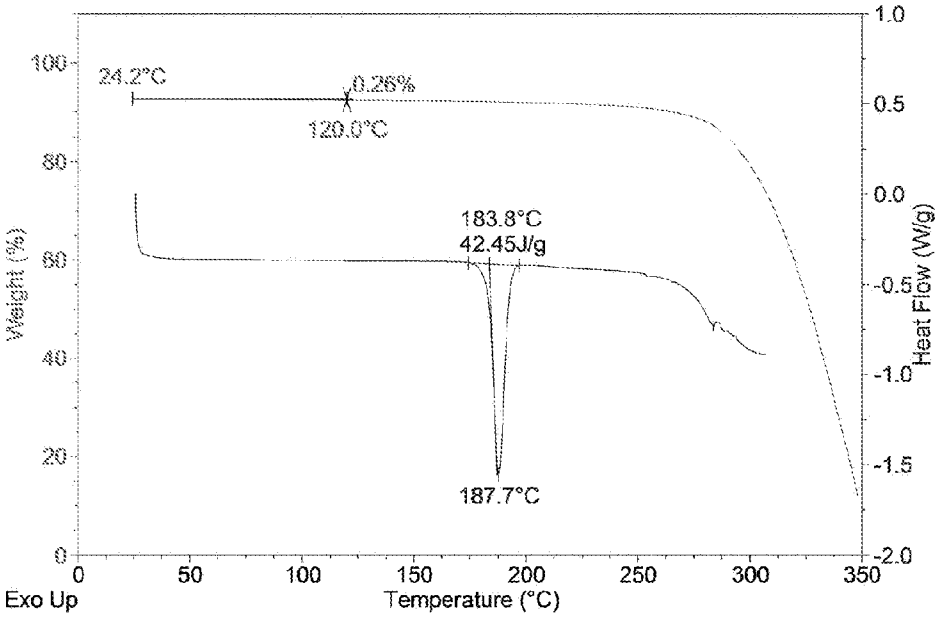

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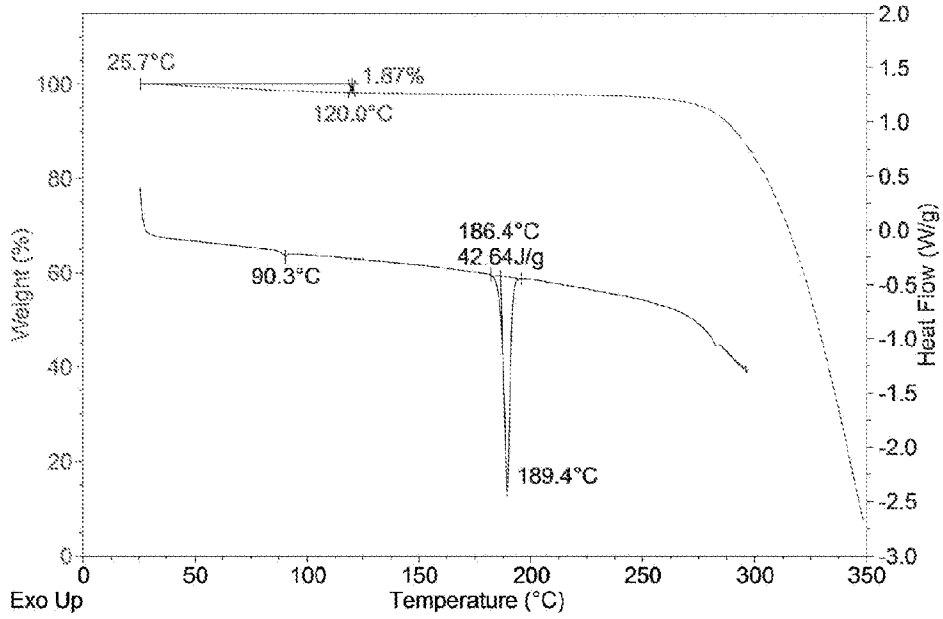

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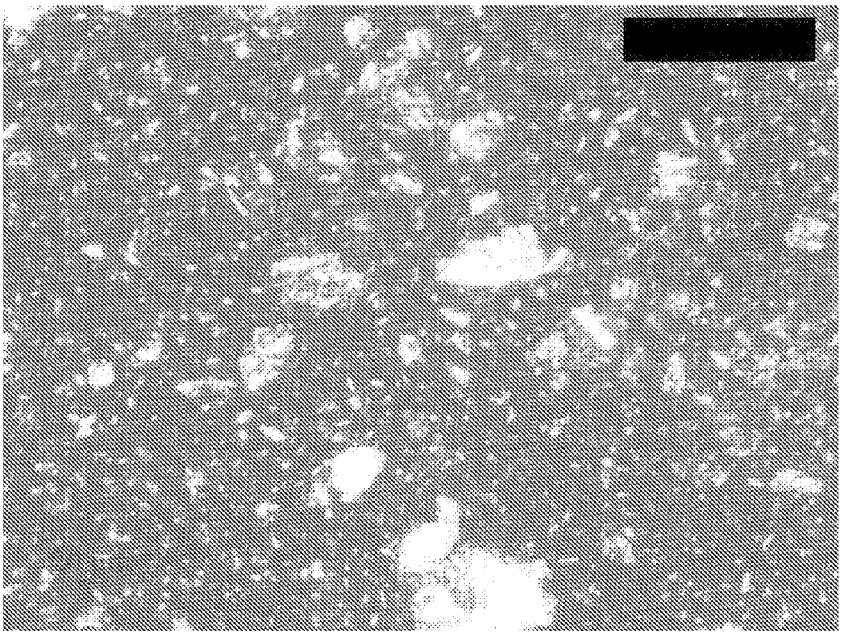

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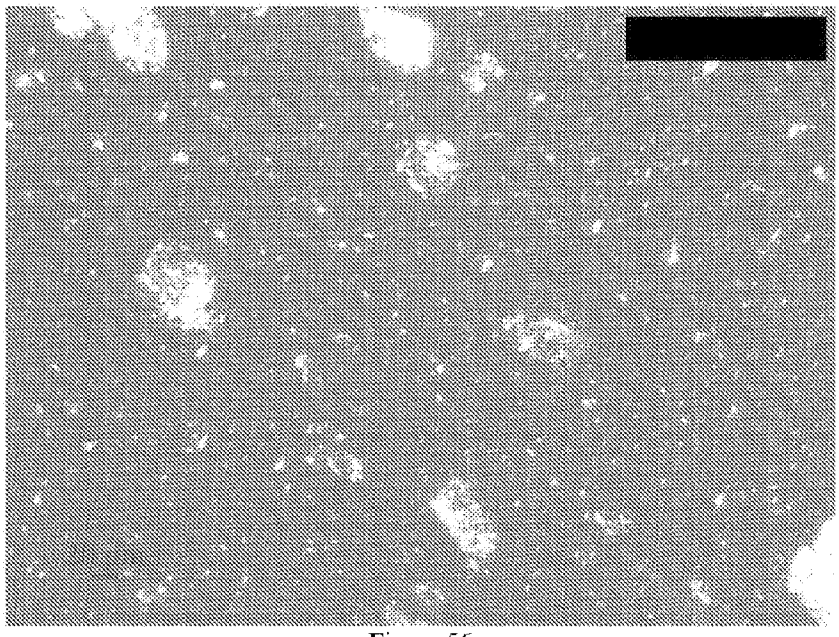

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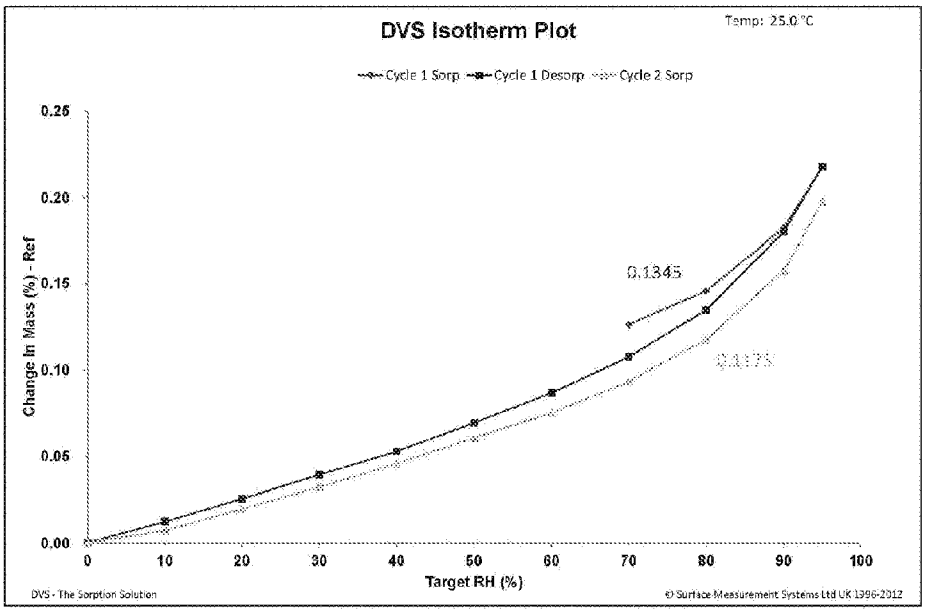

Figure 57

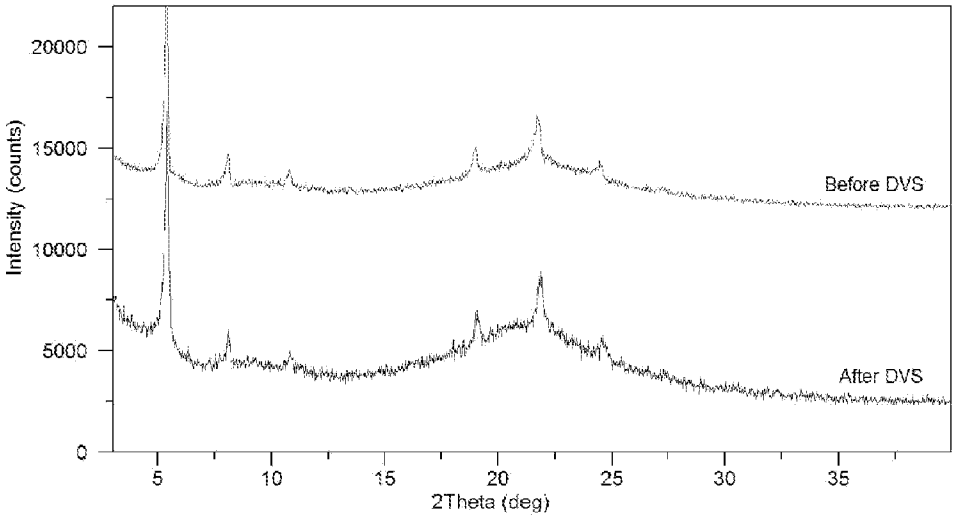

Figure 58

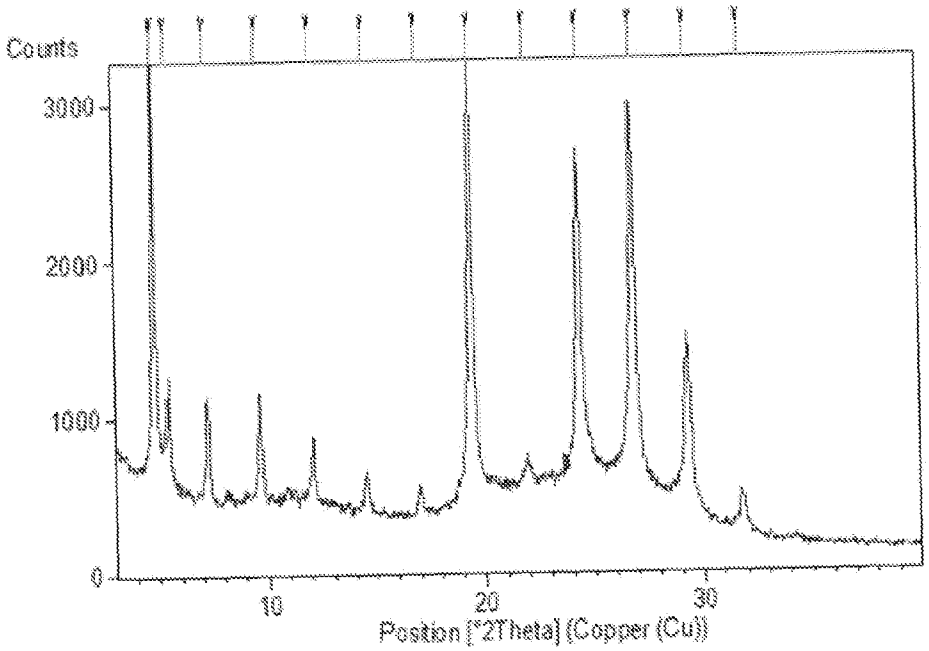

Figure 59

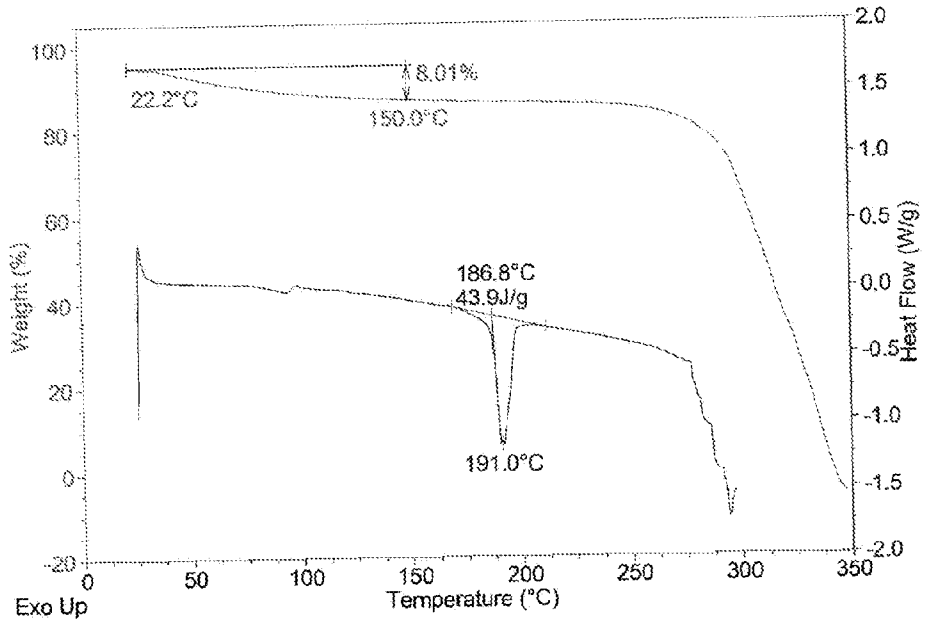

Figure 60

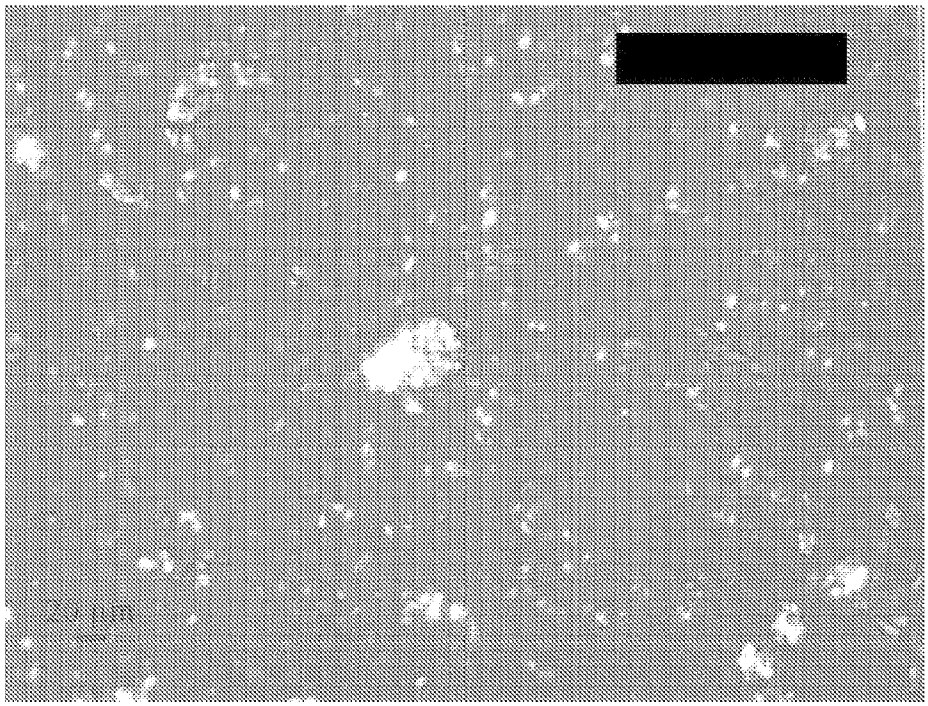

Figure 61