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The use of high-speed differential scanning calorimetry (Hyper-DSC™) to study the thermal properties of carbamazepine polymorphs

Caroline McGregor [a], Mark H. Saunders [b], Graham Buckton [c,*], Robert D. Saklatvala [a]

[a] *Merck Sharp and Dohme, Hertford Road, Hoddesdon, Hertfordshire EN11 9BU, UK*
[b] *PharMaterials Ltd., 29-39 Brunswick Square, London WC1N 1AX, UK*
[c] *The London School of Pharmacy, 29-39 Brunswick Square, London WC1N 1AX, UK*

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Abstract

The thermal properties of two polymorphs of the drug carbamazepine, Forms I and III, were studied using high-speed differential scanning calorimetry (DSC). Previously, accurate determination of the heat enthalpy of fusion of Form III has not been possible using DSC at typical heating rates, due to concurrent exothermic recrystallisation to the higher-melting Form I. Here, it is demonstrated that heating rates of 250° C/min altered the kinetics of the melting transition of Form III such that this concurrent exothermic recrystallisation was inhibited. This allowed direct measurement of the enthalpy of the melting endotherm for Form III from a single transition. The enthalpy of this transition was found to be 109.5 J/g. Further investigations were then performed to test the utility of this technique in quantifying relative amounts of Forms I and III in mixtures of the two polymorphs. It was demonstrated that a limit of detection of 1% (w/w) was possible in this system. However, accurate quantification was not possible due to seeding effects initiating recrystallisation to Form I in these mixtures, even at these elevated heating rates. The utility of this novel technique as a fast analytical tool for studying the polymorphic behaviour of metastable polymorphs has been successfully demonstrated.

Keywords: High-speed DSC; Carbamazepine; Polymorphism

1. Introduction

The ability of an organic molecule to exist in more than one distinct crystal form is known as polymorphism. Different polymorphic forms of a compound may differ greatly in terms of their physicochemical and mechanical properties. Within the pharmaceutical industry, it is extremely important that the polymorphic behaviour of potential drug candidates is fully characterised early in development, as changes in the crystal form can have an effect on the stability and bioavailability of the active pharmaceutical ingredient in solid dosage forms [1]. Different polymorphs of a drug may also influence important pharmaceutical processes, such as tableting characteristics [2] and dissolution rates [3], in addition to the effect on both the physical and chemical stability of the bulk drug.

Many techniques are available with which to study the polymorphic characteristics of drug substances, for example, infrared spectroscopy (IR) [4], solid state nuclear magnetic resonance spectroscopy (SSNMR) [5,6], near infrared spectroscopy (NIR) [7], Raman spectroscopy [8], X-ray powder diffraction (XRPD) [9] and thermal analysis techniques [10]. Differential scanning calorimetry (DSC) is widely used for drug polymorphism studies, mainly as a qualitative tool. DSC can also provide information on events that result in a change in the specific heat capacity of a material—a common example being the study of glass transitions [11,12].

The advantages of using conventional DSC for testing pharmaceutical compounds are the ease of sample preparation, relatively fast analysis time and the wide temperature range that can be studied. There are, however, some limits to the usefulness of DSC when studying the polymorphic behaviour of some compounds. The thermal characterisation of the lower melting polymorphs of a compound is a common problem. On heating at standard heating rates such species may exhibit multiple thermal events due to concurrent

* Corresponding author. Tel.: +44-207-753-5858.
E-mail address: graham.buckton@ulsop.ac.uk (G. Buckton).

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recrystallisation to an alternative crystal form and subsequent melting of this new form [12]. Hence, the determination of the polymorphic purity of such species by DSC can be problematic. Further, for a polymorph that undergoes concurrent recrystallisation during melting, it is not possible to accurately determine from a single transition, the thermodynamic parameters, such as the enthalpy of fusion, associated with this event. One method for overcoming such issues is the use of accelerated heating rates, which can lead to the inhibition of recrystallisation of the lower melting polymorph. At higher heating rates, the kinetics of the melting transition are changed such that there is not sufficient time for recrystallisation of the higher melting form from the melt. As a result, only a single melting endotherm associated with the lower melting polymorph is observed.

This paper focuses on the use of high-speed differential scanning calorimetry (Hyper-DSC^{TM}) in the study of carbamazepine. Carbamazepine is a well established drug used in the treatment of epilepsy. There are at least four anhydrous polymorphs of this molecule and a dihydrate [13,14]. Forms I and III of the drug constitute an enantiotropic pair, whose relative thermodynamic stability changes at 70 °C. Below this temperature Form III is the more stable form, while above this temperature Form I is more stable [15]. This polymorphic system was chosen as an ideal model for the evaluation of high-speed DSC in the investigation of the thermodynamic properties of metastable polymorphs, as described below.

2. Experimental

2.1. Materials

Carbamazepine Form III was obtained from Aldrich Chemical Company (Dorset, UK). Form I was prepared by heating Form III at 165 °C for 2 h. The transformation of Form III to Form I was verified by XRPD and DSC. A series of mixtures containing known ratios of carbamazepine Forms I and III in the range 0–100% (w/w) was prepared by weighing the appropriate amount of the pure polymorphs and mixing on a vortex mixer.

2.2. Methods

2.2.1. X-ray powder diffraction (XRPD)

XRPD patterns were obtained using a Bruker D8 Advance X-ray Powder Diffractometer using copper radiation Kα1 and Kα2, with tube power of 40 kV and 40 mA and a PSD detector. The samples were prepared and analysed using sample holders containing silicon plates cut in the (5 1 0) plane in order to minimise background radiation.

2.2.2. Differential scanning calorimetry (DSC)

All thermal analysis measurements were performed on a Pyris1 DSC fitted with an Intracooler 2P-cooling unit (Perkin-Elmer). All measurements were performed under a nitrogen gas purge at a flow rate of 20 ml/min. A range of heating rates was studied and these are described below. The instrument was calibrated for temperature and heat flow using indium and zinc as standards. Calibration was performed for each heating rate prior to analysis to account for any changes in the thermal profile and the increase in thermal lag resulting from the increased heating rates.

Samples were encapsulated into closed aluminium pans (Perkin-Elmer) and subsequently crimped to ensure a tight seal. Data acquisition and analysis were performed using the Pyris1 software.

3. Results and discussion

3.1. Analysis of carbamazepine Forms I and III and mixtures of both Forms by X-ray powder diffraction (XRPD)

The XRPD patterns for carbamazepine Forms I and III were consistent with those previously reported by Rustichelli et al. [13]. The mixtures of the two crystal forms were also analysed by XRPD. Comparisons of the diffraction patterns for each of the mixtures and the individual polymorphs are shown in Figs. 1 and 2.

It can be seen that there are distinct differences between the diffraction patterns of Forms I and III. The diffraction pattern for Form I shows five unique peaks in the range 5–10° 2θ and similarly the diffraction pattern for Form III shows three unique peaks at ca. 15° 2θ.

The areas of the peaks associated with Forms I and III were measured using the Bruker X-ray Diffraction Evaluation software. From these areas, a response constant for Form III relative to Form I was determined. The level of Form III present in each of the physical mixtures was then calculated by applying the following equation:

$$\%\text{Form III} = \frac{\text{Area III}}{\text{Area III} + (K \times \text{Area I})} \times 100$$

where Area III the total area of Form III peaks ca, 15° 2θ; Area I the total area of Form I peaks in the range 5–10° 2θ, and K the response constant for Form III relative to Form I.

The calibration curve of the calculated versus actual amount of Form III in the physical mixtures is shown in Fig. 3. The calibration curve was linear with a near-zero intercept and a gradient of 1 suggesting a good correlation between the calculated and expected values.

3.2. Differential scanning calorimetry (DSC) of carbamazepine Forms I and III at conventional heating rates

The DSC heating profiles for carbamazepine Forms I and III obtained at a heating rate of 10 °C/min are shown in Figs. 4 and 5. For Form I (Fig. 4), it can be seen that at this heating rate a single endothermic transition with an onset of

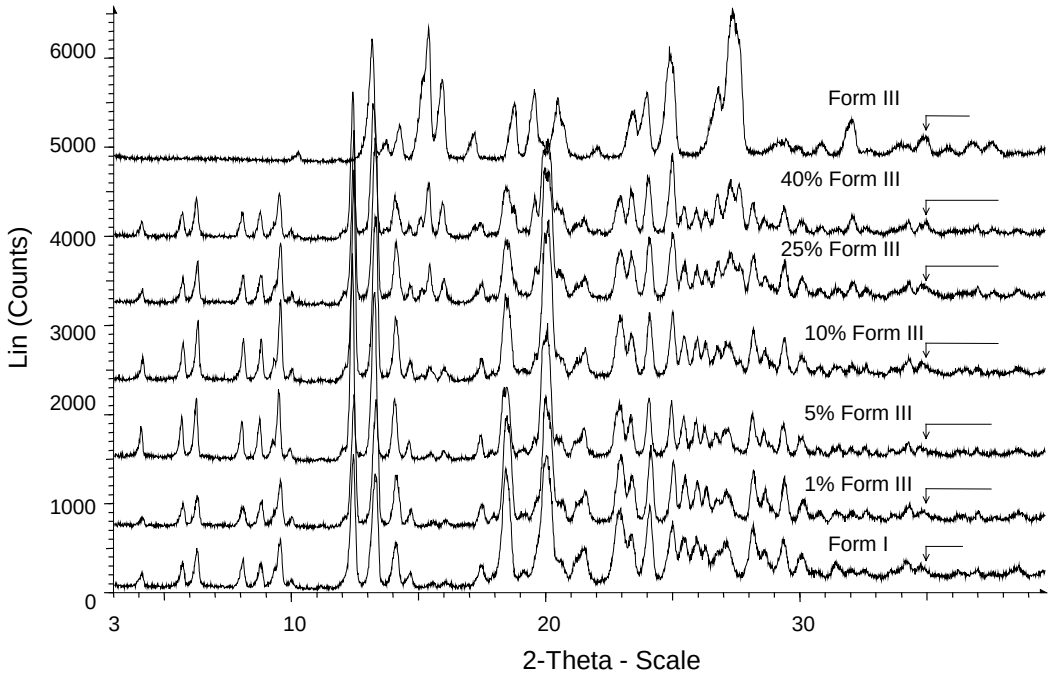

Fig. 1. Comparison plot showing X-ray powder diffractograms of Form I, Form III and physical mixtures containing 1–40% Form III.

191.1 °C and an enthalpy of 108.7 J/g was observed. These values are comparable with those reported previously for this polymorph [15,16]. This single melting peak indicated the presence of only one polymorph suggesting that there were no polymorphic impurities within the sample and no interconversion to other polymorphs. The thermal profile for Form III at the same heating rate was significantly different (Fig. 5). For this polymorph, an endothermic melt with an onset of 174.4 °C was observed, followed immediately by an exothermic transition due to recrystallisation of Form I from the molten Form III. A large endotherm due to melting of Form I was subsequently observed with an onset of 191.3 °C. These findings are consistent with those reported by other authors [13,16].

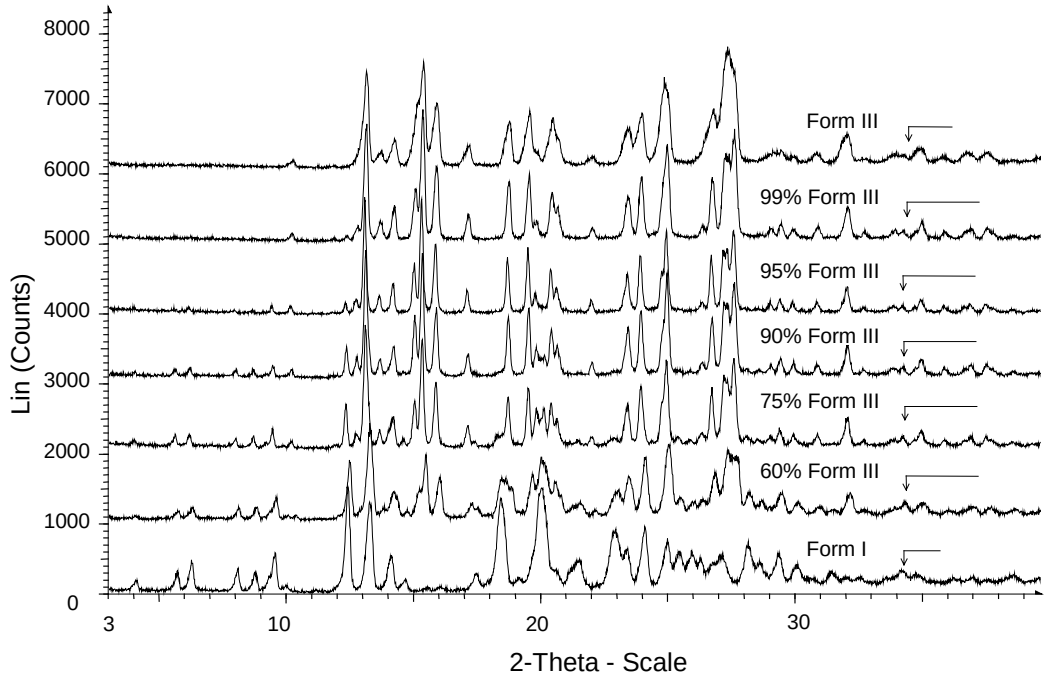

Fig. 2. Comparison plot showing X-ray powder diffractograms of Form I, Form III and physical mixtures containing 60–99% Form III.

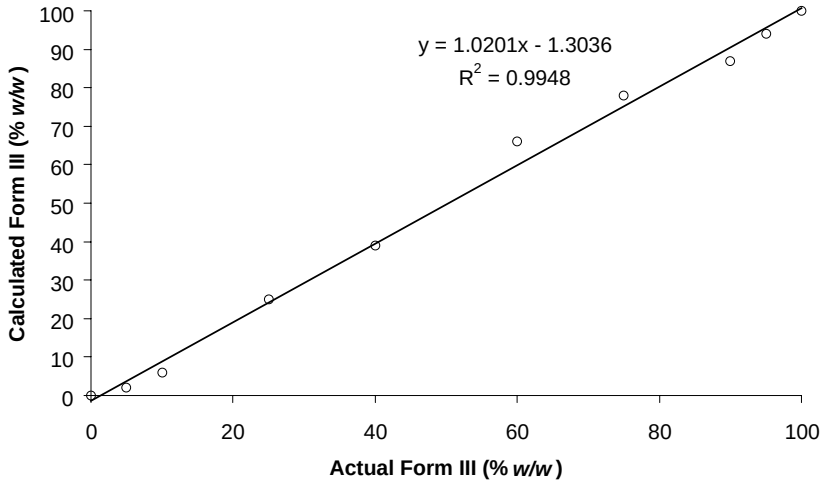

Fig. 3. The relationship between the calculated and actual amounts of Form III of carbamazepine in mixtures of the two crystal forms.

The recrystallisation process prevents direct measurement of the enthalpy of the melting endotherm for the lower melting Form III. Further, the quantification of low levels of either in this form or the higher melting Form I in mixtures of the two crystal forms is not possible. The enthalpy of the melting endotherm for Form III will be reduced due to recrystallisation to Form I. Conversely, the enthalpy of the melting endotherm of Form I would be expected to increase due to an additional contribution from recrystallised Form I originating from the melt.

3.3. Effect of heating rate on the thermal response of form III

The effect of heating rate on the thermal profile of carbamazepine Form III was studied in order to determine whether increasing the rate of temperature change could alter the kinetics of the system such that the recrystallisation of the lower melting polymorph was inhibited. Form III was subjected to heating rates of 50, 100, 150, 200, and 250 °C/min. The resulting thermal profiles are shown in Fig. 6.

Significant differences were observed as the heating rates were increased. Heating rates of 50–200 °C/min resulted in the partial inhibition of recrystallisation of the lower melting polymorph. This was seen as a decrease in the enthalpy of the endothermic transition associated with the recrystallised Form I, and an associated increase in the enthalpy of the melting endotherm for Form III. At heating rates of 250 °C/min, no endothermic transition corresponding to the melting of Form I was detected, indicating that the kinetics of the melting transition for Form III are altered such that there is not sufficient time for the recrystallisation process to occur. The absence of any melting endotherms other than that associated with Form III indicates that the sample

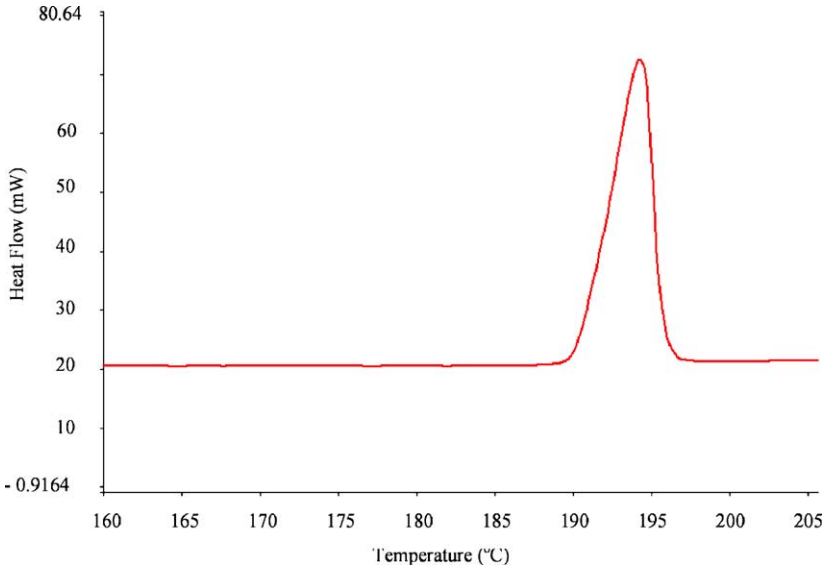

Fig. 4. DSC scan of pure carbamazepine Form I measured at 10 °C/min.

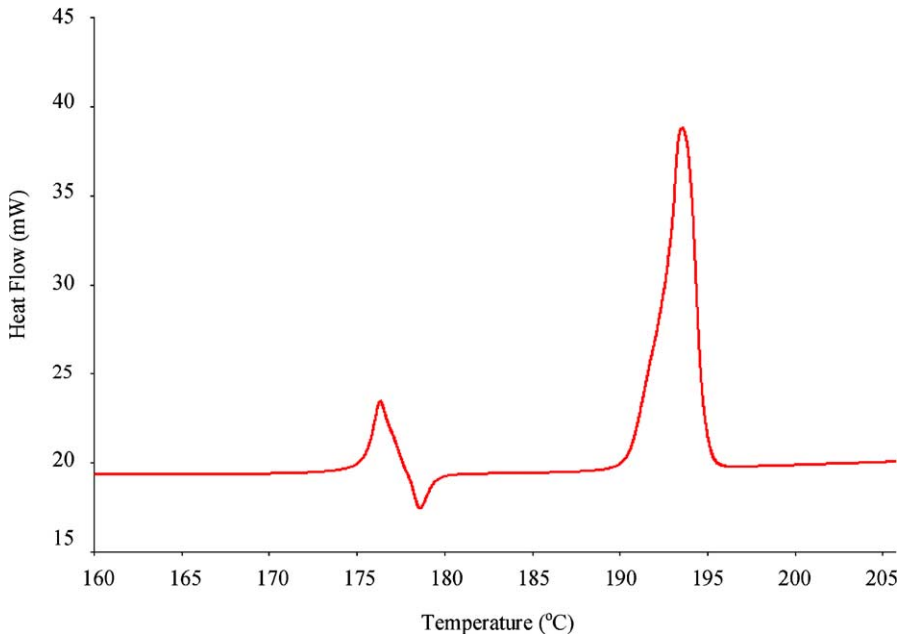

Fig. 5. DSC scan of pure carbamazepine Form III measured at 10 °C/min.

is free from polymorphic impurities. The enthalpy of the melting endotherm for carbamazepine Form III was found to be 109.5 J/g. In previous reports, this enthalpy value has only been estimated, due to the inability to obtain a single melting endotherm for Form III [15].

The ability to inhibit recrystallisation of Form III of carbamazepine was utilised to establish the limit of detection of the DSC apparatus for small quantities of either polymorph in mixtures of Forms I and III. The Pyris1 DSC operates on the principle of power compensation, with separate furnaces for the sample and reference cells. It measures change in heat flow as a function of temperature. As the temperature increases and the sample under investigation experiences a thermal event, that sample will either take energy from (e.g. melting) or release energy to (e.g. recrystallisation) the sample cell. When such an event occurs, energy is either supplied to, or taken from the reference cell in order to maintain a constant temperature difference between the two. The actual energy supplied or removed is calculated by the system and the data interpreted in terms of the type of transition that is taking place, endothermic or exothermic. The data are presented as a function of heat flow (mW), which can also be rewritten as energy per unit time (J/s). As the heating rate is increased, there is a greater input of energy per unit time applied across the sample and reference cells, resulting in an increase in the overall sensitivity of the DSC instrumentation. Therefore, the use of accelerated heating rates with this instrument allows the measurement of transitions that

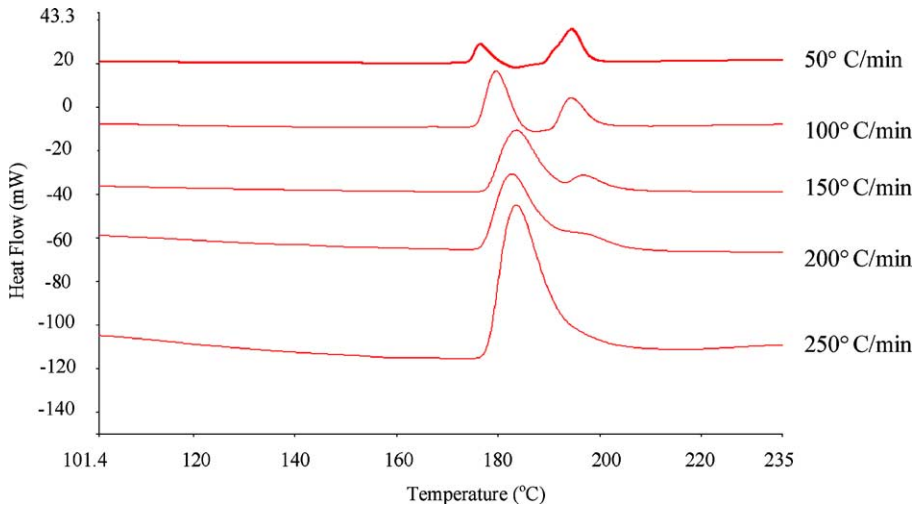

Fig. 6. DSC profiles for carbamazepine Form III at various heating rates.

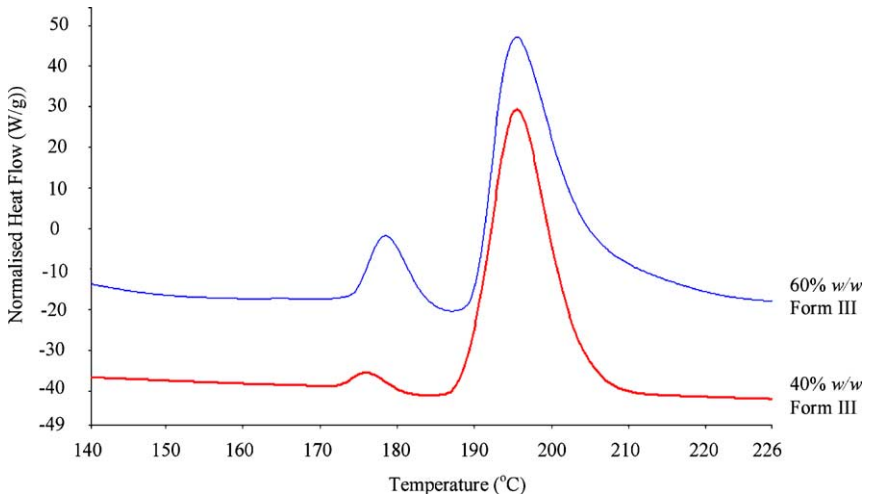

Fig. 7. DSC profiles for mixtures of Forms I and III containing 40 and 60% (w/w) Form III measured at a heating rate of 250 °C/min.

would be below the limit of detection possible at the more typical heating rates employed in conventional DSC.

The mixtures containing known ratios of carbamazepine Forms I and III (0–100%, w/w) were analysed with a heating rate of 250 °C/min and the enthalpy of the melting endotherm was calculated for each mixture. Fig. 7 shows typical thermal profiles for mixtures containing 40% and 60% (w/w) Form III. The endotherms due to melting of both Forms I and III are clearly detected and more importantly complete resolution between the two transitions was achieved. An endotherm due to melting of Form III was detected in mixtures containing as little as 1% (w/w) of this polymorph. When the same sample was analysed at a heating rate of 10 °C/min, this melting endotherm was not detected, indicating the utility of high-speed DSC for detecting low levels of polymorphic impurities, which might otherwise be missed.

A graph of the measured enthalpy of the endothermic transition versus percentage of Form III in the mixture is shown in Fig. 8. A graph of theoretical enthalpy of the endothermic transition versus percentage of Form III is included for comparison. The theoretical enthalpies were calculated from the enthalpy of the endothermic transition for pure Form III and the amount of Form III in the mixture.

The measured enthalpies of the melting endotherm for Form III in mixtures of the two crystal forms were found to be considerably lower than expected from the calculated values across the entire range from 1 to 99% (w/w) for Form III. It has already been shown that at a heating rate of 250 °C/min there is essentially total inhibition of recrystallisation of Form I from the melt of Form III. It was however postulated that the presence of Form I in the mixture prior to analysis resulted in the crystal seeding of Form I and partial recrystallisation of Form III to Form I on melting. The measured enthalpies of the melting endotherm for Form I confirmed this. As shown in Fig. 9, recrystallisation of the lower melting form resulted in an increase in the enthalpy of endothermic transition for Form I relative to the theoretical values. For example, the enthalpy at a level of 99% (w/w) was found to be 162.5 J/g, compared with a calculated value

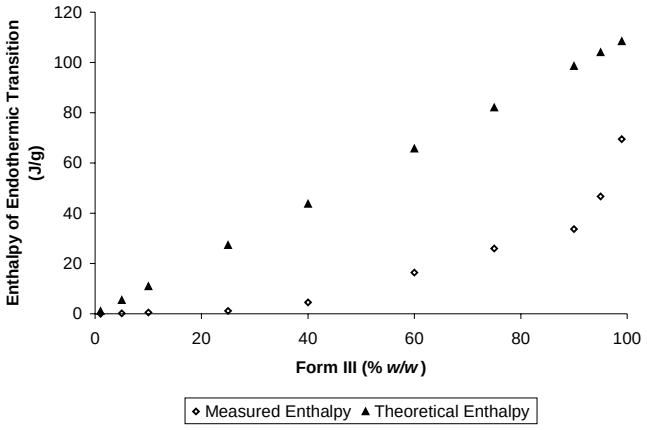

Fig. 8. The effect of mixing Forms I and III of carbamazepine on the measured enthalpy of the melting endotherm for Form III.

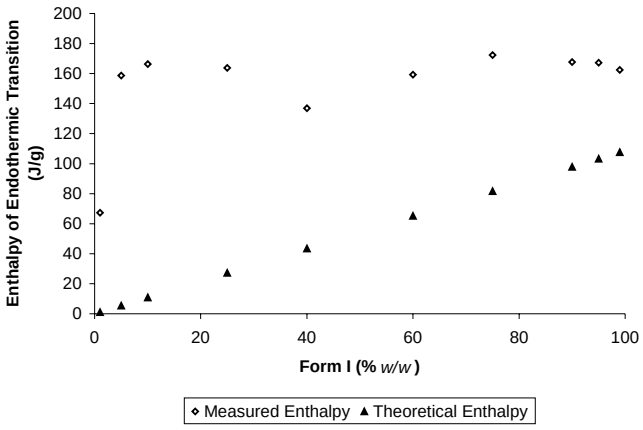

Fig. 9. The effect of mixing Forms I and III of carbamazepine on the measured enthalpy of the melting endotherm for Form I.

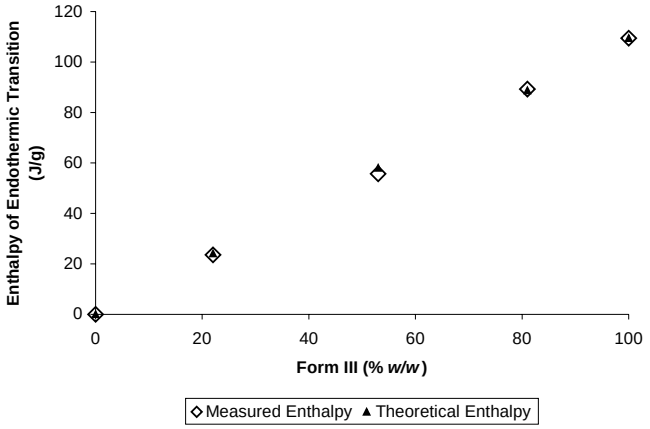

Fig. 10. The effect of separating Forms I and III of carbamazepine in the DSC pan on the measured enthalpy of the melting endotherm for Form III.

of 107.7 J/g. The enthalpy of the endothermic transition for pure Form I measured at a heating rate of 250 °C/min was, as expected, comparable to that measured at 10 °C/min. The theoretical enthalpies were calculated from this value and the amount of Form I in the mixture.

In order to confirm this hypothesis, a series of mixtures of Forms I and III was analysed at the same heating rate but the individual components were separated in the sample pan during analysis to prevent physical mixing of the two polymorphic forms and hence crystal seeding. Fig. 10 shows a graph of the measured enthalpy of the endothermic transition versus percentage Form III. Again the graph of theoretical enthalpy of the endothermic transition versus percentage Form III is included for comparison.

There were no significant differences between the measured enthalpy of the melting endotherms and the calculated values. Separation of the individual polymorphs in the pan successfully prevented mixing. There was no seeding and no partial recrystallisation of Form I in the melt of Form III, as already seen for pure Form III at the same heating rate.

In summary, it has been demonstrated that, utilising DSC with a heating rate of 250 °C/min can inhibit the recrystallisation of Form III of carbamazepine. As a result, a single melting endotherm is observed for this polymorph, thus allowing the determination of thermodynamic parameters such as the enthalpy of the melting endotherm. However, accurate quantification of either Form I or Form III in mixtures of the two crystal forms is not possible. The melting endotherm associated with Form III was detected even at a level of 1% (w/w); however, the presence of Form I in the mixtures resulted in seeding, enabling partial recrystallisation of Form I in the melt of Form III.

If high-speed DSC was to be used for the accurate quantification of small amounts of Forms I or III in mixtures of the two crystal forms then the problem of partial recrystallisation enabled by crystal seeding of Form I would need to be overcome. A potential solution to this problem would be to investigate by increasing the heating rates even further and exploring the use helium as the purge gas in order to improve sensitivity and baseline stability. Further, it could be that seeding occurs as a result of the properties of carbamazepine itself and hence may not be an issue for all compounds.

4. Conclusions

In this paper, the use of high-speed DSC for the characterisation of Forms I and III of the drug carbamazepine was investigated. When Form III is heated at slow heating rates (ca. 10° C/min), the melting endotherm is accompanied by a concurrent exotherm due to recrystallisation of Form I from the melt, behaviour, typical of many drugs. DSC has not previously been used to directly measure the enthalpy of the melting endotherm for species that undergo recrystallisation during heating, since the concurrent endothermic melt and exothermic recrystallisation events cannot be deconvoluted. The use of fast heating rates (in this case 250° C/min) has been shown to successfully inhibit the recrystallisation process, allowing accurate determination of the enthalpy of the melting endotherm for Form III of carbamazepine from a single transition. However, when the technique was applied to potential quantification of relative amounts of the two forms in mixtures, crystal seeding was seen to occur resulting in the partial recrystallisation of Form III to Form I. This suggests that, in this case, the use of fast heating rates may not allow the accurate quantification of small amounts of Forms I or III in mixtures of the two forms. However, a melting endotherm for Form III was successfully detected at a level of 1% (w/w), indicating the utility of the technique as a tool to detect polymorphic impurities that might otherwise have been missed using more typical scanning rates.

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