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The use of high-speed differential scanning calorimetry (Hyper-DSC™) in the study of pharmaceutical polymorphs

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Abstract

The thermal properties of two polymorphs (A and C) of a Merck development compound were studied using high-speed differential scanning calorimetry (Hyper-DSC™). The utility of this novel technique as a fast analytical tool for studying the polymorphic behaviour of metastable polymorphs has previously been demonstrated successfully for Carbamazepine. Accelerated heating rates can alter the kinetics of the melting transition of metastable polymorphs such that concurrent exothermic recrystallisation is inhibited. Here it is demonstrated that at heating rates of 400 °C/min concurrent recrystallisation of Polymorph A of the Merck development compound is inhibited allowing the enthalpy of fusion for the lower melting Polymorph C to be determined. The utility of the technique as a qualitative tool to detect the presence of polymorphic impurities was confirmed for levels much lower than 10% (w/w). However, seeding effects consistent with those reported previously for Carbamazepine were also observed for this structurally distinct molecule limiting the utility of the technique for accurate quantification of low levels of polymorphic impurities.

Keywords: High speed DSC; Hyper-DSC™; Polymorphism

1. Introduction

The ability of an organic molecule to exist as 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 on 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 (Leonidov, 1996). Different polymorphs of a drug may also influence important pharmaceutical processes, such as tableting characteristics (Burger and Lettenbichler, 2000) and dissolution rates (Garcia et al., 1999) in addition to the effect on both the physical and chemical stability of the bulk drug (Walking et al., 1986; Giron, 1988).

Many techniques are available with which to study the polymorphic characteristics of drug substances, for example infrared spectroscopy (IR) (Agatonovic-Kustrin et al., 1999), solid state nuclear magnetic resonance spectroscopy (SSNMR) (Bugay, 1993; Brittain, 1999), near infrared spectroscopy (NIR) (Patel et al., 2000), Raman spectroscopy (Findlay and Bugay, 1998), X-ray powder diffraction (XRPD) (Suryanarayanan and Herman, 1991) and thermal analysis techniques (Giron, 1995).

Differential scanning calorimetry (DSC) is widely used for drug polymorphism studies, mainly as a qualitative tool. 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 recrystallisation to an alternative crystal form and subsequent melting of this new form (Verdonck et al., 1999). Hence 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

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parameters, such as the enthalpy of fusion, associated with this event. One technique for overcoming such issues is high-speed differential scanning calorimetry (Hyper-DSC™), a modified form of conventional DSC using accelerated heating rates. This technique has been shown to inhibit kinetically controlled processes such as recrystallisation without inhibiting the sample from responding to the energy supplied during heating (McGregor et al., 2004; Gramaglia et al., 2005). 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.

Previous studies have focussed on the use of Hyper-DSC™ in the study of Forms I and III of the epilepsy drug Carbamazepine (McGregor et al., 2004). This work demonstrated that heating rates of 250 °C/min altered the kinetics of the melting transition of Form III such that concurrent exothermic recrystallisation to Form I was inhibited. This subsequently allowed direct measurement of the enthalpy of fusion for Form III from a single transition. 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 (LOD) of 1% (w/w) was possible in this system. However, accurate quantification was not possible due to seeding effects. The presence of the higher melting Form I in the mixture prior to analysis resulted in crystal seeding and partial recrystallisation of that form from the melt of Form III.

This problem of partial recrystallisation enabled by crystal seeding of Form I would need to be overcome if Hyper-DSC™ was to be used for the accurate quantification of low levels of polymorphic impurities for this or any other polymorphic system. It was postulated that this could potentially be achieved by increasing the heating rates even further or even exploring the use helium as the purge gas in order to improve sensitivity and baseline stability. Further, it was not known if the seeding occurred as a result of the properties of Carbamazepine itself and hence may not be an issue for all compounds.

This paper investigates the use of Hyper-DSC™ in the study of a Merck development compound. This compound is structurally distinct from Carbamazepine and has been shown to exist as several different polymorphs, hydrates and solvates (Cooper et al., 2003). Polymorph C is anhydrous and on heating undergoes melting and concurrent recrystallisation to anhydrous Polymorph A. This polymorphic system was chosen as an additional model for the further evaluation of Hyper-DSC™ as a tool to determine the thermodynamic properties of metastable polymorphs and to quantify low levels of polymorphic impurities.

2. Material and methods

2.1. Materials

Polymorphs A and C of the Merck development compound were available in-house (Merck, Sharp and Dohme, UK). A series of mixtures containing known ratios of Polymorphs A and C in the range 0–100% (w/w) were prepared by weighing the appropriate amount of the pure polymorphs and mixing on a vortex mixer.

2.2. Methods

2.2.1. Differential scanning calorimetry

All thermal analysis measurements were performed on a Diamond DSC fitted with an Intracooler 2P-cooling unit (Perkin-Elmer). All measurements were performed under a helium gas purge at a flow rate of 20 mL/min. A range of heating rates were studied and these are described below. The instrument was calibrated for temperature and heat flow using indium as a standard. 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. Sample massed of 2–5 mg were used for analyses run under conventional heating rates or for heating rate optimisation. Smaller sample masses of 0.2–0.5 mg were used for analysis of the polymorph mixtures at accelerated heating rates to give improved heat transfer through the sample for sharper melt transitions and optimum resolution. Data acquisition and analysis were performed using the Pyris Manager software.

3. Results and discussion

3.1. Differential scanning calorimetry of Polymorphs A and C at conventional heating rates

The DSC heating profiles for Polymorphs A and C obtained at a heating rate of 10 °C/min are shown in Fig. 1. For Polymorph A, it can be seen that at this heating rate a single endothermic transition with an onset of 183 °C and an enthalpy of 96 ± 1 J/g was observed. 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 Polymorph C at the same heating rate was significantly different. For this polymorph,

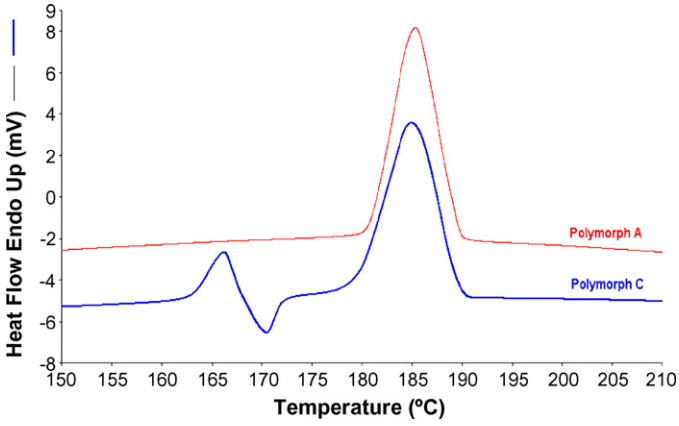

Fig. 1. DSC thermograms of pure Polymorph A and pure Polymorph C measured at 10 °C/min.

an endothermic melt with an onset of 164 °C was observed, followed immediately by an exothermic transition due to recrystallisation of Polymorph A from the molten Polymorph C. A large endotherm due to melting of Polymorph A was subsequently observed with an onset of 181 °C.

Similarly to Carbamazepine, the recrystallisation process prevents direct measurement of the enthalpy of fusion for the lower melting Polymorph C. Further, the confirmation of polymorphic purity and subsequent quantification of low levels of either form in mixtures of the two crystal forms is not possible. The enthalpy of fusion for Polymorph C will be reduced due to recrystallisation to Polymorph A. Conversely, the enthalpy of fusion of Polymorph A would be expected to increase due to an additional contribution from recrystallised Polymorph A originating from the melt.

3.2. Effect of heating rate on the thermal response of Polymorph C

The effect of heating rate on the thermal profile of Polymorph C was studied in order to confirm that increasing the rate of temperature change would alter the kinetics of the system such that the recrystallisation of the lower melting polymorph was inhibited. Polymorph C was subjected to heating rates of 100, 200, 250, 300, 400, and 500 °C/min. The resulting thermal profiles are shown in Fig. 2.

Significant differences were observed as the heating rates were increased. The enthalpy of the endothermic transition associated with the recrystallised Polymorph A was seen to decrease while the enthalpy of fusion for Polymorph C increased. Heating rates of 100–300 °C/min resulted in the partial inhibition of recrystallisation of the lower melting polymorph with the melting endotherm for Polymorph A still clearly visible. At heating rates of 400 °C/min and above, no endothermic transition corresponding to the melting of Polymorph A was detected, indicating complete inhibition of recrystallisation. The kinetics of the melting transition for Polymorph C 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 Polymorph C indicates that this sample is free from polymorphic impurities. It was noted that the heating rate required for complete inhibition of recrystallisation was much higher than that reported previously for Carbamazepine (250 °C/min). The enthalpy of fusion for Polymorph C was found to be 97 ± 6 and 87 ± 7 J/g at heating rates of 400 and 500 °C/min, respectively. The enthalpy values for the different heating rates show reasonable agreement within error. It was however noted that Hyper-DSC™ as a technique does not appear to be as robust as conventional DSC and higher variability in the measured enthalpies can be observed as reflected by the magnitude of the reported errors.

It was noted that the overall size of the melting endotherms increased with increasing heating rate implying increased sensitivity. This is because the DSC output is a function of heat flow (mW) or energy per unit time (J/s). As the heating rate is increased, there is a greater input of energy per unit time and hence the same heat flow occurs over a shorter time frame. This results in an increase in the overall sensitivity of the DSC instrumentation and allows the measurement of transitions that may be below the limit of detection possible by conventional DSC; similar trends have been reported by other authors (Saunders et al., 2004; Gramaglia et al., 2005). The increased sensitivity at accelerated heating rates combined with the ability to inhibit recrystallisation has been shown to be suitable for confirming the presence of low levels of polymorphic impurities but limitations have been identified in the ability to quantify these polymorphic impurities (McGregor et al., 2004). The mixtures containing known ratios of Polymorphs A and C (0–100%, w/w) were used to evaluate this application further.

The mixtures were analysed with a heating rate of 400 °C/min where full inhibition of recrystallisation was achieved and the enthalpy of the melting endotherms was calculated for each mixture. Fig. 3 shows typical thermal profiles for mixtures containing 10, 40, 60 and 90% (w/w) Polymorph C. The endotherms due to melting of both Polymorph A and C are clearly detected with complete resolution achieved between the transitions. An endotherm due to melting of Polymorph C was detected for

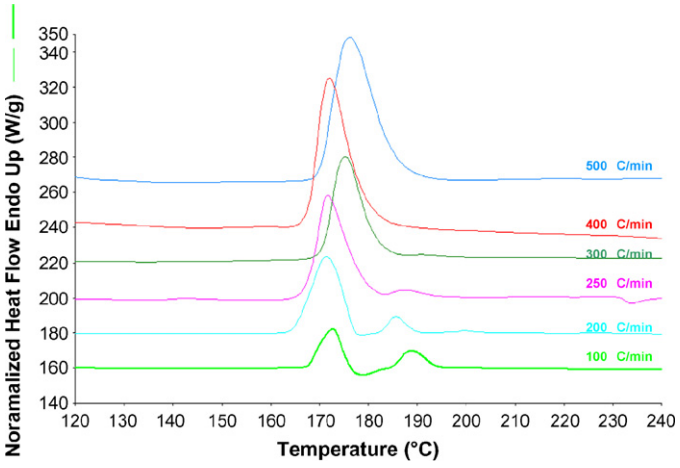

Fig. 2. DSC thermograms for Polymorph C at various heating rates.

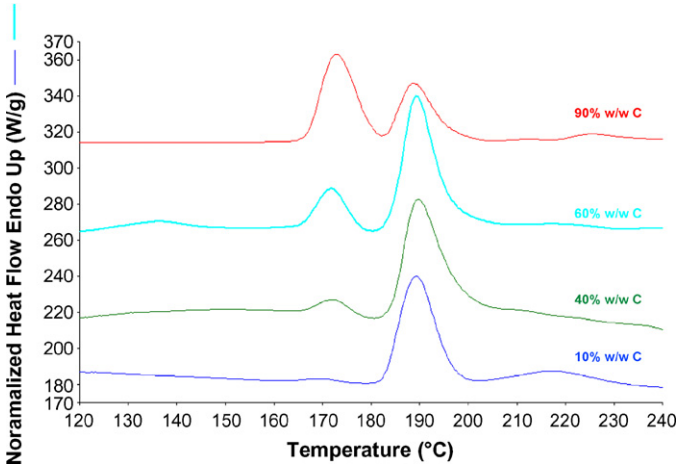

Fig. 3. DSC thermograms for mixtures of Polymorph A and C containing 10, 40, 60 and 90% (w/w) Polymorph C measured at a heating rate of 400 °C/min.

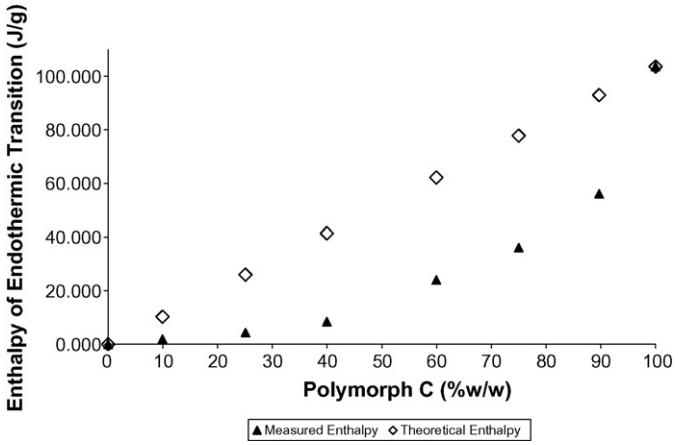

Fig. 4. The effect of mixing Polymorphs A and C on the measured enthalpy of fusion for Polymorph C.

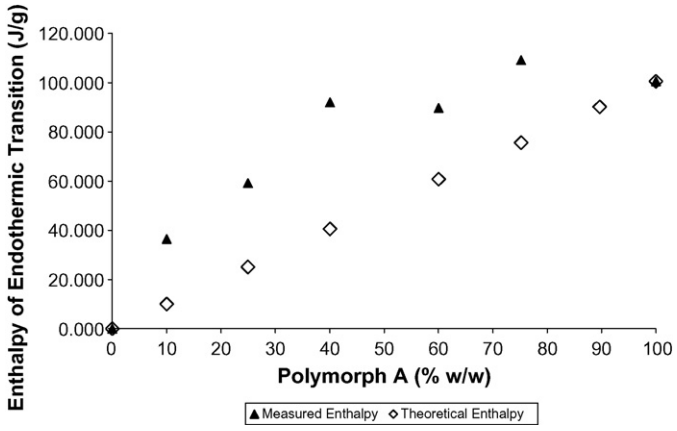

Fig. 5. The effect of mixing Polymorphs A and C on the measured enthalpy of fusion for Polymorph A.

mixtures containing 10% (w/w) of this polymorph. Mixtures containing less than 10% (w/w) were not studied in this case but it was reported previously for Carbamazepine that an endotherm due to melting of the lower melting Form III was detected for mixtures containing as little as 1% (w/w) of this polymorph (McGregor et al., 2004). The magnitude of the transition in the sample containing 10% (w/w) Polymorph A suggests that in mixtures with Polymorph C levels lower than 10% (w/w) could easily be detected.

The measured enthalpy of the endothermic transition was plotted against the percentage of Polymorph C in the mixtures as shown in Fig. 4. The theoretical enthalpy expected for the endothermic transition was calculated for each mixture based on the enthalpy of the endothermic transition for pure Polymorph C and the amount of Polymorph C in the mixture and is included for comparison.

The measured enthalpies of the melting endotherm for Polymorph C in the mixtures were found to be considerably lower than expected from the calculated values across the entire range from 10 to 90% (w/w) Polymorph C, despite the selected heating rate providing complete inhibition of recrystallisation. The observed trend is consistent with that reported previously for Forms I and III of Carbamazepine (McGregor et al., 2004). For that study it was hypothesised that the observations could be attributed to crystal seeding and partial recrystallisation of the higher melting polymorph from the melt due to the presence of that polymorph in the mixture prior to analysis.

Fig. 5 shows a graph of the measured enthalpies of the melting endotherm for Polymorph A versus the percentage of Polymorph A in the mixtures. Here, recrystallisation of the lower melting form resulted in an increase in the enthalpy of the endothermic transition for that form relative to the theoretical values. This is again consistent with the data for Carbamazepine and supports the crystal seeding hypothesis for an alternative polymorphic system.

In addition, mixtures of Polymorphs A and C were prepared for analysis with the individual components separated in the sample pan as previously described (McGregor et al., 2004). These samples were analysed at the same heating rates and Fig. 6 shows the measured enthalpy of the endothermic transition plotted against the percentage of Polymorph A. Again the graph of theoretical enthalpy of the endothermic transition versus percentage Polymorph A is included for comparison. Physically separating the individual components prevents physical mixing of the two polymorphic forms and hence crystal seeding. Partial recrystallisation of Polymorph A from the melt of Polymorph C does not occur and as a result no significant differences were observed between the measured enthalpy of the melting endotherms and the calculated values further confirming the hypothesis of crystal seeding.

In summary, it has been confirmed that utilising DSC with accelerated heating rates can inhibit concurrent recrystallisation in at least two different metastable polymorphic systems which are structurally distinct. In this study, a heating rate of 400 °C/min was shown to inhibit the recrystallisation of Polymorph C of a Merck development compound. The result is a single melting endotherm from which thermodynamic parameters such as the enthalpy of fusion could be determined.

The analysis of mixtures of Polymorphs A and C by Hyper-DSC™ indicated the potential to detect polymorphic impurities

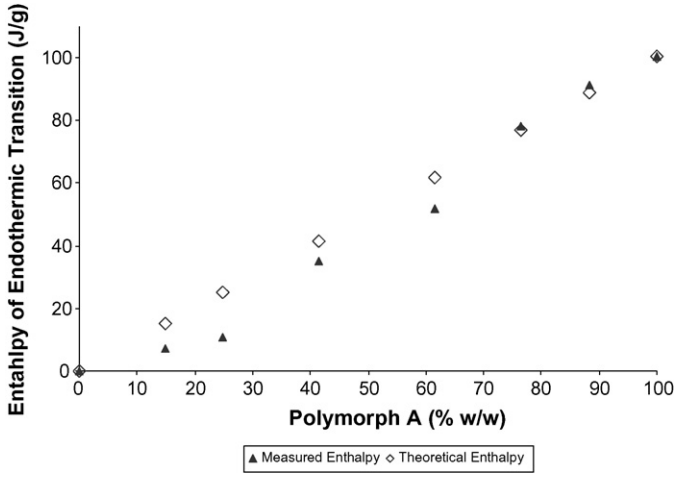

Fig. 6. The effect of separating Polymorphs A and C in the DSC pan on the measured enthalpy of fusion for Polymorph A.

at levels lower than 10% (w/w). However, the crystal seeding and partial recrystallisation phenomenon reported previously during this type of analysis was again observed. Thus, the ability of this technique to accurately quantify levels of either polymorph in mixtures of the two crystal forms is severely limited.

It has been recognised that the utility of Hyper-DSC™ for accurate quantification of polymorphic impurities would require the ability to overcome the issue of partial recrystallisation enabled by crystal seeding. This study employed a helium purge gas to give improved sensitivity and baseline stability and heating rates up to the maximum heating rate for the instrument have been investigated with little impact on crystal seeding. For the early work on Carbamazepine it was also suggested that the seeding effect may occur as a result of the properties of the compound. Based on the data presented here for a structurally distinct molecule, this now seems less likely. Hyper-DSC™ has been confirmed as a useful tool for the study of the polymorphic behaviour of metastable polymorphs. It offers the possibility of accurate determination of thermodynamic parameters previously not obtainable and also allows a qualitative assessment of polymorphic purity. However, the ability to accurately quantify those polymorphic impurities seems likely to be limited with no acceptable techniques to prevent crystal seeding without physical separation of the individual components of any mixture.

4. Conclusions

In this paper the use of Hyper-DSC™ for the characterisation of pharmaceutical polymorphs is investigated further with Polymorphs A and C of Merck development compound used as an alternative model system. When Polymorph C is heated at conventional heating rates, the melting endotherm is accompanied by an exotherm due to concurrent recrystallisation of Polymorph A from the melt. This is consistent with the behaviour of many drug molecules including the Carbamazepine system used in previous work. The use of accelerated heating rates (in this case 400–500 °C/min) has again been shown to successfully inhibit the recrystallisation process, allowing accurate determination of the enthalpy of fusion for Polymorph C from a single endothermic transition. However, when the potential for quantification of relative amounts of the individual polymorphs in mixtures was reconsidered partial recrystallisation of Polymorph A was seen to occur. This is consistent with the crystal seeding effects observed previously for Carbamazepine and suggests that the applicability of Hyper-DSC™ to accurate quantification of low levels of polymorphic impurities may be limited. The technique has however shown utility as a qualitative tool to identify the presence of polymorphic impurities that might otherwise have been missed at conventional scanning rates. It is expected that such polymorphic impurities will be detectable at levels lower than 10% (w/w).

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