

Solid State Forms of 5-[[6-[(2-fluorophenyl)methoxy]-2-naphthalenyl]methyl]- 2,4-Thiazolidinedione

CROSS-REFERENCE TO RELATED APPLICATION

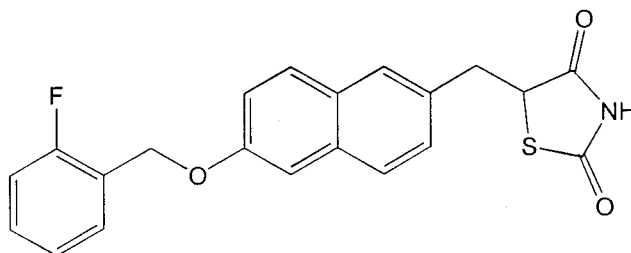
5 This application utilizes nomenclature system for the polymorph forms of MCC-555, 5-[[6-[(2-fluorophenyl)methoxy]-2-naphthalenyl]methyl]- 2,4-Thiazolidinedione, in common with a copending and related United States patent application, docket #99397M, assigned to the Mitsubishi Chemical Corporation.

10 FIELD OF THE INVENTION

This invention relates to a discovery of novel solid state forms, defined as amorphous, polymorphs and pseudomorphs, of MCC-555 and the process for the preparation of these novel forms of MCC-555.

15 BACKGROUND OF THE INVENTION

MCC-555 is 5-[[6-[(2-fluorophenyl)methoxy]-2-naphthalenyl]methyl]- 2,4-Thiazolidinedione, having the formula I shown below. The polymorphic forms prepared by the processes of the present invention are useful as an active ingredient in therapeutic medicaments.



Formula I

20 Polymorphism in drugs may alter the stability, solubility and dissolution rate of the drug and results in different therapeutic efficacy of the different polymorphic

forms of a given drug. By the term polymorphism we mean to include different physical forms, crystal forms, and crystalline/liquid crystalline/non-crystalline (amorphous) forms. This has especially become very interesting after observing that many antibiotics, antibacterials, tranquilizers etc., exhibit polymorphism and some/one of the polymorphic forms of a given drug may exhibit superior bio-availability and consequently show much higher activity compared to other polymorphs. For example, Sertraline, Frentizole, Ranitidine, Sulfathiazole, Indomethacine are some of the pharmaceuticals that exhibit polymorphism.

5-[[6-[(2-fluorophenyl)methoxy]-2-naphthalenyl]methyl]- 2,4-Thiazolidinedione is a PPAR γ agonist compound useful as an agent to treat non-insulin dependent diabetes mellitus having excellent hypoglycemic and hypolipidemic action described in United States patent 5,594,016. Japanese patent unexamined publication (KOKAI) 10-139768, filed on November 14, 1996 is directed to an industrial process of manufacture of MCC-555.

The present invention provides a novel crystal form and an amorphous form of MCC-555 not previously described. The methods described in United States patent 5,594,016 and Japanese patent unexamined publication (KOKAI) 10-139768, filed on November 14, 1996 conclude with a recrystallizations step, but these applications do not describe any specific polymorph forms. In the method of synthesis and recrystallization disclosed in United States patent 5,594,016, MCC-555 is recrystallized in the presence of a mixed solvent of ethyl acetate and hexane. The product of the aforementioned method yields an impure crystalline form, herein designated as the D form, or mixtures of the D form with a second form, herein designated the A form. According to the method of synthesis and recrystallization disclosed in Japanese Patent Unexamined Publication 10-139768, MCC-555 is recrystallized in toluene as a solvent. The product of this method yields a mixture of crystal forms comprising A form and the D form. The content ratio of these two forms varies based on factors including the heating temperature,

cooling rate, and amount of solvent utilized. Neither of these two methods yields the novel crystal form, hereafter designated E form, or the amorphous form.

Summary of the Invention

5 The present invention is directed to a novel crystal form, the E form, and a novel amorphous form of 5-[[6-[(2-fluorophenyl)methoxy]-2-naphthalenyl]methyl]-2,4-Thiazolidinedione (MCC-555) each of which are distinguishable from known solid forms of the molecule.

10 The present invention is directed to the E crystal form of 5-[[6-[(2-fluorophenyl)methoxy]-2-naphthalenyl]methyl]- 2,4-Thiazolidinedione characterized as having absorption peaks (2θ) substantially as shown in figure 1, a X-ray powder diffraction pattern. The present invention also provides a method for preparation thereof and a pharmaceutical composition comprising the E form of 5-
15 [[6-[(2-fluorophenyl)methoxy]-2-naphthalenyl]methyl]- 2,4-Thiazolidinedione.

 The present invention is also directed to an amorphous form of 5-[[6-[(2-fluorophenyl)methoxy]-2-naphthalenyl]methyl]- 2,4-Thiazolidinedione characterized by the absence of any characteristic absorption peaks (2θ) in a
20 powder X-ray diffraction pattern. The present invention further provides a method for preparation thereof and a pharmaceutical composition comprising the amorphous form of 5-[[6-[(2-fluorophenyl)methoxy]-2-naphthalenyl]methyl]- 2,4-Thiazolidinedione.

25 Brief Description of the Drawings

Figure 1. X-ray Powder Diffraction of E form crystal.

Figure 2. Differential scanning calorimetry of E form crystal.

Figure 3. Moisture Balance analysis of E form crystal.

Figure 4. X-ray Powder Diffraction of Amorphous form.

5 Figure 5. Differential scanning calorimetry of amorphous form.

Figure 6. X-ray Powder Diffraction of Amorphous form after reheating to about 100 °C.

10 Detailed Description of the Invention

The E type crystal of MCC-555 is obtained by heating and stirring the crystalline product of the methods described in United States patent 5,594,016, which is incorporated herein by reference, or Japanese Patent Unexamined Publication 10-139768, or similar methods, in a solvent. All known polymorphic
15 forms of MCC-555, or mixtures thereof are suitable to generate the E type crystal of MCC-555.

Type E form crystal is produced by recrystallization from a suitable solvent such as N,N-dimethylformamide (DMF). MCC-555 has an approximate solubility of 108 mg/ml in DMF.

20 The E form crystal can be easily obtained with good reproducibility by dissolving MCC-555 in DMF with stirring at atmospheric pressure or greater pressure and at ambient temperature.

The time required for substantially complete formation of the E type crystal form of MCC-555 according to the aforementioned method may vary from several
25 minutes to about 5 hours or more. An optimum time required for an individual process may vary depending on several factors such as temperature, amount of solvent, amount of MCC-555, and other. The degree of formation of the E type crystal form of MCC-555 can be observed by collecting a sample, cooling the sample to room temperature, isolating precipitates by filtration, and measuring the
30 precipitates by powder X-ray diffractometry, or differential scanning calorimetry.

As described below, the polymorphic form of 5-[[6-[(2-fluorophenyl)methoxy]-2-naphthalenyl]methyl]-2,4-Thiazolidinedione provides respective characteristic absorption bands, and the E type crystal is easily distinguishable from other types of crystal forms. The endothermal peak observed during differential scanning calorimetry also affords a unique character to distinguish the E form crystal from other known crystal forms of MCC-555.

More particularly, the E form crystal of 5-[[6-[(2-fluorophenyl)methoxy]-2-naphthalenyl]methyl]-2,4-Thiazolidinedione can be obtained by recrystallization of any one of the known crystal forms or a mixture thereof from an organic solvent such as N,N-dimethylformamide (DMF). The temperature is not particularly limiting and E type polymorph form may be obtained from about ambient temperature to about the refluxing temperature of DMF. More particularly, a preferred temperature range is about 15 – 30 °C. The method to produce the E form crystal is advantageous because it can be performed at larger scale to produce pure, or substantially pure E form crystal.

The powder X-ray diffraction data and the differential scanning calorimetry data clearly demonstrate that the E form crystal is distinguishable from the known crystal forms of 5-[[6-[(2-fluorophenyl)methoxy]-2-naphthalenyl]methyl]-2,4-Thiazolidinedione. Particularly the X-ray powder diffraction pattern contains 20 peaks substantially as shown in figure 1, and the corresponding numerical data shown in Table 1. The differential scanning calorimetry is characterized by an endotherm at about 150 °C.

Table 1: Peak positions and relative intensities for Form E

Peak position ($^{\circ}2\theta$)	d-spacing	Relative intensity ^a
11.42	7.743	10
14.89	5.945	77
16.18	5.475	18
17.30	5.123	33
17.64	5.025	42
18.66	4.752	20
19.09	4.644	19
22.16	4.008	100
23.35	3.807	15
24.07	3.695	19
25.29	3.519	72
26.48	3.363	36
27.93	3.192	57
29.20	3.056	13
29.88	2.988	18
31.06	2.877	22
31.88	2.805	10
32.60	2.744	12
33.82	2.649	16
34.40	2.605	13
35.54	2.524	7
36.22	2.478	10
37.84	2.376	9
38.24	2.352	12
38.94	2.311	9
39.76	2.265	12

The present invention also provides an amorphous form of MCC-555. The
 5 amorphous form can be obtained by heating a solid form of MCC-555 until it melts,
 and then rapidly cooling the molten substance to yield the amorphous form. Solid
 forms of MCC-555 suitable for use to generate the amorphous form comprise the
 A form, B form, C form, D form, E form, or mixtures thereof. The particular
 temperature required to obtain molten substance can be evaluated by visually
 10 observing the solid substance phase change. Particularly, the crystalline form, or
 mixtures thereof, may be heated to a temperature in the range from about 152 ° to

about 200 °C, to yield a molten substance, and then quickly cooled to yield the amorphous form.

X-ray powder diffraction pattern and differential scanning calorimetry data clearly distinguish the amorphous form of MCC-555 from other known crystal forms of the drug substance. Particularly the X-ray powder diffraction pattern lacks any distinct 2θ peaks, and the differential scanning calorimetry is characterized by an endotherm at about 151 °C, with minor transitions at about 131 °C and about 139 °C.

Pharmaceutically useful compositions comprising E type crystals or the amorphous form of MCC-555 may be formulated according to known methods such as by the admixture of a pharmaceutically acceptable carrier. To form a pharmaceutically acceptable composition suitable for effective administration, such compositions will contain a therapeutically effective amount of the E type crystals or the amorphous form of MCC-555.

Therapeutic or diagnostic compositions of the invention are administered to an individual in amounts sufficient to treat or diagnose disorders in which modulation of E type crystals or the amorphous form of MCC-555-related activity is indicated, including diabetes, hyperlipidemia, hyperuricemia, leukemia, and pancreatitis. The effective amount may vary according to a variety of factors such as the individual's condition, weight, sex and age. Other factors include the mode of administration. The pharmaceutical compositions may be provided to the individual by a variety of routes such as subcutaneous, topical, oral and intramuscular.

The present invention also has the objective of providing suitable topical, oral, systemic and parenteral pharmaceutical formulations for use in the novel methods of treatment of the present invention. The compositions containing compounds according to this invention as the active ingredient can be administered in a wide variety of therapeutic dosage forms in conventional

vehicles for administration. For example, the compounds or modulators can be administered in such oral dosage forms as tablets, capsules (each including timed release and sustained release formulations), pills, powders, granules, elixirs, tinctures, solutions, suspensions, syrups and emulsions, or by injection. Likewise, they may also be administered in intravenous (both bolus and infusion), intraperitoneal, subcutaneous, topical with or without occlusion, or intramuscular form, all using forms well known to those of ordinary skill in the pharmaceutical arts.

The daily dosage of the products may be varied over a wide range from 0.01 to 1,000 mg per patient, per day. For oral administration, the compositions are preferably provided in the form of scored or unscored tablets containing 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, and 50.0 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. An effective amount of the drug is ordinarily supplied at a dosage level of from about 0.0001 mg/kg to about 100 mg/kg of body weight per day. The range is more particularly from about 0.001 mg/kg to 10 mg/kg of body weight per day.

Advantageously, pharmaceutical compositions comprising E type crystals or the amorphous form of MCC-555 of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily. Furthermore, compounds or modulators for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

For combination treatment with more than one active agent, where the active agents are in separate dosage formulations, the active agents can be administered concurrently, or they each can be administered at separately staggered times.

The dosage regimen utilizing pharmaceutical compositions of the present invention is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and others. A physician or veterinarian of ordinary skill can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition. Optimal precision in achieving concentrations of drug within the range that yields efficacy without toxicity requires a regimen based on the kinetics of the drug's availability to target sites. This involves a consideration of the distribution, equilibrium, and elimination of a drug.

In the methods of the present invention, the compounds herein described in detail can form the active ingredient, and are typically administered in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as "carrier" materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include, without limitation, starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include, without limitation, sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like.

For liquid forms the active drug component can be combined in suitably flavored suspending or dispersing agents such as the synthetic and natural gums, for example, tragacanth, acacia, methyl-cellulose and the like. Other dispersing

agents that may be employed include glycerin and the like. For parenteral administration, sterile suspensions and solutions are desired. Isotonic preparations, which generally contain suitable preservatives, are employed when intravenous administration is desired.

5 Topical preparations containing the active drug component can be admixed with a variety of carrier materials well known in the art, such as, e.g., alcohols, aloe vera gel, allantoin, glycerine, vitamin A and E oils, mineral oil, PPG2 myristyl propionate, and the like, to form, e.g., alcoholic solutions, topical cleansers, cleansing creams, skin gels, skin lotions, and shampoos in cream or gel
10 formulations.

 The compositions derived from the E type crystals or the amorphous form of MCC-555 can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as
15 cholesterol, stearylamine or phosphatidylcholines.

 For oral administration, the compounds or modulators may be administered in capsule, tablet, or bolus form. The capsules, tablets, and boluses are comprised of the active ingredient in combination with an appropriate carrier
20 vehicle such as starch, talc, magnesium stearate, or di-calcium phosphate. These unit dosage forms are prepared by intimately mixing the active ingredient with suitable finely-powdered inert ingredients including diluents, fillers, disintegrating agents, and/or binders such that a uniform mixture is obtained. An inert ingredient is one that will not react with the compounds or modulators and which is non-toxic
25 to the subject being treated. Suitable inert ingredients include starch, lactose, talc, magnesium stearate, vegetable gums and oils, and the like.

 The compounds may alternatively be administered parenterally via injection of a formulation consisting of the active ingredient dissolved in an inert liquid carrier. Injection may be either intramuscular, intraruminal, intratracheal, or
30 subcutaneous. The injectable formulation consists of the active ingredient mixed with an appropriate inert liquid carrier. Acceptable liquid carriers include the

vegetable oils such as peanut oil, cottonseed oil, sesame oil and the like as well as organic solvents such as solketal, glycerol formal and the like. As an alternative, aqueous parenteral formulations may also be used. The vegetable oils are the preferred liquid carriers. The formulations are prepared by dissolving or
5 suspending the active ingredient in the liquid carrier such that the final formulation contains from 0.005 to 10% by weight of the active ingredient.

The following examples illustrate the present invention without, however, limiting the same thereto.

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EXAMPLE 1

Generation of E type crystal – fast evaporation

15 The starting material of 5-[[6-[(2-fluorophenyl)methoxy]-2-naphthalenyl]methyl]-2,4-Thiazolidinedione was determined to be the type A crystal form by X-ray powder diffraction (XRDP). The material was dissolved at ambient temperature in N,N-dimethylformamide (DMF) in a sealed container. Then the container was unsealed, and the solvent was allowed to evaporate against an
20 open atmosphere at ambient temperature. A single crystal form, the E form, was obtained using this method.

Generation of E type crystal – slow evaporation

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The starting material of 5-[[6-[(2-fluorophenyl)methoxy]-2-naphthalenyl]methyl]-2,4-Thiazolidinedione was determined to be the type A crystal form by X-ray powder diffraction (XRDP). The material was dissolved at ambient temperature in N,N-dimethylformamide (DMF) in a sealed container. A
30 single pin-sized hole was generated in the seal, and then the solvent was allowed to slowly evaporate against an open atmosphere at ambient temperature. The

evaporation rate is significantly reduced due compared to an open container. A single crystal form, the E form, was obtained using this method.

EXAMPLE 2

5 *Evaluation of Type E crystal of MCC-555*

Characterization of crystal forms Produced during the screen was performed using x-ray powder diffraction (XRPD), differential scanning calorimetry (DSC), and thermogravimetry (TG).

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X-Ray Powder Diffraction

XRPD data were collected on either a Shimadzu XRD-6000 or a Siemens D-500 X-ray powder diffractometer.

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The XRPD analyses that were carried out on the Shimadzu XRD-6000 X-ray powder diffractometer used Cu K α radiation (1.5406 Å), and were set up as follows. The instrument was equipped with a fine-focus X-ray tube. The tube voltage and amperage was set at 4.0 kV and 40 mA, respectively. The divergence and scattering slits were set at 1° and the receiving slit was set at 0.15 mm.

20

Diffracted radiation was detected by a NaI scintillation detector. A theta-two theta continuous scan at 3°/min (0.4 sec/0.02° step) from 2.5 to 40° was used. A silicon standard was analyzed each day to check the instrument alignment. Each sample was prepared for analysis by pressing it with a spatula onto a glass or quartz sample holder.

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The XRPD analyses that were carried out on the Siemens D-500 X-ray Powder Diffractometer-Kristalloflex with an IBM-compatible interface and DIFFRAC AT software (SOCABIM, 1994) used Cu K α radiation (1.5406 Å), and were set up as follows. Slits I and II were set at 1° and the radiation was electronically filtered by

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a Kevex Psi Peltier Cooled Silicon [Si(Li)] detector with slits III at 1° and IV at 0.15°. A theta-two theta continuous scan at 6°/min (0.4 sec./0.04° step) from 2.5 to 40.0° was used. A silicon standard was run each day to check the X-ray tube alignment. Each sample was prepared for analysis by pressing it with a glass
5 slide onto a zero-background quartz-in-aluminum sample holder.

As shown in figure 1, the E type polymorph form of MCC-555 is characterized by 2θ peaks as shown.

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Thermogravimetry and Differential scanning calorimetry

TG analyses were carried out on a TA Instruments TGA 2050. The calibration standards were nickel and alumel. Approximately 10 mg of crystalline E type
15 MCC-555 was placed on the pan, accurately weighed, and inserted into the TG furnace. The samples were heated in nitrogen at a rate of 10°C/min, up to a final temperature of 200 °C.

The E type crystal form of MCC-555 indicated a weightloss of <0.1%, measured at
20 150°C.

DSC data were obtained on a TA 2920 instrument. The calibration standard was indium. Approximately 3 - 5 mg samples were placed into a DSC pan, and the weight accurately recorded. The pans were crimped to allow for pressure release.
25 The samples were heated under nitrogen at a rate of 10°C/min, up to a final temperature of 200°C.

Differential scanning calorimetry indicated that E type polymorph form has a distinct melting endotherm at approximately 150 °C, as shown in Figure 2. (Note

the transition temperatures are a function of the heating rate, sample packing, particle size, atmosphere, etc..)

Hot-stage microscopy was carried out using a Wagner & Munz apparatus

- 5 consisting of a Kofier stage mounted on a Leica Microscope. The instrument was calibrated using USP standards.

The melting onset of form E was observed to be at 139 °C.

10 Spectroscopy

- The mid-IR spectra were acquired on a Nicolet model 860 Fourier transform IR spectrophotometer equipped with a globar source, Ge/KBr beamsplitter, and deuterated triglycine sulfate (DTGS) detector. A Spectra-Tech, Inc. diffuse
15 reflectancy accessory was utilized for sampling. Each spectrum represents 64 co-added scans at a spectral resolution of 1 or 4 cm^{-1} . Sample preparation for the drug substance consisted of placing the sample into the 25mm diameter cup and leveling the material with a frosted glass slide. A background data set was acquired with an alignment mirror in place. A single beam sample data set was
20 then acquired. Subsequently, a Log 1/R (R=Reflectance) spectrum was acquired by ratioing the two data sets against each other. The spectrophotometer was calibrated (wavelength) with polystyrene at the time of use.

Raman spectra were acquired on a Nicolet model 750 Fourier transform Raman spectrometer utilizing an excitation wavelength of 1064 nm and approximately 0.5 W of ND:YAG laser power. The spectra represent 512 co-added scans acquired at 1 or 4 cm^{-1} resolution. The drug substance samples were prepared for analysis by placing the material in a 5-mm diameter glass tube and positioning this tube in the spectrometer. The spectrometer was calibrated (wavelength) with sulfur and cyclohexane at the time of use.

Table 2 shows distinct peaks, characterized as strong (s), medium (m), or weak (w) obtained for the E type crystal of MCC-555.

Table 2.

Raman Features	IR Features
3061 (s), 2919 (m), 1736 (s), 1618 (s), 1466 (w), 973 (w), 135 (s)	3840 (w), 3413 (m), 3375 (m), 2053 (m), 1965 (m), 1932 (s), 1901 (s), 1464 (s), 1428 (m), 999 (m), 983 (m), 952 (s), 886 (s), 873 (s), 713 (m)

15 Moisture Balance

Moisture sorption/desorption data was collected on a VTI SGA-100 moisture balance system. For sorption isotherms, a sorption range of 5 to 95% relative humidity (RH) and a desorption range of 95 to 5% RH in 10% RH increments was used for analysis. The sample was not dried prior to analysis. Equilibrium criteria used for analysis were less than 0.0100 weight % change in 5 minutes with a maximum equilibration time of 3 hours if the weight criterion was not met. Data were not corrected for the initial moisture content of the samples.

25 As seen in Figure 3, the E type polymorph form of MCC-555 indicated a 0.6% uptake at 95% relative humidity (RH).

EXAMPLE 3

Generation and Evaluation of an amorphous form of MCC-555

5 Solid MCC-555 was heated until it was visually melted and quickly cooled to produce samples of an amorphous form of MCC-555. MCC-555 was pulverized and the powder was placed on a microscope slide. Then the slide was placed on a hot bench and heated until the powder was melted by visual observation. The slide was removed and quenched on the laboratory bench, thus quickly cooling the
10 molten material to room temperature.

X-ray powder diffraction was conducted on the material using methods as described in Example 2. As shown in Figure 4, the amorphous form is characterized by the absence of distinct 2θ peaks. Similar results were observed
15 with multiple samples of the amorphous material, generated at separate times.

The DSC and TG curves of the amorphous material are shown in Figure 5. Minimal weight loss was observed in the TG curve, as seen at the top of the figure. In the DSC curve, a minor transition was observed around 40 °C, but this
20 represents the glass transition temperature. An exothermic transition observed at approximately 85°C was attributed to recrystallization, discussed below. Minor transitions observed in the DSC curve at approximately 131 and 139 °C were not further characterized. The major endotherm observed at 151.1 °C is similar to the melting point observed for E form.

25 A sample of amorphous material was heated to approximately 100 °C on the hot bench to confirm the recrystallization observed during the DSC evaluation. The material was heated to approximately 100°C and then cooled to ambient temperature. Then the sample was analyzed by XRPD, using methods described
30 in Example 2. The pattern is shown in Figure 6 and is most similar to form E with

an extra peak observed around $17.8^\circ 2\theta$.