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ARTICLE *in* CRYSTAL GROWTH & DESIGN · APRIL 2011

Impact Factor: 4.89 · DOI: 10.1021/cg101377u

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Characterization of Carbamazepine-Nicatinamide Cocrystal Polymorphs with Rapid Heating DSC and XRPD

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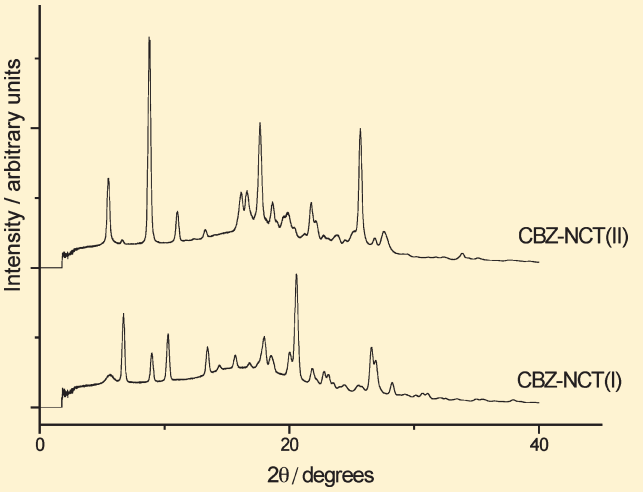
ABSTRACT: Rapid-heating differential scanning calorimetry (RHDSC) was used to isolate and characterize the metastable carbamazepine-nicatinamide cocrystal polymorph, CBZ-NCT-(II). The metastable form was prepared in situ in RHDSC by isothermal crystallization from the glass. The glass was prepared by quench-cooling the stable CBZ-NCT(I) form. At heating rates up to 400 °C min^{-1} the RHDSC traces showed an endotherm-exotherm-endotherm triplet of peaks, characteristic of the melt of CBZ-NCT(II), crystallization to CBZ-NCT(I) and subsequent melt of the stable form. At a heating rate of 500 °C min^{-1}, only the first endotherm, corresponding to the melt of CBZ-NCT(II) was seen, indicating that crystallization to the stable form had been inhibited. It is reported that CBZ-NCT(II) has an onset temperature of melting of 131.8 ± 0.3 °C and $\Delta_f H$ = 125.1 ± 2.4 J g^{1-}. CBZ-NCT(I) has an onset temperature of melting of 157.2 ± 0.3 °C, $\Delta_f H$ = 157.6 ± 4.5 J g^{1-}. Accordingly, the system is monotropic, by Burger-Ramberger's heat of fusion rule, as the higher melting polymorph has the higher heat of fusion.



INTRODUCTION

The increasing prevalence of Biopharmaceutical Classification System (BCS)[1] class II drugs means that overcoming poor aqueous solubility is becoming a major focus of drug formulation strategy. Central to this paradigm is selection of physical form. Drug candidates, especially small molecular weight organic molecules, may often exhibit polymorphic or pseudopolymorphic forms. Usually, the less thermodynamically stable the form, the faster its dissolution rate (leading, as a consequence, to higher nonequilibrium solubility and better bioavailability) so there is often a compromise to be made between stability and bioavailability.

Recently, the concept of pharmaceutical cocrystals has been introduced, defined as unit cells comprising at least two compounds, both of which interact by hydrogen bonding and/or any other noncovalent bonds and which are solids at room temperature and pressure.[2] This distinguishes them from solvates and hydrates. Co-crystals open the intriguing formulation strategy of combining two active compounds in one crystal structure, the physicochemical properties of which are more advantageous than those of either of the actives in their pure form. Typically an improvement in solubility is seen, for example, in cocrystals of indomethacin-saccharin,[3] norfloxacin-isonicotinamide cocrystals,[4] or carbamazepine with various compounds,[5−8] although improvements in hygroscopic properties, for instance, in piracetam-L-tartaric acid cocrystals, has been reported.[9]

In addition, it has been suggested that formulation as a co-crystal would reduce the impact of polymorphism for highly polymorphic compounds,[10] although this presupposes that fewer polymorphic arrangements are available when two compounds are present in the unit cell. Several studies have reported polymorphism in pharmaceutical cocrystals (for instance, carbamazepine-saccharin (CBZ-SAC),[8] carbamazepine-isonicotinamide,[11] and carbamazepine-nicotinamide (CBZ-NCT)[8,12]). Because these studies imply that pharmaceutical cocrystals may be polymorphic, it is important to develop analytical methods that allow both formation and characterization of the various forms.

Differential scanning calorimetry (DSC) is particularly useful for polymorph characterization because distinct polymorphs will have different melting temperatures. In addition, metastable polymorphs can be formed in the instrument, by quench-cooling the molten sample to form a glass and then allowing the glass to crystallize by holding it isothermally at a temperature above its glass transition. The glass should crystallize via progression through any available polymorphic forms, starting with the least stable; see Ostwald's rule of stages.[13] Such an approach was the basis of a study of CBZ-NCT forms I and II by Seefeldt et al.[12]

One drawback of DSC is that melting of a metastable form will usually be followed by crystallization to a more stable form. If the heating rate of the experiment is not sufficiently high these events will overlap in the DSC thermogram, meaning that while polymorphic forms can be identified their heats of fusion cannot

Received: October 15, 2010
Revised: January 14, 2011
Published: February 18, 2011

dx.doi.org/10.1021/cg101377u | *Cryst. Growth Des.* 2011, 11, 1177–1181

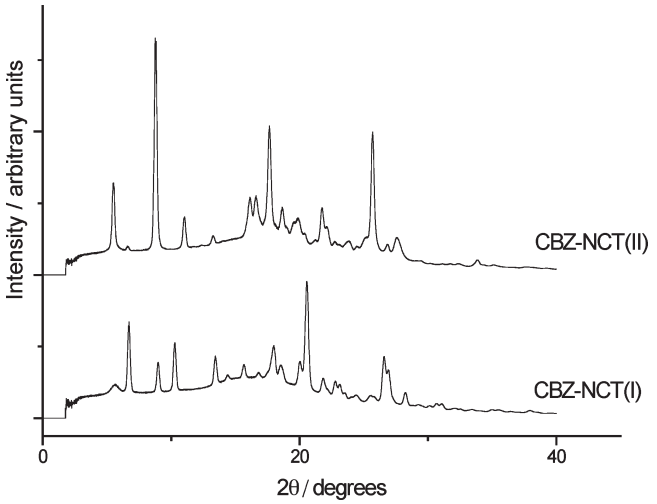


Figure 1. XRPD spectra of CBZ-NCT(I) and CBZ-NCT(II).

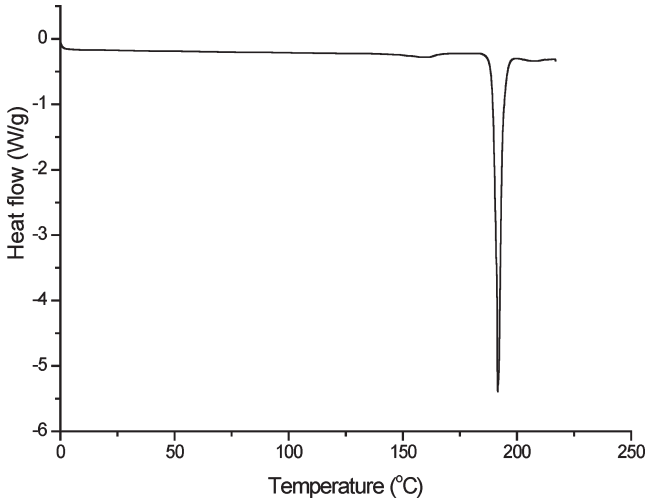


Figure 2. DSC trace of CBZ-NCT (I) (heating rate 10 °C min^{-1}).

be measured. The temperatures at which thermodynamic transitions (such as melts) are seen can be considered independent of heating rate (at least for small molecular weight organic molecules) while those at which predominantly kinetic transitions (such as crystallizations) are seen are dependent upon heating rate (appearing to increase in temperature with increasing heating rate). Thus fast (on the order of hundreds of degrees per minute) heating rates can be used to separate melting and crystallization events, allowing full characterization of metastable polymorphs.[14] The specific aim of this work therefore was to employ rapid-heating DSC (RHDSC) to identify, isolate, and characterize CBZ-NCT forms I and II.

MATERIALS AND METHODS

Carbamazepine (CBZ) (T_m = 191−192 °C) and nicatinamide (NCT) (T_m = 128−131 °C) were purchased from Sigma-Aldrich (Dorset, UK). Ethyl acetate (HPLC grade) was purchased from Fisher Scientific (Leicestershire, UK). All materials were used as received.

Preparation of CBZ-NCT Form I. Form I CBZ-NCT (CBZ-NCT(I)) cocrystals were prepared by the solvothermal (i.e., controlling solvent choice and temperature) methods described by Nehm et al.;[6] a hot solution of NCT (350 mg) and CBZ (670 mg) in ethyl acetate (50 g) was cooled with agitation to room temperature to create a supersaturated solution. The cocrystals formed (1:1 molar ratio) were filtered under reduced pressure using a Whatman number 50 filter paper for 30 min to remove any remaining solvent and then stored over silica gel in a desiccator at 5 °C until use.

X-ray Powder Diffraction. X-ray powder diffraction experiments (XRPD) were all performed on an Oxford Diffraction Xcalibur microfocus NovaT, X-ray diffractometer, using Cu K_α (1.54178 Å, 50 kV 98 mA) radiation. The powdered samples were mounted and sealed in 0.5 mm capillary tubes and using transmission geometry rotated at a constant speed (0.75° s^{-1}) about the phi axis (φ) over 360°. CCD image data were collected at room temperature (18 °C) at 0° 2θ, 95 mm (sample to detector distance) and processed by $CrysAlis^{Pro}$ (Oxford Diffraction, 2009) software, generating X-ray powder scattering data (intensity vs scattering angle). The results of the data collections are shown in Figure 1.

FTIR. Fourier-transform infrared (FTIR) spectra were collected with a PerkinElmer Spectrum 100 FTIR spectrometer in the range of 4000 to 650 cm^{-1} with a resolution of 4 cm^{-1} at ambient conditions. Spectra were analyzed with Spectrum Express software (application version: 1.02.00.0014, 2008).

Differential Scanning Calorimetry. Measurements were performed with Q2000 and RHDSC instruments (TA Instruments, LLC, USA). The instruments operate on similar principles, being heat-flux designs, but RHC has a very small furnace (<1 cm diameter) and an array of infrared lights is used to raise temperature. The result of this is that the instruments have different heating rate capabilities (Q2000 up to 200 °C min^{-1}; RHDSC up to 2000 °C min^{-1}) and sample sizes (Q2000 ca. 5 mg; RCDSC ca. 0.1 mg). Both instruments use aluminum pans and lids, but those of RHC are ca. 1.5 mm in diameter whereas those of Q2000 are ca. 10 mm in diameter. Further details of the design and construction of RHDSC are available in the literature.[14,15] Experiments were conducted in triplicate. The cell constant and enthalpy calibrations were performed with indium (Certified Reference Material LGC2601, Batch E1, LGC, London, T_m = 156.61 °C, $\Delta_f H$ = 28.70 J/g) in accordance with the manufacturer's instructions. Calibrations were performed at each heating rate. The measured values were always in excellent agreement with those of the reference material ($T_m \pm 0.03$ °C, $\Delta_f H \pm 0.1$ J/g). Nitrogen (50 mL min^{-1}) was used as a purge gas.

Data were analyzed with Universal Analysis 2000 (TA Instruments LLC) and all melting, crystallization and glass transition temperatures are calculated as extrapolated onsets. Peak areas were calculated using an extrapolated linear baseline.

In situ preparation of the metastable CBZ-NCT form II (CBZ-NCT(II)) was achieved by heating CBZ-NCT(I) to 170 °C (Form I melting point; 158 °C),[11] cooling to -30 °C to form a glass, heating at 100 °C min^{-1} to 100 °C, holding isothermally for 5 min and cooling to −30 °C. Scanning at heating rates of 100 to 500 °C min^{-1} was performed to study the metastable form II. To prepare CBZ-NCT(II) for XRPD and FTIR analysis the DSC pan (Q2000) was lined with greaseproof paper (Tesco own brand, UK, formed to the shape of the pan with the press used for sealing the lid) prior to quench-cooling and crystallization—thus the metastable form could be removed without the need for application of any mechanical stress with, for instance, a spatula, that might have precipitated a change in form to the stable form I polymorph.

RESULTS AND DISCUSSION

XRPD data (Figure 1), DSC data (T_m =159.1 ± 0.2 at 10 °C min^{-1}) (Figure 2) and FTIR data (Figure 3) of CBZ-NCT(I) were in accordance with those reported in the literature (significant spectral peaks are tabulated in Tables 1 and 2 along with reference literature data[8]), thus confirming successful preparation of the stable cocrystal.

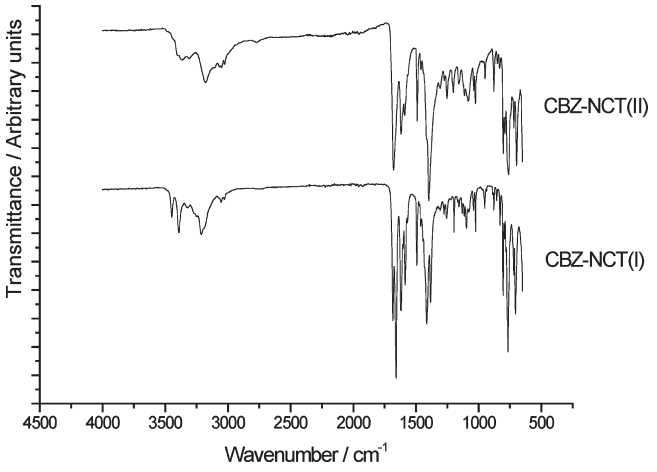


Figure 3. FTIR spectra of CBZ-NCT(I) and CBZ-NCT(II).

Table 1. XRPD Peaks for CBZ-NCT(I) and CBZ-NCT(II) Recorded in This Work and Compared with Literature Values

CBZ-NCT(I)		CBZ-NCT(II)	
this work	literature[8]	this work	literature[8,a]
6.7	6.6	6.6	5.1
9.0	8.9	8.8	8.9
10.3	10.1	11.0	10.4
13.4	13.3	13.3	15.7
14.4	14.2	16.1	17.1
15.7	15.5	16.6	17.6
16.8	16.6	17.7	18.0
18.0	17.8	18.7	18.8
18.6	18.5	19.6	19.8
20.6	20.4	19.9	21.0
21.9	21.7	21.8	21.8
22.8	22.7	22.1	22.5
23.2	23.0	23.8	23.4
26.6	26.5	25.7	24.6
28.3	28.1	26.8	26.0
30.7	30.5	27.7	26.5
31.1	30.9		27.5

[a] For polymer-nucleated form.

The underlying experimental principle for formation of metastable CBZ-NCT(II) is based on Ostwald's rule of isolation in stages.[13] Briefly, this posits that when a material crystallizes from a nonequilibrium, high-energy state (such as a glass) it will do so via progression through any available lower energy states; the physical manifestation of this is that the sample will crystallize in a sequence, progressing through any available metastable polymorphs to the stable crystalline form.

Melting CBZ-NCT(I) in the DSC and subsequent quench-cooling in situ resulted in formation of a glass (data not shown). To prepare CBZ-NCT(II) the glass was heated to 100 °C and held isothermally for 5 min. When performed with RHDSC crystallization to CBZ-NCT(II) was observed during the isothermal period (Figure 4) while when performed with Q2000 crystallization was observed during heating to 100 °C (data not shown). The latter behavior is consistent with the observation of

Table 2. FTIR Absorbance Bands for CBZ-NCT(I) and CBZ-NCT(II) Recorded in This Work and Compared with Literature Values

CBZ-NCT(I)		CBZ-NCT(II)	
this work	literature[8]	this work	literature[8,a]
3448	3446	3365	3347
3392	3387	3305	3302
3322	3327	3178	3186
3210	3209	3067	3066
3053	3051	3060	3048
3026	3027	3026	3026
1683	1683	2769	2764
1657	1656	1679	1670
1618	1618	1617	1615
1601	1601	1606	1602
1584	1585	1590	1586
1567	1568	1489	1490
1492	1491	1459	1459
1413	1413	1439	1439
1382	1383	1397	1400

[a] For polymer-nucleated form.

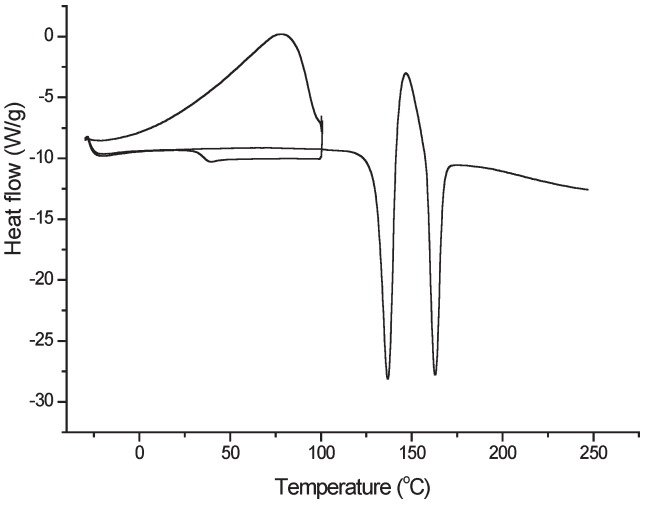


Figure 4. DSC trace for the heat−cool−heat cycle for CBZ-NCT(II), showing a glass transition upon initial heating and the melt of form II, crystallization to form I, and melt of form I on the second heat.

Seefeldt et al.,[12] but the delayed crystallization observed with RHDSC was surprising. Since the aluminum pan used in RHDSC is so small (ca. 1 mm internal diameter) one possibility is that surface tension effects exerted when the sample is molten become important, potentially affecting the degree of short-range order in the glassy phase and hence the crystallization kinetics. In any event, the subsequent thermal behavior of CBZ-NCT(II) was consistent whether formed in RHDSC or Q2000. When the CBZ-NCT glass was heated at rates of 100 °C min^{-1} and higher, only a glass transition (T_g= 32.4 ± 0.28 at 100 °C min^{-1}) was seen, implying that all crystallization events were inhibited (Figure 5).

Post-crystallization, CBZ-NCT(II) was removed from the DSC and characterized with FTIR and XRPD. XRPD CBZ-NCT(II)

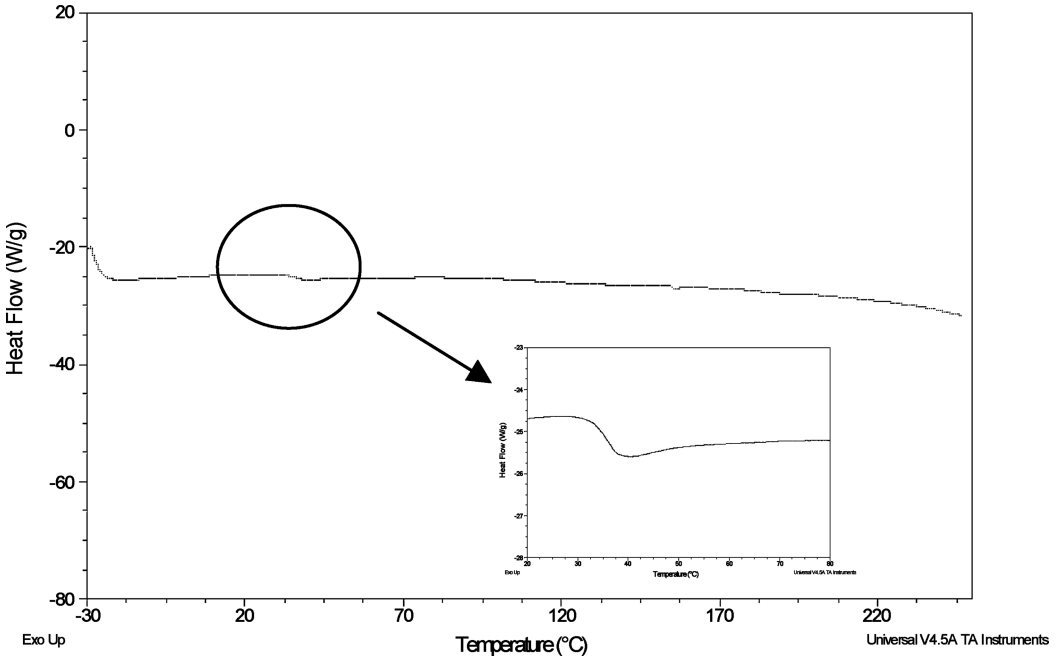


Figure 5. DSC trace of CBZ-NCT glass heated at 100 °C min^{-1}.

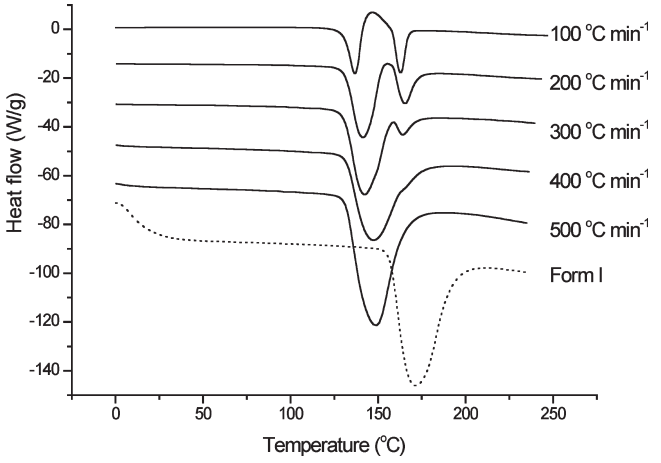


Figure 6. DSC traces for CBZ-NCT(II) at heating rates from 100 to 500 °C min^{-1} (solid lines). Also shown is the DSC trace for CBZ-NCT(I) for reference (dashed line).

data are given in Figure 1 (top) and show a clear difference from CBZ-NCT(I), Figure 1 (bottom). The work of Seefeldt et al[12] uses Raman analysis to differentiate forms and hence direct comparison with their data is not possible but the work of Porter et al[8] reports an XRPD spectrum for a form related to CBZ-NCT(II) (termed PN-CBZ-NCT(II), because it used polymer nucleation as a preparation method). PN-CBZ-NCT(II) is said to be structurally similar to CBZ-NCT(II) differing only in respect of some crystal lattice defects.[8] Significant XRPD peaks reported for PN-CBZ-NCT(II) and CBZ-NCT(II) are given in Table 1; clear differences are apparent, which suggests that PN-CBZ-NCT(II) may be more structurally distinct from CBZ-NCT(II) than previously assumed. However, the data do confirm that CBZ-NCT(II) is structurally distinct from CBZ-NCT-(I). The FTIR spectrum of CBZ-NCT(II) (Figure 3, top) also differs considerably from that CBZ-NCT(I) (Figure 3, bottom). Significant absorbance bands and literature reference data are given in Table 2. Again, good correlation with literature values for CBZ-NCT(I) is seen, while some differences compared with PN-CBZ-NCT(II) are observed.

Because CBZ-NCT(II) is metastable, it will crystallize to CBZ-NCT(I) upon heating. This is shown in Figure 4, where the (endothermic) melt of CBZ-NCT(II) is seen at ca. 130 °C, followed immediately by (exothermic) crystallization to CBZ-NCT(I). Form I then melts (endothermic) at ca. 157 °C. Using temperature-scanning Raman spectroscopy Porter et al.[7] observed the PN-CBZ-NCT(II) to CBZ-NCT(I) transition at 124−128 °C, whereas Seefeldt et al.[12] saw melt and subsequent crystallization at 125−128 °C with DSC (at 10 °C min^{-1}); both observations are thus in excellent agreement with this work. Rapid crystallization postmelting of a metastable polymorph is very common, and prevents determination of the enthalpy of fusion, $\Delta_f H$, because the area of the melting endotherm cannot be determined.

Crystallization, requiring movement of molecules to occur, is predominantly a kinetic event while melting, requiring the sample only to have a certain minimum amount of energy, is termed a thermodynamic event. This is fortuitous, because increasing the heating rate at which a DSC experiment is performed will cause the temperature at which kinetic events are seen to rise while the positions of thermodynamic events are unaffected.[14] If the heating rate is fast enough, such that the temperature at which crystallization occurs becomes higher than the melting temperature of the next available polymorphic form, crystallization will effectively be 'inhibited'. Thus, application of fast heating rates to CBZ-NCT(II) should enable isolation of its melt. DSC data for heating rates up to 500 °C min^{-1} are shown in Figure 6.

At heating rates up to 400 °C min^{-1}, the melt of CBZ-NCT(II) at 130 °C is always observed. Because the sample should consist entirely of the metastable form, if the heating rate used is sufficiently fast to inhibit crystallization, no melt for the

stable CBZ-NCT(I) should be seen (it is difficult to use the exothermic crystallization peak as an indicator of crystallization because the extent of crystallization will fall with increasing heating rates and thus while it is still present it becomes masked by the melting endotherms). At a heating rate of 500 °C min^{-1}; however, no CBZ-NCT(I) melt was detectable, implying that this is the minimum heating rate required to inhibit conversion between polymorphs. This is consistent with two earlier studies of metastable polymorphs,[16,17] where heating rates of 400−500 °C min^{-1} were required to prevent conversion between forms. The single endotherm observed at a heating rate of 500 °C min^{-1} for CBZ-NCT(II) occurred with an onset temperature of 131.8 ± 0.3 °C and $\Delta_f H$ = 125.1 ± 2.4 J g^{-1}. Also shown in Figure 6 is the melting endotherm for CBZ-NCT(I) at a heating rate of 500 °C min^{-1} (onset temperature 157.2 ± 0.3 °C, $\Delta_f H$ = 157.6 ± 4.5 J g^{-1}). According to Burger-Ramberger's heat of fusion rule,[18] the system is monotropic as the higher melting polymorph has the higher heat of fusion.

CONCLUSION

A metastable polymorphic form of CBZ-NCT has been reported previously but its heat of fusion has not been determined because the melting endotherm could not be separated from the subsequent crystallization to stable form I. Here, CBZ-NCT(II) was prepared from the glass in situ with RHDSC. XRPD and FTIR confirmed successful formation of the metastable form. Heating at a rate of 500 °C min^{-1} was sufficient to inhibit conversion to CBZ-NCT(I) allowing a heat of fusion of 125.1 ± 2.4 J $g^{-1}$to be determined. Comparison with the heat of fusion of CBZ-NCT(I) of 157.6 ± 4.5 J g^{-1} confirms the system exhibits monotropic polymorphism.

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ACKNOWLEDGMENT

The authors thank TA Instruments LLC for the loan of RHDSC and Steve Aubuchon and Peter Caulfield for their valuable technical input.

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