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Research paper

An investigation into the effects of thermal history on the crystallisation behaviour of amorphous paracetamol

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Abstract

The effects of thermal history and sample preparation on the polymorphic transformation profile from amorphous paracetamol have been investigated. The crystallisation behaviour of slow and quench cooled amorphous paracetamol was studied using DSC. Quench cooled paracetamol showed a glass transition (T_g) at 25.2 °C, a single exothermic transition at 64.9 °C and an endotherm at 167.7 °C. The initial degree of crystallinity was calculated as a function of time and recrystallisation circa 20 °C below T_g was demonstrated. Slow cooled material in pinholed or hermetic pans (sealed under nitrogen) showed a T_g at 25.1 °C, two exothermic transitions at circa 80–85 °C and 120–130 °C followed by melting at 156.9 °C; a single exotherm at 83 °C was observed for material sealed in hermetic pans under ambient conditions. Hot stage microscopy yielded complementary information on crystal growth and transformation profile. A transformation scheme is proposed which indicates that amorphous paracetamol may transform into Form III, II or I depending on the thermal history and the gaseous environment in which recrystallisation takes place. The study has demonstrated that the thermal history and encapsulation method may profoundly influence the polymorphic forms generated from amorphous paracetamol.

Keywords: Amorphous; Crystallisation; Glass; Paracetamol; Thermal

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1. Introduction

Amorphous materials continue to attract strong interest within the pharmaceutical field, both in terms of their use as dosage forms and their accidental generation. Such systems are considered to have no long range regularity, although short range order may exist within a neighbour molecule distance of 20–25 Å. The molecular arrangement within the glass influences the physical and performance properties of the material, many of which (e.g. solubility, stability and mechanical properties) have considerable pharmaceutical significance [1–4]. In terms of stability in particular, many glassy systems may exhibit considerable kinetic stability around T_g whereas others exhibit relatively rapid crystallisation below the glass transition temperature. A related aspect of their behaviour that has been the subject of comparatively little study has been the crystallisation of glasses into different polymorphic forms. Indeed, there remains considerable uncertainty as to the predictability of amorphous recrystallisation behaviour, both in terms of the kinetics and the crystal structure of the product material.

In this investigation we study the amorphous form of a model drug, paracetamol, which exhibits both considerable instability in the amorphous state and the potential for recrystallisation into different polymorphic forms. This has been conducted with a view to establishing whether and how the thermal history of the sample may influence the polymorphic preference associated with the subsequent recrystallisation behaviour. Paracetamol, also known as acetominophen, is an extremely widely used analgesic and

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Table 1
Summery of physical transformations of paracetamol reported in the literature

Reference	[5]	[6]	[7]	[8]	[9]	[11]	[12]	[13]	[14]
T_g (°C)			23				25	25	
T_m (Form I) (°C)	169	168–169	172	171		169		169	157
T_m (Form II) (°C)	157	157–158	158	157	167	156		157	158
T_m (Form III) (°C)		158							140
A–Form II[a,b]	76	>70	78–83			76–79		70	
Form II–Form I[b]		156	161	122	120	115–126			
Form III–Form I[b]									130
Form III–Form II[b]		70–120					120–130		125–140

T_g, glass transition temperature; T_m, melting point.
[a] A represents the amorphous form of paracetamol.
[b] The transition temperature between different physical forms of paracetamol.

antipyretic but is also an example of an amorphous system with low stability at ambient conditions due to its low glass transition temperature. The properties of amorphous paracetamol have not been substantially addressed due to its poor stability and hence low usability in pharmaceutical formulations. In contrast, the properties of its polymorphs are highly relevant to pharmaceutical processing and have been the subject of considerable study [5–14]. Three polymorphic forms of paracetamol have been described: monoclinic Form I which is the usual commercial form but has low compressability, orthorhombic Form II which shows improved tabletting properties and the highly metastable Form III which transforms into Form II when heated to 120–130 °C [6]. The molecular structures of Form I and Form II have been established using a range of analytical methods [8,9,13,15–17] while the solid-state conversion between Form II and Form I has been studied extensively [5–10,13]. Nevertheless, disagreement remains regarding the transformation behaviour between these three polymorphs during heating; the transition temperatures reported by various laboratories are summarised in Table 1. The effect of pressure on the polymorphic transitions of paracetamol has also been studied [10,11,13], with obvious implications for tabletting behaviour. These pressure-induced transformations are associated with shifts between the planes of the phenyl ring and the acetamido groups of the paracetamol crystal arrays [11,18]. This functional group in the molecule seems somewhat prone to reorientation in the solid state; comparison of the 15 structures available from the Cambridge Crystallographic Structure Database the variability of this dihedral angle if of about 4.5% spanning from the monoclinic, hydrated form to a triclinic solvate of morpholine and piperazine.

In contrast, amorphous paracetamol has not been studied systematically to date although a low T_g of approximately 23 °C has been reported [7,12,19]. Further study of this material is of use for two reasons. Firstly it represents an example of a low T_g glass and consequently provides a model for the investigation of stabilisation strategies. Secondly, given the established existence of several crystal species it also provides a suitable system for the study of crystallisation behaviour into different polymorphic forms. Interestingly, comparatively fewer studies have been conducted on the factors that influence the crystal form generated from the amorphous state. We have therefore examined the recrystallisation behaviour of paracetamol from the amorphous form, with particular emphasis on examining cooling rate to the glassy state, storage time and temperature, headspace environment and heating rate as variables.

2. Materials and methods

2.1. Materials

Paracetamol (BP) (Form I with melting point 169–170 °C) was purchased from Rhodia Organics (Lyon, France). Amorphous paracetamol was prepared by two processes, quench cooling and slow cooling. Quench cooled amorphous paracetamol was prepared by melting paracetamol on a piece of aluminium foil which was then transferred into liquid N_2. Slow cooled amorphous paracetamol was prepared inside the DSC pans by melting the paracetamol by heating at 20 °C/min to 200 °C, holding the temperature at 200 °C for 5 min, then cooling the molten paracetamol to −10 °C at cooling rate of 50, 20, 10, 5, 2 and 1 °C/min, respectively. The sample pans were opened after the DSC tests and the colour of the each sample was recorded. For the ageing studies, the quench cooled amorphous material was stored in a refrigerator at a temperature of circa 5 °C and examined by DSC daily over a period of 2 weeks. Paracetamol Form III was prepared by applying two heat–cool cycles on paracetamol form I in DSC pans. This involved heating from 35 to 180 °C, holding at 180 °C for 5 min, cooling to 35 °C, reheating from 35 to 113 °C and holding for 2 min, then cooling to ambient temperature [14].

2.2. Methods

2.2.1. Differential scanning calorimetry (DSC)

All DSC experiments were performed on a 2920 MDSC (TA Instruments, Newcastle, USA). The instrument was calibrated for each scanning rate (50, 20, 10, 5, 2, 1 °C/

min) using indium. N_2 gas was purged through the DSC cell at a rate of 50 ml/min for all the experiments. Perkin-Elmer hermetic and pinhole pans (Perkins-Elmer LAS Ltd., Bucks, UK) were used as indicated with a sample size of approximately 5 mg. The colour of each sample after completion of the DSC experiment was recorded after reopening the sample pan. The glass transition temperatures of the amorphous paracetamol measured using different heating rate were used to calculate the activation energy of the process and the fragility index of the sample. Slow cooled amorphous paracetamol with a cooling rate of 20 °C/min was used as an example to study how the reheating rate of the DSC programme can influence the crystallisation behaviour of the amorphous material. All melting and crystallisation temperatures reported in this study were measured as the extrapolated onset temperatures of the peaks.

2.2.2. Hot stage microscopy and powder X-ray diffraction

A Mettler Toledo FP82HT hot stage (Mettler Toledo, Beaumont Leys, Leicester, UK) was controlled by a Mettler Toledo FP 90 central processor (Mettler Toledo, Beaumont Leys, Leicester, UK). The hot stage was equipped with a Leica DM LS2 polarised light microscope (Wetzlar GmbH, Germany) connected to a video capture system. Slow cooled amorphous paracetamol was prepared by melting and cooling between a sample slide and cover slide. The approximate cooling rate of the experiment was 20 °C/min. However, since the cooling rate of the instrument is not well controlled the HSM results presented here can only be correlated to the thermal behaviour of the amorphous paracetamol prepared by 20 °C/min cooling in the DSC. The powder diffraction data were obtained using a Bruker D8 diffractometer (Karlsruhe, Germany) with a graphite monochromator and the diffracted beam path generated Cu Kα radiation. The PXRD patterns were collected with 40 kV of tube voltage and 35 mA of tube current in the angular range (2θ) of 5°–35° in a step scan mode (step width of 0.03°). The instrument was calibrated using silicon powder reference standard prior to use.

3. Results

3.1. Characterisation of constituent materials

While Form I and Form II paracetamol have been widely studied, there is comparatively little information available on either amorphous or Form III paracetamol. To this effect a range of basic studies were conducted on these two materials in isolation from considerations of phase transformations in order to facilitate interpretation of the other results.

3.1.1. Glass transition and fragility of amorphous paracetamol

The glass transition of amorphous paracetamol was found to be in the region of 22–26 °C, depending on the thermal history. This aspect of the glassy behaviour is discussed in more detail below in the context of the crystallisation behaviour. Here we describe further studies on the transition itself. More specifically, we examine the fragility of the glass as this parameter as a means of understanding the structural relaxation dynamics of supercooled liquids. The concept was introduced by Angell et al. [20] and describes the temperature dependence of the relaxation time of glassy systems between T_g and T_m. While the correlation between molecular structure and fragility remains the subject of debate, the parameter is attracting interest in the pharmaceutical area as a potential means of understanding physical stability [17,21].

At temperatures below T_g the relaxation time of a glass τ follows Arrhenius kinetics, while above T_g the system follows a relationship often described by the Vogel–Tamman–Fulcher (VTF) equation

$$\tau = \tau_0 \exp\left(\frac{DT_0}{T - T_0}\right) \tag{1}$$

where T is the temperature and T_0/τ_0 are the reference temperature and relaxation time. The parameter D is a constant which may be related to the fragility of the system. In brief, fragile systems show large values of D and consequently large values of ΔC_p at the glass transition, while strong liquids show smaller D values and heat capacity changes at T_g. The most commonly used metric for fragility is the steepness index m [22], with strong and fragile (weak) liquids having values of $m < 100$ and $100 < m < 200$, respectively [23].

The fragility of the amorphous paracetamol in this study was calculated using the theory of extrapolating configurational entropy to zero. The activation enthalpy of the structural relaxation at the glass transition was estimated by using different scanning rates to achieve different glass transition temperatures and glass transition widths as expressed in the following equation:

$$m = \frac{\mathrm{d}\log_{10}(\tau)}{\mathrm{d}\frac{T_g}{T}} = \frac{E_a^*}{2.303RT_g}(T = T_g) \tag{2}$$

where m is the fragility index of the material, E_a^* is the activation energy and R is the gas constant. As described in Eq. (3) below, $-E_a^*/R$ is the slope of the plot $1/T_f$ against $\ln(q)$ (q as cooling/heating rate).

$$\frac{\mathrm{d}\ln|q|}{\mathrm{d}\left(\frac{1}{T_f}\right)} = -\frac{E_a^*}{R}. \tag{3}$$

The fictive temperature (T_f) is defined as the temperature of intersection between the equilibrium volume or entropy/temperature liquid curve and the linear extrapolation of the glassy curve. However in this study T_f was replaced by using T_g which has been proved to have a similar value to T_f [23].

The T_g values of the slow cooled paracetamol were measured using a range of cooling rates from 1 to 50 °C/min. The T_g values used for the calculation were all obtained from the cooling cycles. Fig. 1 shows the plot of $\ln(q)$ against $1000/T_g$, from which the value of E_a^*/R is calculated as 58473 (1/K). Therefore by using Eq. (2) the fragility index (m) of the amorphous paracetamol prepared under the nitrogen atmosphere can be calculated as 86.7. This indicates a strong glass and is in line with values calculated for other drug systems of similar molecular weight [20,21].

3.1.2. Form III paracetamol

The PXRD patterns of the three forms of crystalline paracetamol match the published data (data not shown) [14]. It was interesting to note from DSC studies that the Form III material tested in hermetically sealed (under ambient conditions) and pinhole pans exhibited different thermal behaviour, as seen in Fig. 2. The Form III sealed in hermetic pans displayed a single melting transition with an extrapolated onset at 155.9 °C and a peak temperature at 158.1 °C which corresponds to the melting point of Form III reported [6], while the Form III crystals enclosed in the pinhole pans showed an exothermic transition at 128.3 °C followed by melting with an extrapolated onset at 157.1 °C and a peak temperature at 160.3 °C; this corresponds to the melting of Form II. It is therefore suggested that the Form III in pinholed pans undergoes a solid-state transformation to Form II during the heating process, possibly reflecting a pressure or headspace gas dependence of the behaviour. It is also interesting to note that according to Bergers rules [24] an exothermic solid-state transition corresponds to a monotropic unstable to stable transformation, which would be consistent with the observed instability profile of Form III.

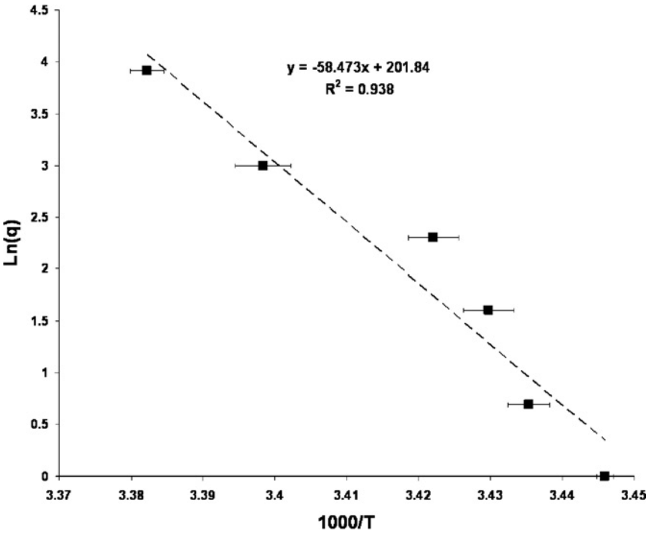

Fig. 1. Plot of $\ln(q)$ (where q is cooling rate) against inverse glass transition (K) of amorphous paracetamol ($n = 3$, each data point = average value ± SD).

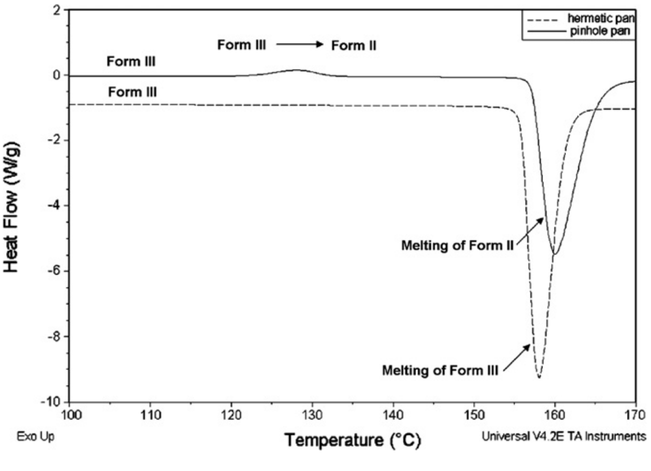

Fig. 2. DSC response of paracetamol Form III heated to 170 °C in hermetic and pinhole pans (heating rate 20 °C/min).

3.2. Thermal investigation into the crystallisation of amorphous paracetamol

3.2.1. DSC of quench cooled amorphous paracetamol

The quench cooled paracetamol showed a glass transition temperature at circa 25 °C which remained constant throughout the 2 week ageing process at 5 °C, as seen in Table 2. On heating in hermetic pans (sealed under ambient conditions) an exothermic transition was seen at circa 55.8 °C (tentatively ascribed to crystallisation) followed by a melting transition with peak maximum at circa 170.7 °C (corresponding to the literature values of the melting of Form I); the recrystallisation behaviour remained constant for all aged samples. A typical DSC trace is shown in Fig. 3 for quench cooled material heated in hermetic pans at 10 °C/min.

It is possible to use the magnitude of the crystallisation peak to estimate the degree of crystallinity of the sample (Fig. 4). In brief, if one assumes the freshly prepared sample to represent the completely amorphous material then one may calculate the amorphous content by comparing the magnitudes of this peak as a function of a factor of interest (noting that there is an assumption of invariance of the temperature of recrystallisation, which was found to be reasonable in this case). In this case we examined the effect of storage at 5 °C on the degree of crystallinity and noted a rapid decrease in the magnitude of the crystallisation peak, indicating prior recrystallisation. The amorphous paracetamol partially recrystallised immediately after quench cooling and the entire crystallisation process was completed in 14 days, even though the material was being stored well below T_g. The isothermal crystallisation kinetics of the amorphous paracetamol in the first 4 days was approached using Avrami–Erpfeev rate equation [24] fitting, as seen in the following equation:

$$[-\ln(1-\alpha)]^{1/n} = kt \tag{4}$$

where α refers to the amount of crystalline paracetamol present in the sample at time t, exponent $n = \beta + \lambda$ (β represents the nucleation law and λ is the number of dimensions of nuclei growth), k is the reaction constant and t is

Table 2
Quench cooled paracetamol aged for different period, then heated at 10 °C/min using hermetic pan sealed under ambient conditions ($n = 3$, ±SD < 0.5)

Ageing period (days)	1	2	3	4	14
T_g (°C)	25.18 ± 0.3	24.78 ± 0.4	23.76 ± 0.3	22.91 ± 0.5	22.01 ± 0.8
ΔC_p (J/g °C)	0.614 ± 0.06	0.485 ± 0.04	0.397 ± 0.05	0.241 ± 0.05	0.136 ± 0.09
Onset R_1 (°C)	55.82 ± 0.3	56.84 ± 0.4	54.77 ± 0.3	52.02 ± 0.2	57.57 ± 0.2
T_{r1} (°C)	64.88 ± 0.2	65.26 ± 0.2	64.09 ± 0.3	63.04 ± 0.1	66.95 ± 0.1
Enthalpy (J/g)	73.77 ± 0.4	71.01 ± 0.5	54.28 ± 0.6	40.96 ± 0.3	3.203 ± 0.3
Onset T_m (°C)	167.95 ± 0.2	167.35 ± 0.1	163.32 ± 0.3	164.87 ± 0.2	165.24 ± 0.2
T_m (°C)	171.14 ± 0.1	170.94 ± 0.1	169.99 ± 0.2	170.45 ± 0.1	170.69 ± 0.1
Enthalpy (J/g)	166.5 ± 0.3	168.1 ± 0.1	161.0 ± 0.7	164.5 ± 0.2	171.6 ± 0.2

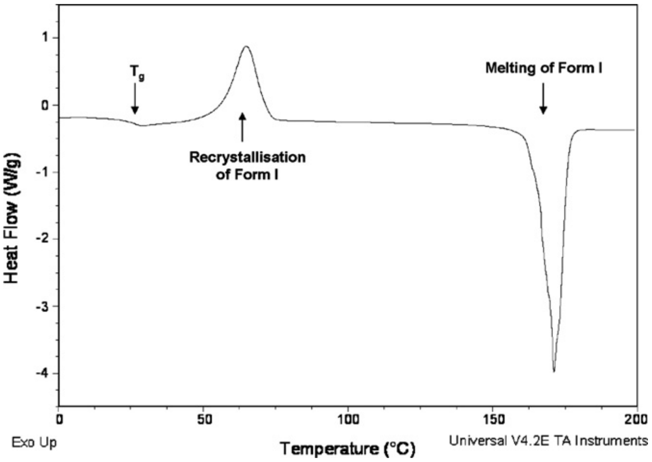

Fig. 3. DSC response of quench cooled paracetamol on heating in hermetic pans at 10 °C/min.

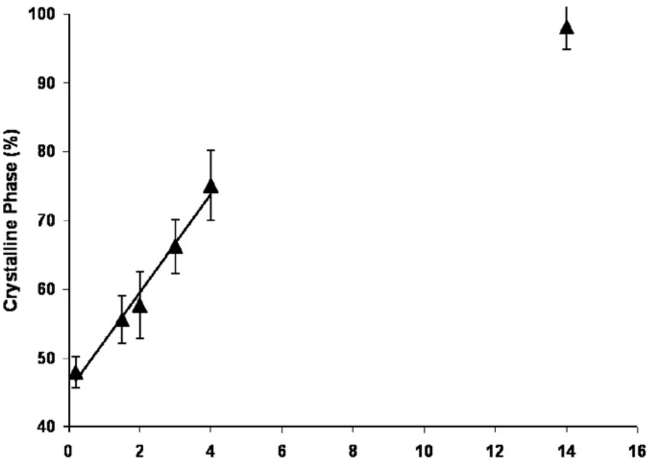

Fig. 4. Percent crystallinity versus time for the quench cooled amorphous paracetamol stored at 5 °C under ambient condition ($n = 3$, each data point = average value ± SD).

the time (days). By using the Avrami–Erofeev rate equation, the nuclei growth is assumed without any inhibiting effect. In this case, the best fitting of the first 4 days isothermal crystallisation data to the Avrami–Erpfeev equation gives the n value of 2. This indicates instantaneous nucleation ($\beta = 0$) followed by two-dimensional nucleus growth ($\lambda = 2$) of paracetamol form I crystals.

3.2.2. DSC of slow cooled amorphous paracetamol

Slow cooled paracetamol also showed the general pattern of exhibiting a T_g, intermediate responses and melting (all described in more detail below). However, we also studied the effect of reheating rate, pan atmosphere and the type of sample pan used, all of which were found to have an impact on the behaviour. On increasing the heating rate from 1 to 20 °C/min, the T_g showed an increase of circa 5–7 °C in all cases; the sensitivity of the measurement increased as one would expect from standard DSC theory [25]. However, the general form of the profiles obtained remained unchanged. Of particular note was that the samples prepared in hermetic pans under N_2 atmosphere (Fig. 5) and run at 20, 10, 5 and 1 °C/min showed double exothermic transitions in the regions of 60–80 and 100–120 °C depending on the scanning rate followed by melting that corresponded to Form II (extrapolated onset at circa 157.1 °C); one may reasonably conclude that the material transformed to Form III in the first instance (corresponding the first, larger exotherm) and then underwent a transformation to Form II

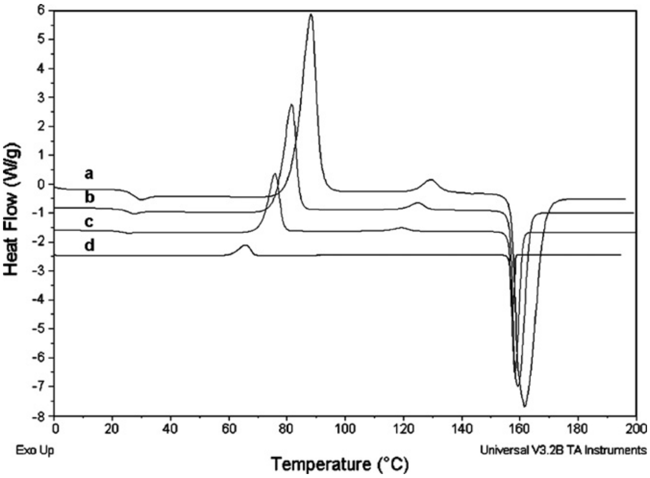

Fig. 5. DSC responses of paracetamol samples prepared under N_2 atmosphere at different reheating rates (hermetic pan; sample cooled at 20 °C/min). The samples were reheated at (a) 20 °C/min; (b) 10 °C/min; (c) 5 °C/min; (d) 1 °C/min.

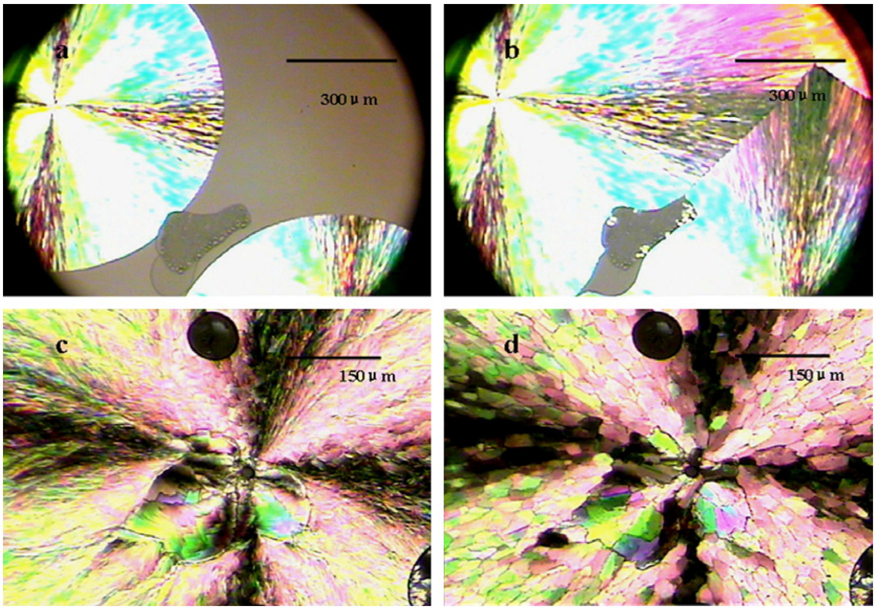

Fig. 6. Hot stage microscopy images showing typical reheating process include (a) the nucleation/initiation of crystal growth (78.4 °C); (b) further crystal growth (87.6 °C); and polymorphic transformation from (c) (102.2 °C) to (d) (125.5 °C) of amorphous paracetamol prepared by slow cooling (10 °C/min).

(the second smaller exotherm). The samples prepared in hermetic pans under ambient atmosphere showed single exothermic transitions in the region between 60 and 80 °C (data not shown) followed by a single melting with an extroplated onset temperature at 155.5 °C; this may be tentatively ascribed to crystallisation to Form III which subsequently melts. This section of the study again indicates a dependence of the polymorphic transformation on encapsulation method.

3.2.3. Hot stage microscopy studies of slow cooled amorphous paracetamol

The crystallisation behaviour of the glassy paracetamol produced by slow cooling is shown in Fig. 6. The images show clear nucleation and crystal growth within the temperature region 70–90 °C (Figs. 6a and 7b), corresponding to the exotherms seen in the DSC studies. However in addition it is possible to observe a crystal transformation process at 100–130 °C which is accompanied by a change in the pattern of the spherulites generated between the glass slides as seen in Figs. 6c and 7d. The spherulites in Fig. 6c show fine strands of fibre-like appearance; whereas with increasing temperature the ones in Fig. 6d show coarse domains with clear edges. Melting of the crystals was observed at 158–160 °C. Since the paracetamol was entrapped between two glass slides, the behaviour of sample was expected to be similar to that of the sample studied under nitrogen environment. The HSM data can be considered to be in reasonable agreement with the DSC data (at least in terms of the material sealed under nitrogen or measured in pinholed pans) and suggest that the slow cooled sample undergoes crystal growth (Form III) followed by a solid-state transformation to Form II and subsequent melting.

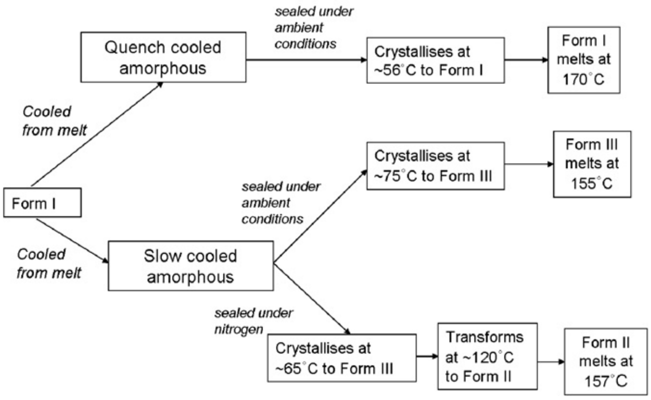

Fig. 7. Schematic representation of transformation between polymorphic forms of paracetamol on heating from the glassy state.

3.3. Summary and visual observations

In summary, therefore, the quench cooled material underwent crystallisation to Form I. The slow cooled material either underwent a single crystallisation to Form III which then melted (sealed under ambient conditions) or crystallisation to Form III which then transformed to Form II which subsequently melted (sealed under nitrogen or pinholed pans). This is summarised in the schematic given in Fig. 7. These observations suggest that the recrystallisation profile may be dependent on the nature of the headspace gas, with the presence of oxygen and/or trace moisture resulting in a greater preponderance for the formation of metastable polymorphs.

It was noted that there was evidence for a colour change to pink in several of the samples after heating, particularly those sealed under ambient conditions with markedly less colour change seen for those sealed under N_2. This implies that the material undergoes oxidation or possibly hydrolysis to some extent, although spectroscopic studies indicated that the extent of the conversion was small. It is not possible to determine whether the appearance of the colour change is linked directly to the recrystallisation behaviour or whether both the colour change and the formation of metastable polymorphs are both consequences of the presence of headspace gases. However irrespective of the mechanism we are not aware of previous studies which have indicated that the nature of the headspace gas may influence recrystallisation in this way.

4. Discussion

The principal focus of the study was to examine the recrystallisation behaviour of amorphous paracetamol with a view to delineating the factors associated with this process. In the first instance, the glass transition and fragility of amorphous paracetamol have been measured, thereby providing a baseline data set by which subsequent behaviour may be considered. It is particularly noteworthy that the DSC response of the Form III paracetamol is dependent on the pan conditions, with sealed pans (i.e. with ambient atmosphere entrapped with the sample) leading to a simple crystallisation to Form III while the sample was measured in pinholed pans transformed from Form III to Form II. This would imply a dependence on either headspace pressure (which will be greater for the sealed systems) or, more probably, headspace composition (which will be nitrogen for the pinholed pans but will contain atmospheric gases and trace moisture for the sealed pans).

The quench cooled material showed a relatively simple transformation process to Form I while the slow cooled material crystallised to Form III which then transformed to Form II in the presence of nitrogen but not when sealed under ambient conditions, mirroring the behaviour shown above. The fact that the samples sealed under nitrogen also showed this transformation implies that the key factor is the nature of the headspace rather than the pressure and the latter would be very similar for pans sealed under nitrogen and ambient atmosphere. This is clearly a complex issue as both the HSM data showed the ‘nitrogen’ rather than the ‘ambient’ behaviour, although the different sample presentation conditions for these techniques make the drawing of absolute conclusions difficult. The most important point is that there is a clear dependence of transformation behaviour on cooling rate and pan conditions. In terms of the effect of cooling rate, the ‘law of stages’ has suggested that an amorphous material will crystallise into successively stable forms [25]. Here we show that this succession is dependent on thermal history. This may be either due to the persistence of Form I nuclei for the quench cooled sample due to the lower time in the molten state or alternatively may reflect differences in molecular mobility which translate into different form generation. Carpentier et al. [26] has suggested that quench cooled indomethacin retains a degree of molecular mobility that correlates with the mobility of the form into which the material crystallises, hence a similar phenomen may be of relevance here. A further confounding factor is the possible role of minor degradation processes, probably as a result of oxidation [9]; no products were detected using spectroscopic methods and it is common for drugs to show some degree of degradation on melting. Whether there is a direct link between degradation and polymorphic transformation requires further investigation, although no clear correlation was observed between the discolouration and the crystallisation behaviour.

One may therefore firmly conclude that the thermal history and sample presentation clearly influence the crystallisation behaviour, with slow cooling tending to lead to the generation of unstable forms. Perhaps surprisingly, our data indicate that the thermal history is more important than the subsequent heating rate which appeared to have limited influence on the recrystallisation profile, at least in this case. A pertinent point is the possibility of using this recrystallisation process as a means of identifying new polymorphs. More specifically, we suggest that a routine test for unstable polymorph generation could be the preparation of amorphous material, preferably by slow cooling, followed by reheating under nitrogen and careful analysis of the forms so generated. One may also conclude that this system shows physical instability well below the glass transition temperature; while such behaviour has been noted for a range of other drugs the remarkable speed by which $<T_g$ recrystallisation took place in this case gives some cause for concern with regard to the reliability of the general belief that storage below T_g is a reasonable starting point in controlling stability.

5. Conclusions

The study has demonstrated that the crystallisation behaviour of amorphous paracetamol is dependent on both the thermal history of the sample and the method of sample presentation. More specifically, quench cooled material (in hermetically sealed pans) formed the stable Form I on heating, while slow cooled material formed Form III in reheating which either melted or transformed to Form II depending on the pan conditions. Additional information has been provided with regard to the glass transition and fragility of paracetamol and the stability of amorphous paracetamol below T_g. We suggest that the generation of polymorphic forms from amorphous material may be a useful means of identifying unstable polymorphs for new drug substances and that by varying the thermal history of the amorphous form so generated it may be possible to visualise transformations to less stable polymorphs.

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