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Characterisation of paracetamol form III with rapid-heating DSC

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ABSTRACT

Form III is the most unstable polymorph of paracetamol discovered and has not been fully characterized. Its instability in air means that it must be formed in situ in whichever instrument is used for analysis and even its melting point is the subject of discussion, because it undergoes a solid–solid conversion to form II when heated. The recent development of rapid-heat differential scanning calorimetry (RHDSC), which offers heating rates up to 2000 °C/min, provides a new opportunity to characterize unstable polymorphs because of the likelihood that form changes can be inhibited at higher heating rates. Hence the specific aim of this work was to use RHDSC to isolate and characterize paracetamol form III. Form III was prepared from the glass by holding isothermally at 113 °C for 2 min. Upon heating at slow scan rates (up to 300 °C min^{-1}) a solid–solid transition to form II at ca. 120 °C was seen, followed by melting of form II at 156 °C. At heating rates of 400 °C min^{-1} and higher, the solid–solid transition was absent and two endotherms were observed; the form II melt at 156 °C and a new, lower temperature endotherm at 143 °C. We ascribe the transition at 143 °C to the melting of form III. The form II melt was present in all experiments, irrespective of heating rate; thus we presume the paracetamol crystallizes to a mixture of forms II and III during preparation, indicative again of the unstable nature of form III. Experiments conducted with a crystal growth modifier (hydroxypropylmethylcellulose, HPMC) showed that increasing the HPMC molecular mass, or increasing the HPMC:paracetamol ratio, resulted in a concomitant increase in the form III peak, relative to the form II peak, which supports the hypothesis that the sample coexisted in both forms prior to crystallization.

1. Introduction

Paracetamol (acetaminophen) has three known polymorphic forms, numbered I, II and III [1]. Form I is a stable, monoclinic polymorph that exhibits poor compressibility while form II is orthorhombic and shows good compressibility [2]. Form III was first proposed in 1982 [3] and is considered too unstable to isolate. Hence, characterisation of the physical properties of form III, including determination of its melting temperature, has never been achieved, although some work on stabilising form III with hydroxypropylmethylcellulose (HPMC) did result in a tentative melting temperature of 139–141 °C [4] and one report suggests form III can be isolated in hermetic differential scanning calorimetry (DSC) pans [5].

Recently, a method of preparation of form III has been reported [6] based on Ostwald's rule of isolation in stages [7]. Although they managed to isolate form III using this method, Burley et al. [6] could not determine the melting temperature with DSC because the sample underwent a solid–solid transition to form II before any melting occurred. Hence, at the scan rates they employed (1–100 °C min^{-1}) only the melt of form II at 159 °C was seen. Since the solid–solid transition is a kinetic event, its position on the temperature axis of a DSC plot will be influence by the scan rate (occurring at a higher temperature with an increase in heating rate). If a high enough scan rate can be used that the temperature at which the solid–solid transition occurs becomes higher than the melting point of the polymorph, the solid–solid transition will in effect be inhibited [8] and only a melting transition will be observed. The recent development of rapid-heating DSC (RHDSC) instrumentation (up to 2000 °C min^{-1}) [9] means that the range over which physical characterisation of materials can be performed has expanded. Hence, the aim of this work was to employ RHDSC to isolate paracetamol form III and heat it fast enough to inhibit the solid–solid transition. A secondary aim was to investigate paracetamol form III in the presence of a crystal habit modifier, hydroxypropylmethylcellulose (HPMC), to expand and interpret the existing literature data.

2. Materials and methods

Paracetamol form I (USP grade) was purchased from Sigma-Aldrich and used as received. Various grades of HPMC (Methocel E5, K4M and K100M) were purchased from Colorcon Ltd and used as received. The HMPC grades vary according to their viscosities when dissolved to 2% (w/v) in water (E5 – 5 mPa s; K4M – 4000 mPa s; K100M – 100,000 mPa s).

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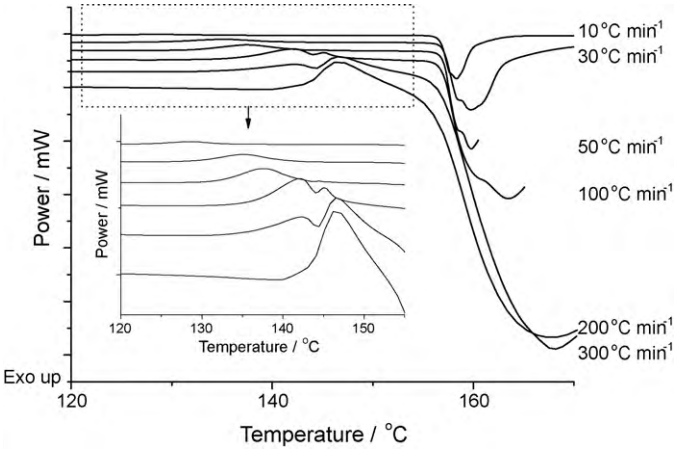

Fig. 1. DSC data for paracetamol, following crystallisation from the glass at 113 °C, at heating rates up to 300 °C min^{-1} (inset graph expands region showing solid–solid transition).

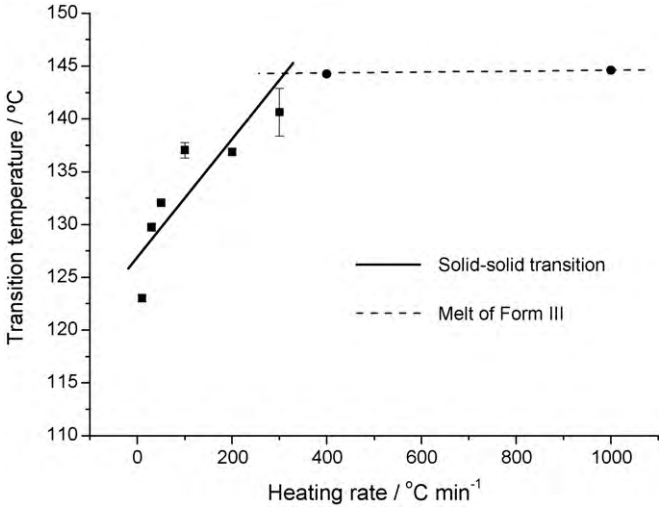

Fig. 2. Transition temperature versus DSC scan rate for paracetamol form III. Note that data up to 100 °C min^{-1} were recorded with Q2000, while data faster than 100 °C min^{-1} were recorded with RHDSC.

Experiments at heating rates up to 100 °C min^{-1} were performed with a Q2000 DSC (TA Instruments LLC). Samples were loaded into non-hermetic aluminium Tzero pans. A nitrogen purge gas (50 mL min^{-1}) was used for all experiments and an empty aluminium pan, matched in weight to the sample pan, was used as a reference. The instrument was calibrated with indium prior to use, using the Tzero calibration wizard.

Experiments at heating rates faster than 100 °C min^{-1} were performed with a rapid-heat DSC (RHDSC, TA Instruments LLC). Detailed design aspects of RHDSC have been detailed elsewhere [9] but, briefly, it uses an infrared 'massless' furnace and small (ca. 0.1 mg) samples to achieve heating rates up to 2000 °C min^{-1}. Aluminium pans were loaded with sample and non-hermetically sealed with an aluminium lid. An empty aluminium pan and lid, matched for weight with the sample, were used as a reference. Nitrogen (50 mL min^{-1}) was used as a purge gas. Data were recorded with the dedicated instrument software. As in the case of the Q2000, the RHDSC was calibrated with indium prior to use, using the Tzero calibration wizard. All melting and crystallization temperatures are reported as extrapolated onset temperatures of the peaks and data were analysed using TA Instruments Universal Analysis 2000.

2.1. Preparation of paracetamol form III

Paracetamol form III was prepared in accordance with the method of Rossi et al. [4]; the as-received drug (form I) was heated to 180 °C and held isothermally for 5 min before being cooled to room temperature. The resulting glass was heated to 113 °C and held isothermally for 2 min. The sample was then cooled to room temperature, prior to being heated to 180 °C at various heating rates, from 100 to 1000 °C min^{-1}.

2.2. Preparation of paracetamol:HPMC mixtures

The appropriate masses of paracetamol and HPMC (to make a final mass ratio of 9:1, 8:2, 7:3, 6:4 or 5:5 respectively) were gently mixed in a pestle and mortar for 5 min, in accordance with the method of Rossi et al. [4].

3. Results and discussion

3.1. Pure paracetamol

The underlying experimental principle for formation of form III is based on Ostwald's rule of isolation in stages [7]. Briefly, this supposes that when a material crystallises from a non-equilibrium, 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 crystallise in a sequence, progressing through any available metastable polymorphs to the stable crystalline form. Thus the expectation here is that it is form III that crystallises from the glass during the isothermal hold period at 113 °C. DSC data at heating rates up to 300 °C min^{-1} for this material are shown in Fig. 1. In all cases a small exotherm (the position of which varies from 120 to 140 °C depending upon heating rate) is seen prior to an endotherm at 156–7 °C. These data are consistent with previous literature observations [1,2,4–6,10,11] and correspond to the form III to form II solid–solid transition and melt of form II respectively. The solid–solid transition is very small, occurring with an enthalpy change of ca. −0.6 kJ mol^{-1} (at 50 °C min^{-1}) in reasonable agreement with the value of −1 kJ mol^{-1} reported by Burley at al [6], although acceptance of this value presupposes that all the sample was present as form III initially; this point is discussed in more detail below. The solid–solid transition is a kinetic event and thus its position should be, and is, influenced by heating rate; this phenomenon is seen in the data in Fig. 1 (as the heating rate increases above 100 °C min^{-1} the transition appears as two events, which may represent some altered kinetics) and represented graphically in Fig. 2. Note that the data recorded up to heating rates of 100 °C min^{-1} were recorded with the Q2000 DSC, while those at faster heating rates with RHDSC and there appears to be a small difference in measured response between instruments—the linear correlation coefficient of the line for data to 400 °C min^{-1} is 0.826, but this improves to 0.996 when only RHDSC data are considered).

At heating rates of 400 °C and faster, shown in Fig. 3, different behaviour is seen; the exothermic solid–solid transition is absent, and a new endotherm is seen at 143 °C, prior to a small exothermic peak and then the form II melt at 159 °C. The endotherm at 143 °C is not influenced by heating rate and thus appears to

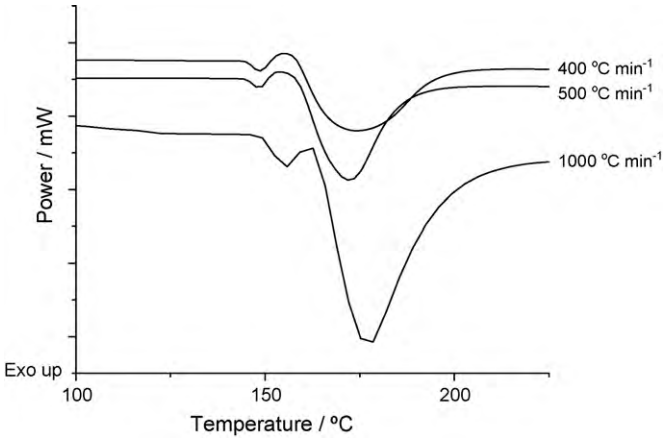

Fig. 3. DSC data for paracetamol, following crystallisation from the glass at 113 °C, at heating rates of 400 °C min^{-1} and faster.

be a thermodynamic event, which we ascribe as melting of form III. The small exotherm likely represents crystallisation to form II prior to the form II melting endotherm. We therefore report that the melting temperature of paracetamol form III is 143 °C, a value slightly higher than that proposed by Rossi et al. [4], although their method required the presence of 10% (w/w) HPMC to stabilise the metastable polymorph. We will return to the subject of HPMC stabilised systems below. One issue with fast DSC heating rates is the data capture rate—here, the data capture rate is 50 Hz (referenced to the frequency of the electricity supply), which has some effect on the resolution of the data as the heating rate reaches 1000 °C min^{-1} and higher, although the trends are still clear.

A major issue with the data concerns the ever-present form II melting endotherm at 159 °C, an event that is seen in all data sets (and is also reported in the literature data). At scan rates slower than 300 °C min^{-1}, the sample undergoes a solid–solid transition to form II and hence its presence is expected. Two hypotheses present themselves as likely explanations for the continuing presence of form II above scan rates of 300 °C min^{-1}, after which we contend that the form III to form II conversion has been inhibited. The first is that following the form III melt the sample immediately crystallizes to form II, a process that would be accompanied by an exothermic peak. Such an exotherm is seen in all data at scan rates below 1000 °C min^{-1}; peak broadening and a lack of data resolution at 1000 °C min^{-1} mean that it is not clear if the exotherm is present in that case. However, thermodynamic analysis of the peak areas does not support this hypothesis, since the area of the crystallisation peak should be equal and opposite to that of the form II melt, which it clearly is not. This then casts doubt on the value for the solid–solid transition enthalpy quoted by Burley et al. [6], since it presupposes that the entire sample was form III before the transition occurred.

The alternative hypothesis is that the sample did not crystallise fully to form III during the isothermal phase, but rather to a mixture of forms II and III. Hence, at the start of each heating run form II was already present. The evidence in the literature for true isolation of pure form III from the glassy state is inconclusive and several authors [6,10] imply that it is possible to isolate mixed forms III and II. Holding paracetamol glasses at 110 and 107 °C (instead of 113 °C) resulted in slightly increased crystallisation exotherms prior to the form II melt (data not shown); this implies formation of form III is favoured at lower temperatures, in accordance with Ostwald's theory, but that the form II is ever-present. Holding the glasses isothermally at temperatures below 107 °C did not result in any crystallization during the observation period (up to 2 h). Further characterisation of the freshly crystallized material by powder X-ray diffraction was not possible, due to its rapid conversion to form II upon exposure to air, although spectroscopic interrogation of the sample in situ may offer new insight and we hope to record such data in the near future. In a recent study of paracetamol, with combined Raman-DSC, Kauffman et al. [11] suggest that paracetamol converts entirely to form III prior to the solid–solid transition, although their DSC data show the same small solid–solid transition and form II melt as ours.

3.2. Paracetamol/HPMC mixtures

Since we were not able to record spectroscopic data to aid our interpretation of the data, we opted instead to study the effects of inclusion of a crystal modifier. Giordano et al. [10] crystallised paracetamol from the glass in the presence of HPMC K4M, obtaining a mixture of forms III and II. They report a melting point of 139 °C for paracetamol form III, at a heating rate of 10 °C min^{-1}. No solid–solid form III to form II transition was noted, which implied that HPMC stabilised the metastable form.

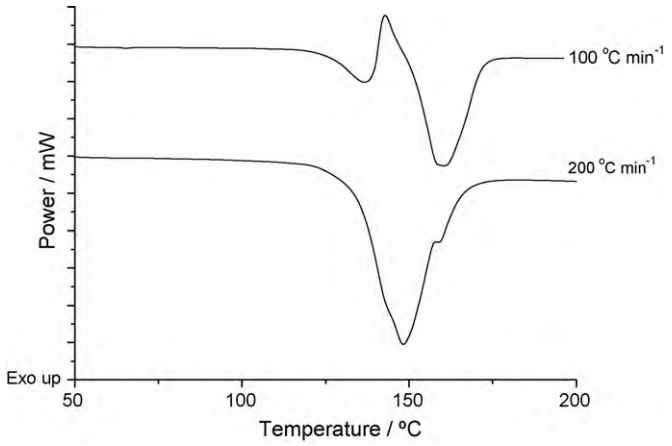

Fig. 4. DSC data for paracetamol, co-mixed with HPMC (9:1 drug:HPMC) and following crystallisation from the glass at 113 °C, at heating rates of 100 and 200 °C min^{-1}.

The data in Fig. 4 show the effect of HPMC K4M with paracetamol at faster heating rates. It is apparent that at a heating rate of 100 °C min^{-1} the same behaviour as noted in [10] is observed; form III melts, crystallises to form II and form II melts; no solid–solid transition is observed prior to these events. At a heating rate of 200 °C min^{-1}, however, no crystallisation exotherm is apparent, and the form III melt becomes correspondingly larger than that of form II.

HPMC acts as a crystal habit modifier by selectively binding to crystal faces; its role here is presumably slightly different, since the drug is initially in a glassy form, and it probably favours formation of the metastable form by restricting molecular mobility. Hence, the smaller molecular movements needed to crystallise to form III favour formation of this polymorph. This being so, there might reasonably be expected to be an effect of HPMC viscosity (i.e. molecular weight). Two alternative HPMC grades, with viscosities at 2% w/v in water either side of K4M, were selected (E5 and K100M); the effect of HPMC grade on paracetamol at a heating rate of 200 °C min^{-1} is shown in Fig. 5. The lowest molecular weight grade (E5) shows crystallisation of form III to form II while the higher grades appear to inhibit crystallisation. Hence it appears there is a limiting HPMC grade beyond which molecular mobility is inhibited sufficiently, within the time frame of the experiment, that crystallisation to form II cannot occur. In all cases, some form II is present, again indicating that the sample crystallised to both forms from the glass.

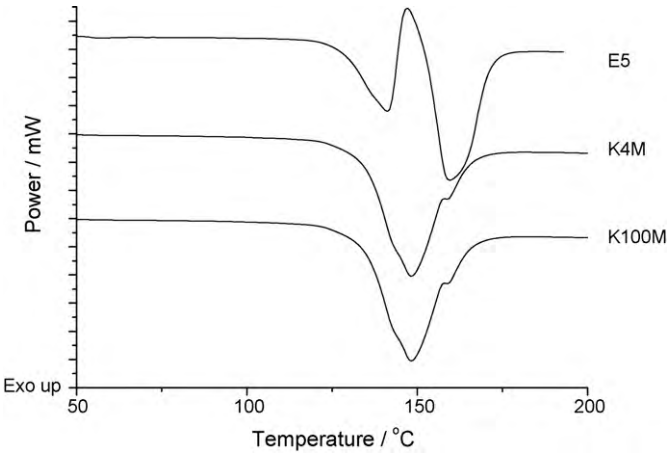

Fig. 5. DSC data for paracetamol, co-mixed with HPMC (9:1 drug:HPMC) grades E5, K4M and K100M and following crystallisation from the glass at 113 °C, at a heating rate of 200 °C min^{-1}.

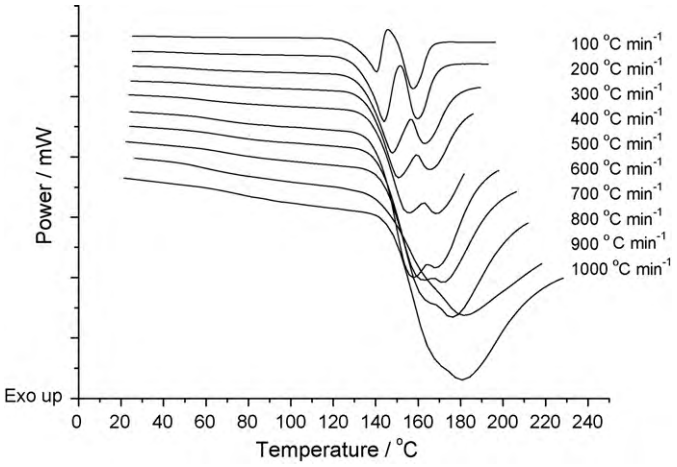

Fig. 6. DSC data for paracetamol, co-mixed with HPMC E5 (9:1 drug:HPMC) and following crystallisation from the glass at 113 °C, at heating rates up to 1000 °C min^{-1}.

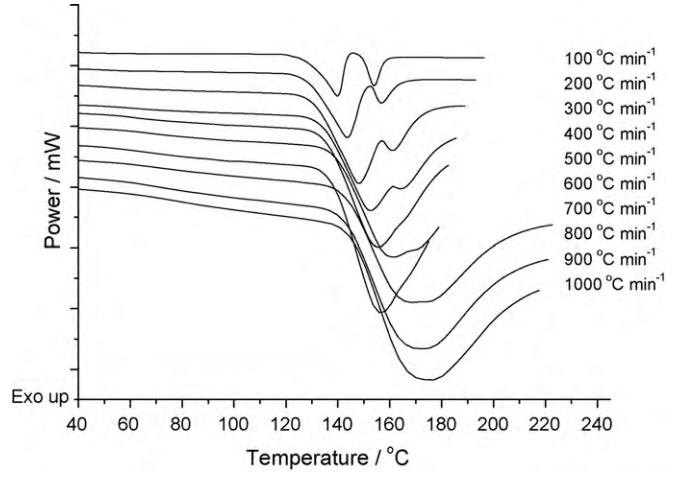

Fig. 7. DSC data for paracetamol, co-mixed with HPMC E5 (8:2 drug:HPMC) and following crystallisation from the glass at 113 °C, at heating rates up to 1000 °C min^{-1}.

If HPMC affects the molecular mobility of the drug then it might also be expected that as the mass ratio of HPMC to drug increases, formation of the metastable form will be favoured. Figs. 6–10 show the effect of HPMC E5 on paracetamol crystallisation as a function of drug:HPMC ratio (9:1, 8:2, 7:3, 6:4 and 5:5 respectively) and

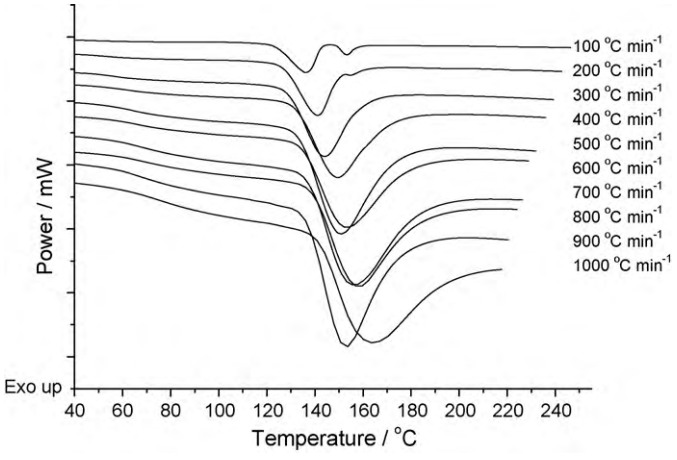

Fig. 8. DSC data for paracetamol, co-mixed with HPMC E5 (7:3 drug:HPMC) and following crystallisation from the glass at 113 °C, at heating rates up to 1000 °C min^{-1}.

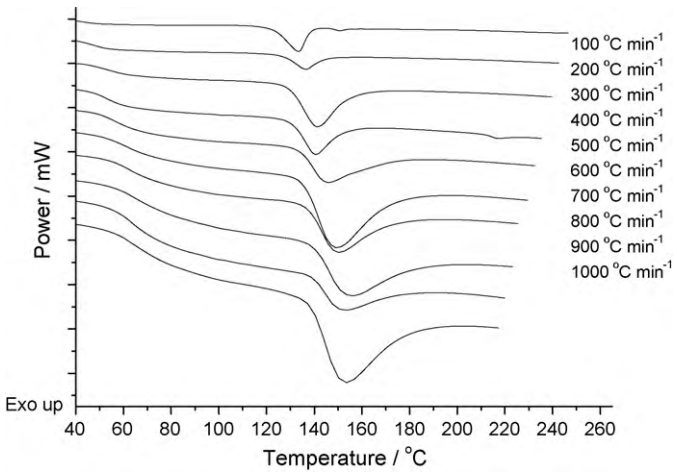

Fig. 9. DSC data for paracetamol, co-mixed with HPMC E5 (6:4 drug:HPMC) and following crystallisation from the glass at 113 °C, at heating rates up to 1000 °C min^{-1}.

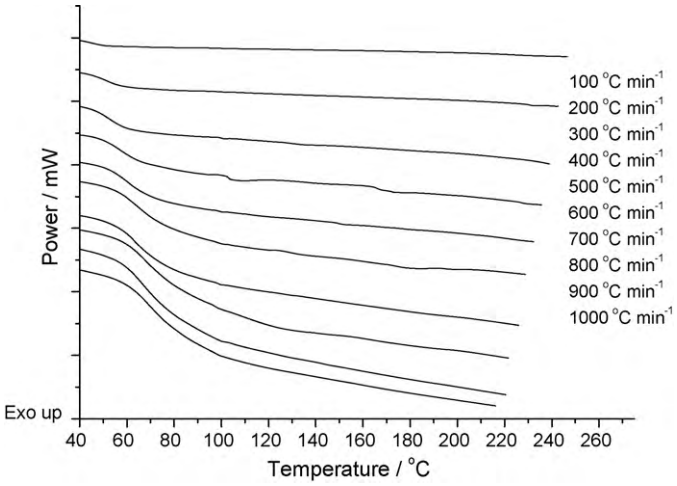

Fig. 10. DSC data for paracetamol, co-mixed with HPMC E5 (5:5 drug:HPMC) and following crystallisation from the glass at 113 °C, at heating rates up to 1000 °C min^{-1}.

as a function of heating rate (up to 1000 °C min^{-1}). As expected, increasing the mass ratio of HPMC increases the proportion of form III in the sample, and increasing scan rate inhibits crystallisation of form III to form II. At mass ratios of 7:3 and higher a glass transition is seen prior to melting, indicating that part of the sample is remaining amorphous. At a mass ratio of 5:5 the sample remains entirely amorphous and none of the drug crystallises to any form. The glass transition temperature is also influenced by heating rate, as expected.

4. Summary

The aim of the work was to isolate paracetamol form III from the glass and then quantify its melting point by heating it fast enough to inhibit the solid–solid transition to form II. This was achieved by using heating rates greater than 400 °C min^{-1}. The melting point of form III is 143 °C. The ever-present occurrence of a form II melt implies that the sample did, in fact, crystallise to a mixture of forms III and II, an outcome seen by other workers. This does not affect determination of the form III melting temperature but does preclude the use of the area of the endotherm for determining the enthalpy of fusion. Lowering the crystallisation temperature affected the ratio of forms III to II produced slightly. Addition of HPMC favoured formation of form III and acted to pre-

vent crystallisation to form II at lower heating rates. At mass ratios of drug to HPMC greater than 7:3 the sample appeared to be partly amorphous and it remained totally amorphous at a mass ratio of 5:5.

Acknowledgements

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References

[1] E.V. Boldyreva, V.A. Drebushchak, I.E. Paukov, Y.A. Kovalevskaya, T.N. Drebushchak, DSC and adiabatic calorimetry study of the polymorphs of paracetamol. An old problem revisited, J. Therm. Anal. Calorim. 77 (2004) 607–623.
[2] P. Di Martino, A.-M. Guyot-Hermann, P. Conflant, M. Drache, J.-C. Guyot, A new pure paracetamol for direct compression: the orthorhombic form, Int. J. Pharm. 128 (1996) 1–8.
[3] A. Bürger, Zur interpretation von polymorphie-untersuchungen, Acta Pharm. Technol. 28 (1982) 1–20.
[4] A. Rossi, A. Savioli, M. Bini, D. Capsoni, V. Massarotti, R. Bettini, A. Gazzaniga, M.E. Sangalli, F. Giordano, Solid-state characterization of paracetamol polymorphs formed in binary mixtures with hydroxypropylmethylcellulose, Thermochim. Acta 406 (2003) 56–67.
[5] S. Qi, P. Avalle, R. Saklatvala, D.Q.M. Craig, An investigation into the effects of thermal history on the crystallisation behaviour of amorphous paracetamol, Eur. J. Pharm. Biopharm. 69 (2008) 364–371.
[6] J.C. Burley, M.J. Duer, R.S. Stein, R.M. Vrcelj, Enforcing Ostwald's rule of stages: Isolation of paracetamol forms III and II, Eur. J Pharm. Sci. 31 (2007) 271–276.
[7] W.Z. Ostwald, Studien uber die bildung and umwandlung fester korper, Zeit. Physik. Chem. 22 (1897) 289–330.
[8] S. Gaisford, Fast-scan differential scanning calorimetry, Eur. Pharm. Rev. 13 (2008) 83–89.
[9] R.L. Danley, P.A. Caulfield, S.R. Aubuchon, A rapid-scanning differential scanning calorimeter, Am. Lab. 40 (2008) 9–11.
[10] F. Giordano, A. Rossi, R. Bettini, A. Savioli, A. Gazzaniga, Cs. Novák, Thermal behaviour of paracetamol-polymeric excipients mixtures, J Therm. Anal. Calorim. 68 (2002) 575–590.
[11] J.F. Kauffman, L.M. Batykefer, D.D. Tuschel, Raman detected differential scanning calorimetry of polymorphic transformations in acetaminophen, J Pharm. Biomed. Anal. 48 (2008) 1310–1315.