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Characterisation of solid dispersions of paracetamol and EUDRAGIT® E prepared by hot-melt extrusion using thermal, microthermal and spectroscopic analysis

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Abstract

Hot-melt extrusion has attracted considerable interest within the pharmaceutical industry. However, there remains some uncertainty as to how to characterise the physical structure of the extruded systems, particularly in terms of identifying the nature of the drug dispersion within the polymer. The aim of the study was to develop a combined thermal, imaging and spectroscopic approach for the identification and characterisation of the drug and polymer structure. Solid dispersions containing 10% and 20% paracetamol in EUDRAGIT® E were prepared by hot-melt extrusion into elongated strands. Differential scanning calorimetry (DSC) run at scanning rates up to 100 °C/min, modulated temperature DSC, microthermal analysis (μ-TA) and Attenuated Reflection Fourier Transform IR (ATR-FTIR) were used to characterise the systems. It was noted that the glass transition of the dispersions were considerably lower than the polymer alone, indicating dispersion of the drug in the polymer on a molecular basis. However, thermal and spectroscopic evidence was also obtained for the presence of crystalline drug at the 10% and 20% loadings, indicating that the drug was present in two physical forms simultaneously. Furthermore, both ATR-FTIR and microthermal analysis indicated that the drug crystals were preferentially located in the centre, rather than on the surface, of the extrudate. The study has indicated that the dispersion of the drug in the polymer may be complex in terms of both physical form and spatial distribution, with potential ramifications for stability and dissolution kinetics. In addition, the investigation has indicated that the combined approach outlined here is highly appropriate, as no single technique may yield all the required information.

Keywords: Thermal; Solid dispersion; Hot-melt extrusion; Spectroscopy

1. Introduction

Hot-melt extrusion (HME) has increasingly been reported in the pharmaceutical literature as a means of preparing solid dispersions of drugs in polymers (Follonier et al., 1994; Breitenbach, 2002; Ghebre-Sellassie and Martin, 2003; Repka et al., 2002). The process involves embedding drugs into a polymeric material either in dissolved form or as a separated phase via heating until softening occurs, and shaping the extrudates into different forms for corresponding delivery purposes (Follonier et al., 1994, 1995; Breitenbach, 2002; Miller et al., 2007; Aitken-Nichol et al., 1996; Nakamichi et al., 2001). The technique has advantages over other solid dispersion preparation methods, particularly in terms of being an industrially feasible single step process which does not involve the use of solvents (Follonier et al., 1994, 1995; Breitenbach, 2002). Disadvantages include the use of heat and the observation that the screw extrusion process may exert strong shear forces on the materials. The uneven force distribution in the die during extrusion may possibly lead to the establishment of gradients in the drug distribution in different region cross the extrudates, although little is currently known in this regard.

It is necessary to have a full understanding of the physical state (or states) of the drug in the extruded formulations, as this may profoundly affect both the stability and the dissolution behaviour of the product. It is well known from the solid dispersion field that the active pharmaceutical ingredient (API) may exist in a number of physical states within the polymer

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(Chiou and Riegelman, 1971; Ford, 1986); these include crystalline dispersions, molecular dispersions, amorphous dispersions (whereby the drug is present as a separate amorphous phase) and eutectics, whereby the drug and polymer are codispersed as small crystallites. Previous studies (Six et al., 2003) have indicated that phase separation in melt-extruded formulations can lead to crystallisation or polymorphic conversions of the API. However, identification and prediction of the dispersion state is, perhaps surprisingly, often difficult and the relationship between dispersion and performance, while acknowledged to be of importance, is not yet understood.

In this study, solid dispersions containing paracetamol and EUDRAGIT® E, a copolymer based on dimethylaminoethyl methacrylate and neutral methacrylic esters, were prepared by melt extrusion on a co-rotating twin-screw extruder. Paracetamol is a suitable model for several reasons. Firstly, it exists in three polymorphic forms (Forms I, II and III in decreasing stability and melting point) (Martino et al., 1996; Rossi et al., 2003) and hence provides an interesting system for studying the effects of processing on crystal form. Secondly, amorphous paracetamol has low stability since the glass transition is around 23 °C (Qi et al., accepted for publication). It is, therefore, an ideal model drug for evaluating the capacity of the extruded formulation for drug stability improvement.

The binary system studied here provides a useful means of assessing the combined technique strategy used here for the characterisation of the physical structure of the HME products. EUDRAGITs are amorphous polymers and will therefore have a characteristic T_g. This parameter may be used to assess drug distribution, as an unchanged T_g will imply phase separation while a lowering of this value will imply molecular dispersion of the drug. Similarly, the appearance of two T_gs would imply the existence of a phase separated amorphous polymer and API regions. However, in this study we take the analysis further in three respects. Firstly, we compare the use of modulated, standard and high speed DSC approaches as a means of studying both the glass transition and recrystallisation behaviour. Modulated techniques are now well established, while more recently there has been interest in using high speed techniques due to the possibility of higher resolution and shorter scan times (Saunders et al., 2004). In theory, one should be able to visualise the T_g events with greater clarity due to the scanning rate dependence of the measured power signal, although this may be at the expense of resolution. Secondly, we use Fourier Transform InfraRed (FTIR) spectroscopy to identify the spectroscopic characteristics of the drug in particular. FTIR (or more specifically in this case attenuated total reflection (ATR) FTIR) is a standard technique for drug characterisation; however there has been less work performed on using it in conjunction with thermal methods for binary systems. Finally we use microthermal analysis (μ-TA) as a means of characterising the location and identifying the physical characteristics of the drug and polymer. This technique has been described in detail elsewhere (Reading et al., 2001; Tsukruk et al., 2002) but in essence it involves the replacement of the tip of a conventional atomic force microscope (AFM) with a thermal probe, thereby allowing site-specific physical characterisation. As will be demonstrated, the use of the three approaches in conjunction is a potentially very useful novel approach to characterising drug dispersion systems.

2. Material and methods

2.1. Materials and hot-melt extrusion

EUDRAGIT® EPO was supplied by Röhm GmbH & Co. (Darmstadt, Germany). Paracetamol Form I was supplied by Rhodia (France) with melting point at 168–172 °C. Hot-melt extrusion (HME) was carried out using a Haake Minilab twin-screw extruder (Thermo Electron Corporation, Germany). Screws were co-rotated at a speed of 200 rpm; the temperature applied was 140 °C. At this temperature, dissolution of the paracetamol in the polymer occurred. 50 g of material were extruded with drug loading of 0%, 10% (w/w) and 20% (w/w) paracetamol. The extrudates were collected as strands with diameter of approximately 1.5 mm. The strands produced from the polymer alone and the 10% dispersions were clear in appearance. For the unloaded extrudate and the material containing 10% (w/w) paracetamol a torque of 70 N cm at 140 °C was measured. The 20% dispersion extrudate was opaque in appearance and the corresponding extrusion torque was 60 N cm.

2.2. Differential scanning calorimetry

Conventional and high speed DSC experiments were carried out using Q-1000 MDSC (TA Instrument, Leatherhead, UK) at heating rates of 2, 5, 10, 20, 50 and 100 °C/min. *n*-Octadecane (99.9%, Aldrich, Gillingham, UK), indium (99.999%, Aldrich, Gillingham, UK) and tin (99.999%, Aldrich, Gillingham, UK) were used for temperature calibration. The heat capacity calibration for the modulated temperature DSC (MTDSC) experiments was carried out using aluminium oxide (99.9%, 100 mesh, Aldrich, Gillingham, UK) with an underlying heating rate of 2 °C/min, a period of 60 s and an amplitude of ±0.32 °C, scanning from −20 to 80 °C. The same parameters were applied for the MTDSC experiments on the HME strands. In all DSC experiments TA crimped aluminium pans (TA Instruments, Leatherhead, UK) were used. The moisture contents of the samples were checked using TA 2950 thermogravimetric analysis (TGA) (TA Instruments, Leatherhead, UK), which were all found to be below 0.8% on heating to 160 °C.

2.3. ATR-FTIR measurements

The FTIR was used to identify the presence of phase separation in the HME samples with no information on the spatial distribution of the phases. The IR spectra of the samples were collected using an FTIR spectrometer (BioRad FTS 165 FTIR, Varian Limited, Oxford, UK) with a mercury/cadmium/telluride detector. The HME strands were directly placed on a single-reflection diamond ATR (attenuated total reflectance) accessory (SPECAC, Orpington, U.K.); this modification allows the extrudate to be examined as is without the need for grinding. Fifty scans were acquired for each sample with a resolution of 2 cm^{-1}. All measurements on the side surface and the cross-section

centre surface of the cylinder-shaped extrudates were preformed triplicate. The spectra of paracetamol Forms I and II were taken as reference. Paracetamol Form II was prepared by melting and slow cooling (5 °C/min) of paracetamol Form I, as described previously by Qi et al. (accepted for publication).

2.4. Microthermal analysis (μ-TA)

Microthermal analyses were performed using a Nano Thermal Analyzer (Anasys Instruments, Santa Barbara, USA) with a Veeco diCaliber scanning probe microscope head (Veeco, CA, USA) and a Wollaston wire thermal probe (Veeco, CA, USA). Samples were fixed to the magnetic stub using double-sided tape and mounted onto an *X–Y* translating microscope stage. The instrument was calibrated for temperature and displacement. Poly(e-caprolactone) (PCL with T_m at 60 °C), polyethylene (PE with T_m at 130 °C) and poly(ethylene terephthalate) (PET with T_m at 238 °C) (Anasys Instruments, Santa Barbara, USA) were used as calibrants for temperature calibration; the room temperature 'kick-in point' was used as the other known temperature point for a four points calibration. In this work, localised thermomechanical analysis (L-TMA) was performed using a net 'force' of 10 ± 1 nA and a heating rate of 10 °C/s from 25 to 200 °C on the surface and the cross-section interface of the strands. All L-TMA experiments were repeated five times.

3. Results

3.1. Thermal analysis of extrudates using DSC and MTDSC

3.1.1. Thermal response of drug-loaded extrudates—glassy behaviour

In the first instance, the properties of the raw materials were studied. Crystalline and, to a lesser extent, amorphous paracetamol has been studied by a number of groups (Martino et al., 1996; Rossi et al., 2003) and a recent paper (Qi et al., accepted for publication) has examined the interchange between the amorphous and crystalline forms and the polymorphic transitions undergone by the latter. In brief, amorphous paracetamol has a glass transition of 23 °C and is known to exhibit three crystal forms, a highly unstable Form III which melts at 148 °C, metastable Form II (with melting point of 160 °C) and stable Form I with melting point at 170 °C. This information was used as a reference for these studies.

EUDRAGITs are amorphous polymers and their glass transitional behaviour has been studied previously by several research groups (Wagner et al., 2005; Csóka et al., 2007). EUDRAGIT® E is a copolymer based on dimethylaminoethyl methacrylate and neutral methacrylic esters. Here we have measured the T_g value of the extrudate using MTDSC (Fig. 1a) and see a glass transition at 48.6 °C in the reversing heat flow signal, accompanied by an endothermic relaxation over the T_g region. These endothermic peaks are well known to reflect the time-dependent relaxation of materials when kept below T_g, necessitating energy sorption during heating through the T_g in order to re-establish the volume and enthalpy of the liquid state. However, the presence of this peak is particularly pertinent in this case as there is the potential

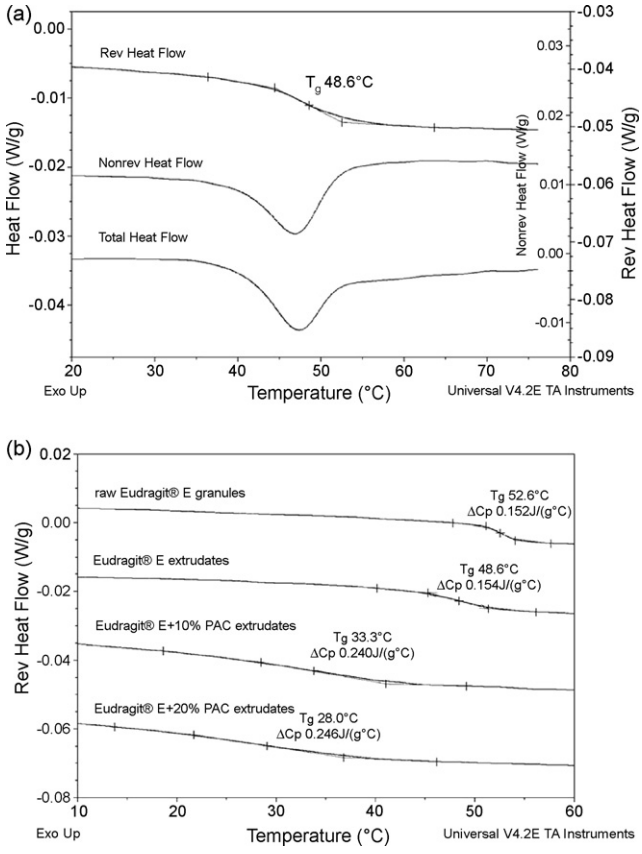

Fig. 1. Modulated Temperature DSC results for hot-melt extruded EUDRAGIT® E and corresponding drug dispersions (a) total, reversing and non-reversing signals of EUDRAGIT® E strands; (b) reversing heat flow signals of EUDRAGIT® E as received and strands, 10% and 20% paracetamol dispersions in EUDRAGIT® E strands.

for confusion with melting and/or dissolution responses associated with dispersed paracetamol, hence it is important to note the presence of this thermal event at this stage.

The reversing heat flow responses of the unloaded, 10% paracetamol and 20% paracetamol systems are shown in Fig. 1b. The reversing heat flow is indicative of the heat capacity of the system and hence allows the operator to visualise the T_g in the absence of the endothermic relaxation. It is interesting to note the lowering of T_g for the polymer alone resulting from the extrusion process. Such process-induced T_g lowering is well recognized in the polymer literature (Mathot, 1994). In particular, the stresses associated with moulding processes may lead to densification which alters the specific volume of the polymer, thereby lowering the T_g. It is also possible that polymer chain orientation effects may play a role. Comparison of the unloaded polymer extrudate with the drug-loaded systems indicated a single T_g for all three systems. It is interesting to note that the T_g was lowered for the disperse systems. More specifically, values of 33.3 °C and 28.0 °C were noted for the 10% and 20% systems, clearly implying that the system had been plasticized by the paracetamol, in turn implying molecular dispersion of the drug.

DSC was then used to study the effect of scanning rate on the dispersions. In the first instance, the effects on T_g are considered. Fig. 2a and b indicate that the T_g increases at higher heating rates.

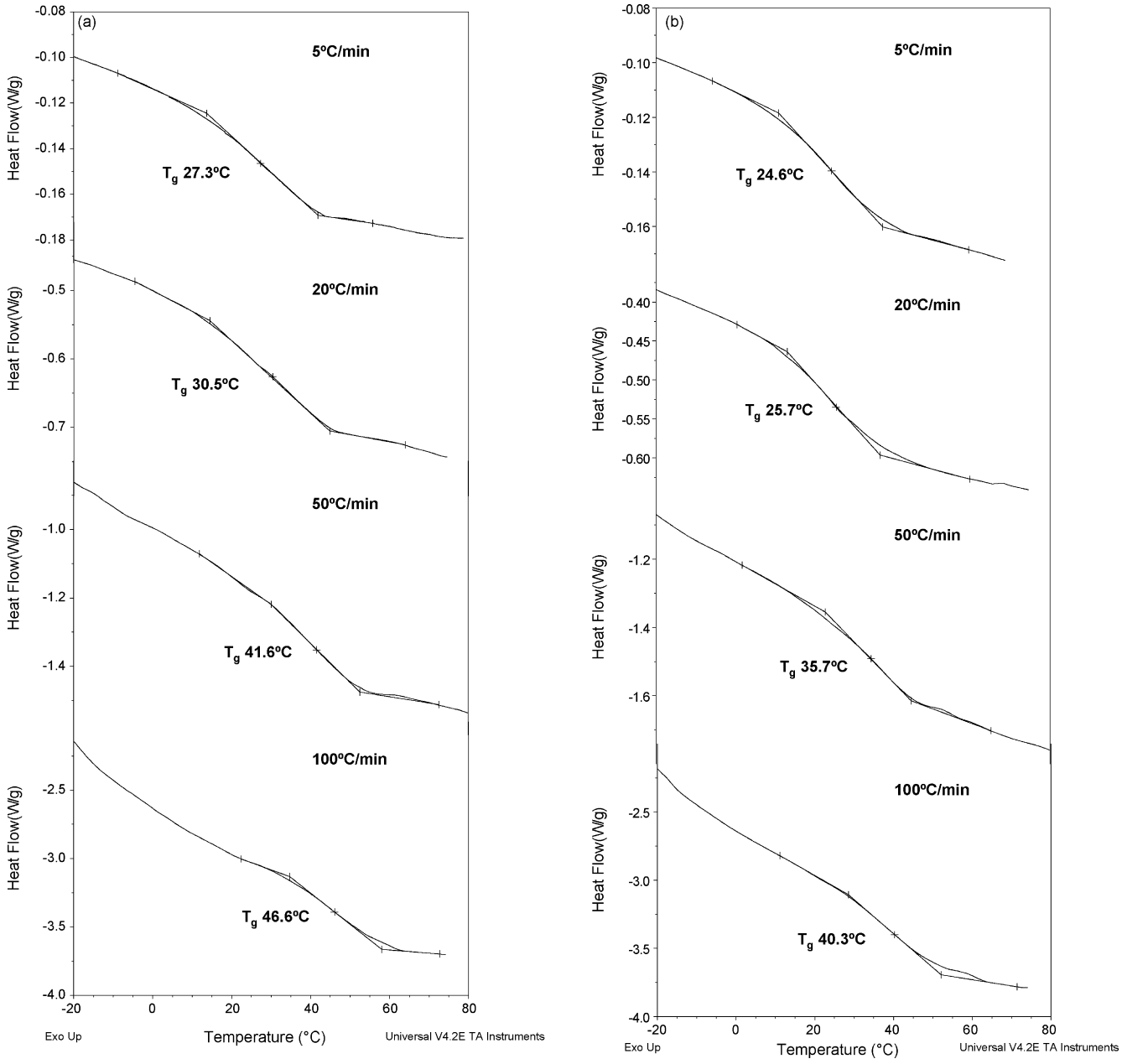

Fig. 2. DSC study of the T_g region of (a) 10% and (b) 20% paracetamol dispersions in EUDRAGIT® E strands detected using different scanning rates.

This is due to the process being an essentially kinetic response to the applied heating signal; we are able to use this heating rate dependence to estimate an activation energy for each system (discussed below).

3.1.2. Thermal response of drug-loaded extrudates—melting behaviour

On considering the higher temperature behaviour (shown separately due to the disparity in energetic magnitude compared to the glassy events), it is necessary to consider that the solubility of the drug in the liquified polymer is such that crystals of paracetamol, if present, may dissolve into the polymer during the experimental run. If this is the case, the use of a range of scanning speeds should allow identification of this phenomenon as one would reasonably expect the dissolution process to be inhibited by the use of higher rates. As seen in Fig. 3a and b, the endothermic transitions of the formulations varied with the concentration of the drug at different scanning rate.

In the case of 10% loaded paracetamol extrudates, no clear endothermic peaks were detected at low rates but on increasing the scan speed to 50–100 °C/min clear evidence of a melting peak was seen at circa 168 °C. The absence of a melting peak at lower temperatures may, as discussed above, be ascribed to gradual dissolution of the drug in the polymer, as has been previously discussed (Lloyd et al., 1997; Harding et al., 2007). On heating at higher rates, the experimental time is greatly reduced and the comparatively slow dissolution process is not seen. At the highest rate used there appears to be some compromise in baseline stability, but nevertheless the evidence for melting is clear. Taken together with the T_g information, the explanations

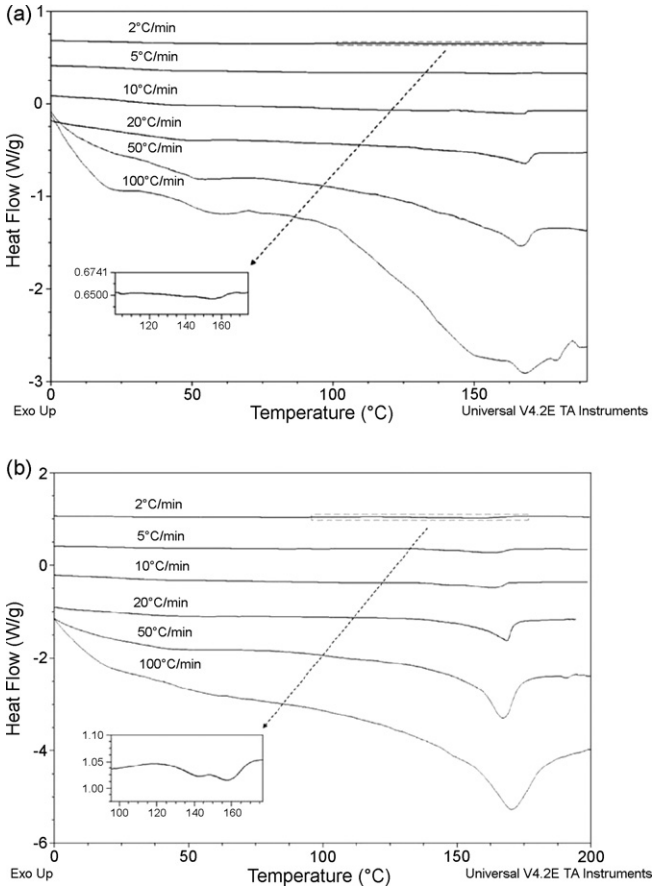

Fig. 3. DSC response in the melting region of (a) 10% and (b) 20% paracetamol dispersions in EUDRAGIT® E strands detected using different scanning rates.

are either that the drug is recrystallising and then melting during the run (which seems extremely unlikely at the high speeds used) or that the drug is present at room temperature in two forms, molecular dispersion and crystals.

The 20% systems show much clearer evidence for the presence of crystalline drug. At the higher rates used (50–100 °C/min) a single melting at 170.3 °C is seen, which corresponds well to the melting of paracetamol Form I. It is interesting to note that the at low heating rates (2 °C/min) there is evidence for one exothermic peak at 120.1 °C followed by a lower endothermic peak at 142.6 °C and a higher endothermic peak at 158.0 °C. The exothermic transition corresponds well with that previously noted for the recrystallisation of paracetamol Form II (Qi et al., accepted for publication). It may be the case that at these rates some recrystallisation of paracetamol takes place, although the multicomponent nature of the material renders direct comparison with the paracetamol alone difficult.

The principal melting peak in corresponds to Form I paracetamol (Qi et al., accepted for publication). In addition, it is possible to use the melting enthalpy for the 50 °C/min system in comparison to that of pure Form I (heat of fusion of paracetamol Form I at 50 °C/min heating rate is 176.6 J/g) to make a rough estimate of the proportion of material that is in the molecularly disperse or crystalline form. This calculation indicates that for the 10% and 20% paracetamol-loaded strands, the crystalline drug load corresponds to circa 1.6% and 8.8%, respectively. This of course assumes that no dissolution has taken place during the run, but nevertheless provides an interesting novel method of estimating the distribution of the drug in two coexisting forms.

3.1.3. ATR-FTIR studies of the dispersions

The FTIR spectra of paracetamol polymorphs have been previously studied (Al-Zoubi et al., 2002) and hence it is possible to compare the data obtained here with previous investigations as well as the spectra generated in this study for the pure components (drug and polymer). As the infrared beam can only penetrate through the samples to a depth of circa 1 μm, it was considered necessary to test both the surface and the cross-section of the extrudate to confirm the homogeneity of the formulation.

The ATR-FTIR spectra of the disperse systems (surface and cross-section) along with pure paracetamol Form I, amorphous paracetamol, and HME EUDRAGIT® E for comparison are presented in Figs. 4 and 5. For the 10% systems the ATR-FTIR results of the surface of the extruded strands show little similarity to the IR spectra of paracetamol in the 3500–2800 cm^{-1} region (Fig. 4a). This may be due to the sensitivity of the technique; the low concentration of paracetamol could contribute to the absence of the paracetamol associated peaks on the spectra. In the 1600–700 cm^{-1} region, some new peaks appear in the spectra of the paracetamol-loaded extrudates, which are absent in the EUDRAGIT® E spectrum, in particular the peak at 1514 cm^{-1}.

Examination of the 900–750 cm^{-1} region (Fig. 4b) reveals a similar set of observations but the increased baseline magnification shows the peaks with considerably greater clarity. There is a peak at 833 cm^{-1} in the spectra of the paracetamol-loaded extrudates that matches the pure material (Fig. 4b). Interestingly, in the extrudate spectra the peak at 807 cm^{-1} shows increased intensity in the cross-section spectrum compared to the extrudate surface. This corresponds to the 805 cm^{-1} peak in pure paracetamol and may indicate a drug concentration difference between the centre and outside surface of the extrudates, although the differences in peak intensity are slight and hence this is merely a tentative suggestion.

For the 20% systems (Fig. 5a), the peak at 1514 cm^{-1} is again seen, although interestingly it is observed with greater intensity for the cross-section compared to the surface. Similarly, in the lower wavenumber region (Fig. 5b) the peak at 805 cm^{-1} cannot be observed clearly in the spectra of the surface but is seen clearly for the cross-section. There is therefore evidence that the dispersion of the drug in the polymer results in changes to the profile, although particular peaks are common to both the pure and dispersed paracetamol. Moreover, there is some evidence that, at least in the 20% systems, the dispersion of the drug may not be homogeneous. For example, as seen in Fig. 5b, the peaks at 835 cm^{-1} (in the spectrum of the extrudates surface) and at 836 cm^{-1} (in the spectrum of the extrudates cross-section) are both asymmetric in shape, possibly as a result of the overlapping of multiple peaks. It is not possible to reliably quantify the relative concentrations in the surface and cross-section samples, given the vagaries of the interpretation of the spectra for the disperse systems and the non-specificity of

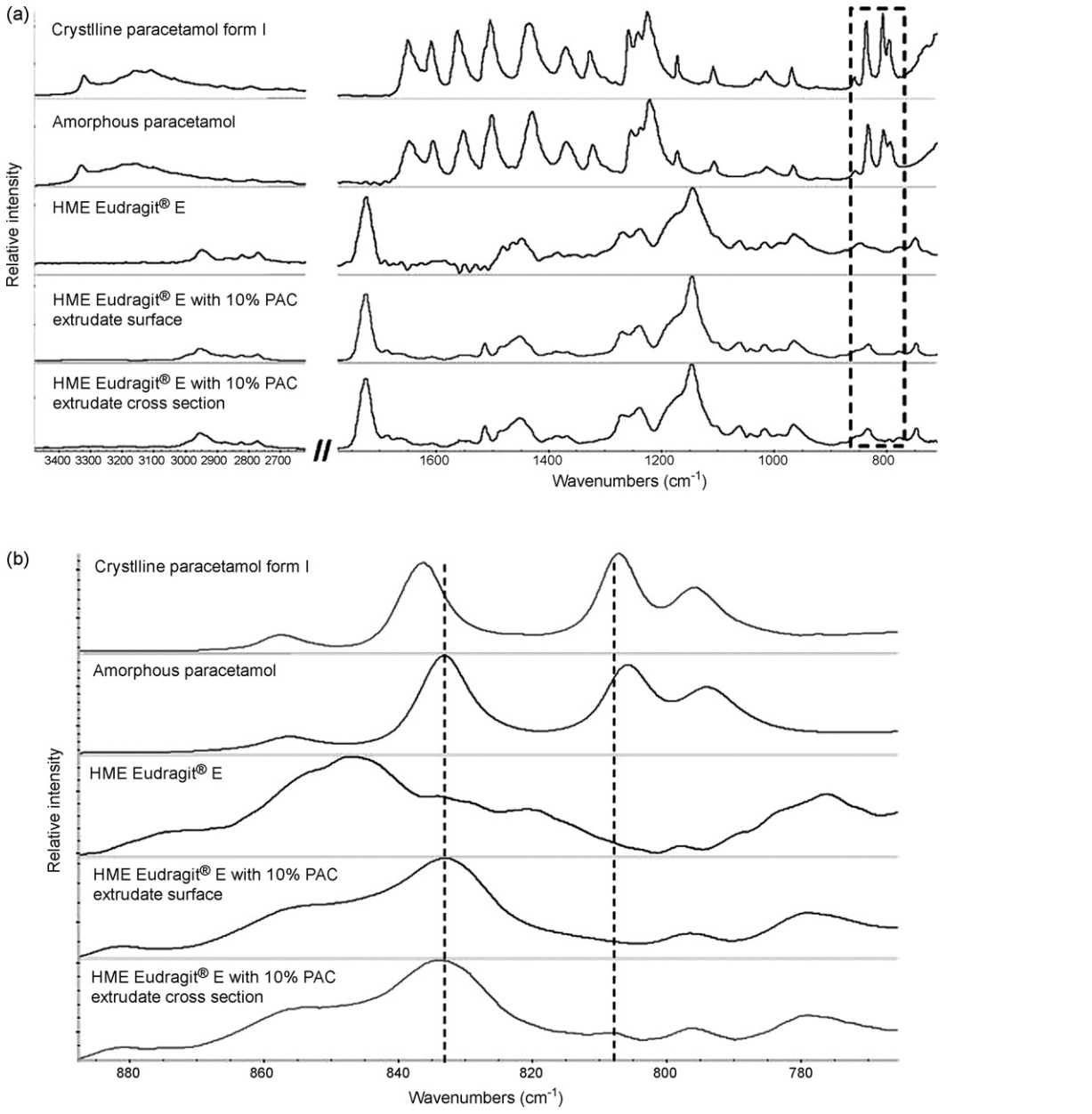

Fig. 4. ATR-FTIR spectrum of the surface and cross-sectional area of 10% paracetamol in EUDRAGIT® E extrudates, showing comparisons to paracetamol Forms I and II (a) full spectra; (b) highlighted 900–750 cm^{-1} region.

the scale of scrutiny involved in the measurement, although the qualitative evidence is reasonably compelling for their being a greater drug concentration within the central region of the extrudates. If verified, this may be of some considerable significance as such non-homogeneity is very likely to be related to performance.

3.1.4. Microthermal analysis of the disperse systems

While the DSC results have provided evidence of the existence of crystalline form paracetamol in both formulations, these data cannot specifically identify the distribution of the drug within the extrudate. On this basis μ-TA was employed to study the surface and cross-sectional samples of the extrudates. In localised thermomechanical analysis (L-TMA) mode, the sensor position of the heated tip was measured, thereby allowing identification of sample softening under the tip as a function of temperature.

The L-TMA results on the surface of the 10% paracetamol strands showed a penetration around 58 °C (Fig. 6a). Given the presence of the glass transition noted from the DSC and the recognized higher values for T_g previously noted for microthermal studies (Royall et al., 2001), it is reasonable to suggest that this corresponds to the observed glass transition. The discrepancy between DSC and μ-TA measurements of this event are believed to be either due to superheating through the T_g or to the fact that the measurement is essentially a thermomechanical one and hence corresponds to softening rather than T_g itself which, at these high scan speeds, will be observed at an elevated temperature. No direct evidence for the melting of the paracetamol particles was detected.

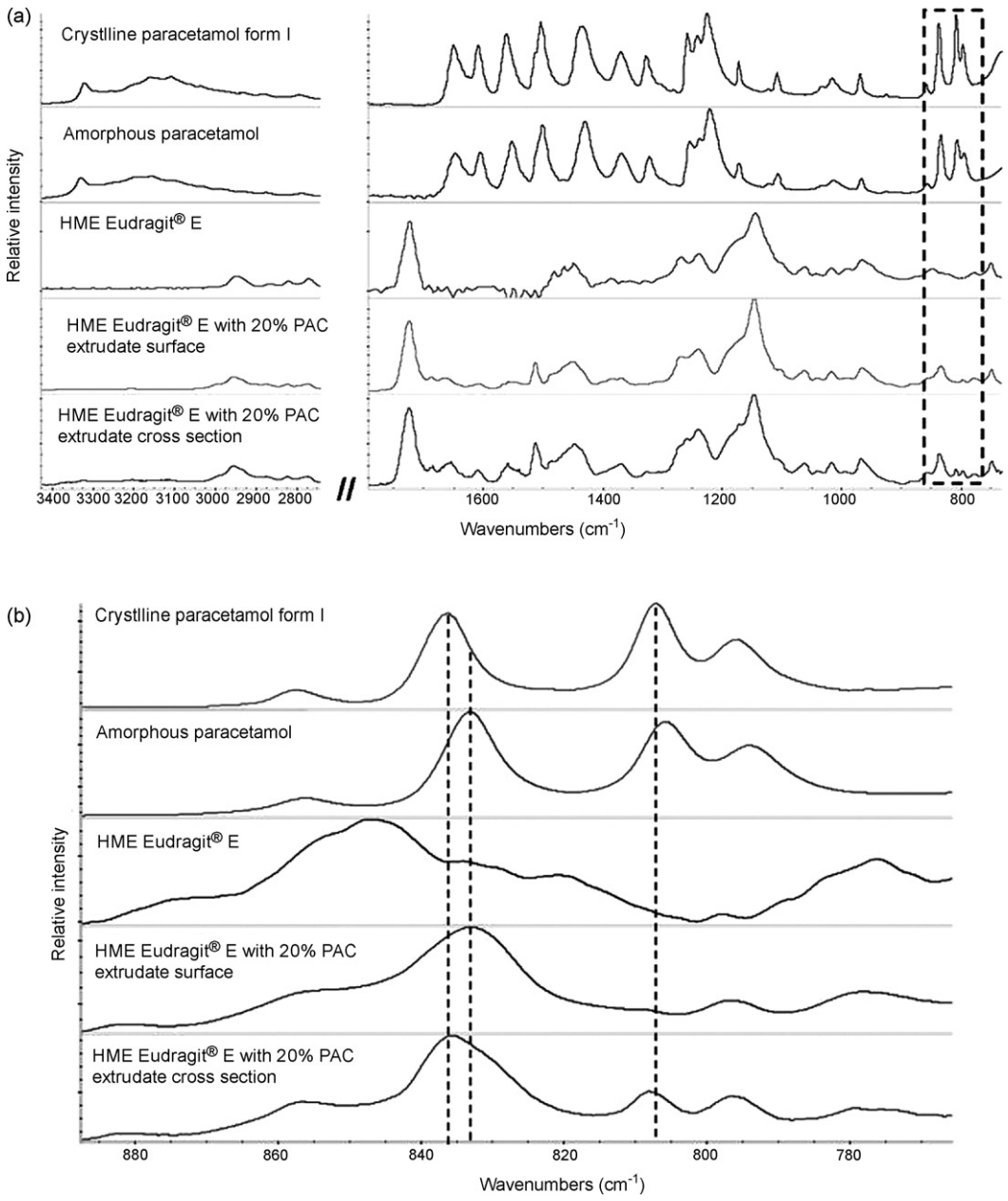

Fig. 5. ATR-FTIR spectrum of the surface and cross-sectional area of 20% paracetamol in EUDRAGIT® E extrudates, showing comparisons to paracetamol Forms I and II (a) full spectra; (b) highlighted 900–750 cm^{-1} region.

The measurements performed on the surface of the 20% loaded strands were highly reproducible (Fig. 6b); a single penetration of the tip was detected at around 62 °C on the surface of the samples. However, when the analyses were performed on the center of strands (cross-section), the sensor response varied dramatically with the location of the measurement taken place. Single and double transitions were detected, with the latter showing penetration temperatures in the region of 158–160 °C, corresponding to the melting of crystalline Form I paracetamol. This provides additional evidence to the ATR-FTIR and DSC results in that, taken together, the data indicate that crystalline paracetamol is preferentially located in the interior of the extrudates, at least at 20% loading.

4. Discussion

The study has addressed the issue of how a model drug is dispersed in an extruded polymer (EUDRAGIT® E), with a view to developing a combined analytical approach that will allow the physical structure of the dispersed drug to be ascertained. Three variants of DSC were employed (MTDSC, conventional DSC and DSC run at relatively high heating rates). It should be noted that it is possible to run the samples at considerably higher rates using custom-built equipment, although it is felt that the basic principle being investigated is demonstrated here using a maximum rate of 100 °C/min.

In the first instance it is clear from the MTDSC studies that there is considerable plasticisation of the polymer by the drug,

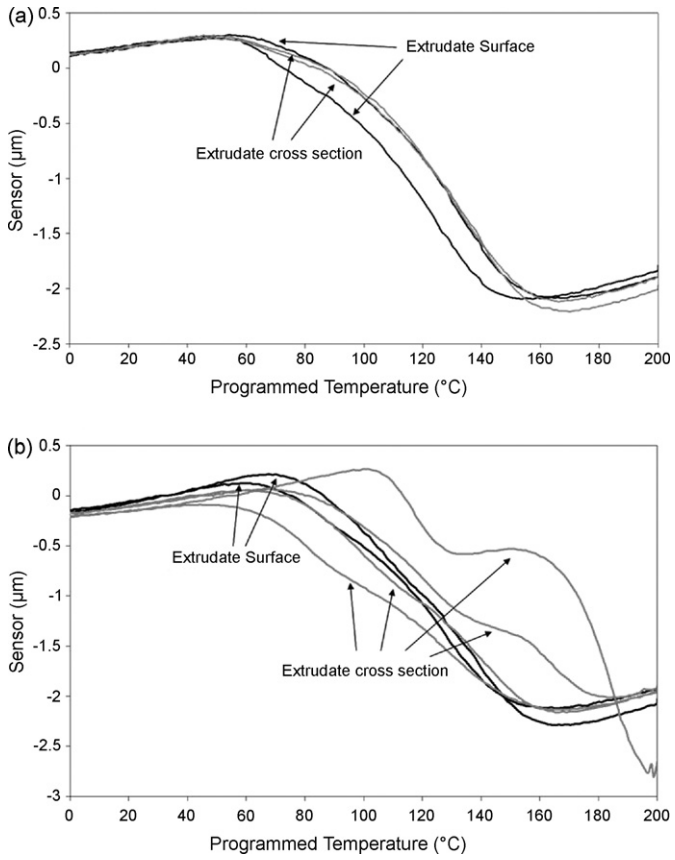

Fig. 6. Microthermal analysis of (a) 10% and (b) 20% paracetamol dispersions in EUDRAGIT® E extrudates, showing representative curves from the surface and centre of the extrudates.

implying the presence of molecularly dispersed drug. The T_g of the amorphous paracetamol is around 25 °C, whereas the T_g of EUDRAGIT® E is 48 °C. If the two components are miscible (molecularly dispersed which leads to a single mixed T_g), the T_g of the extruded samples can be predicted using Gordon–Taylor expression, shown as below:

$$T_g = \frac{w_1 T_{g_1} + K_{w_2} T_{g_2}}{w_1 + K_{w_2}} \quad (1)$$

where the K is a model specific parameter, i.e., $K_{GT} = (\rho_1/\rho_2)(\Delta\alpha_2/\Delta\alpha_1)$. ρ_i are the densities and $\Delta\alpha_i = (\alpha_{melt} - \alpha_{glass})_i$ the increments at T_g of the expansion coefficients of the mixed components. In most mixing systems, the components have very similar densities, and one can consider $(\rho_1/\rho_2) \approx 1$. In this case, the Gordon–Taylor equation can be simplified to the Fox equation:

$$\frac{1}{T_g} = \frac{w_1}{T_{g_1}} + \frac{w_2}{T_{g_2}} \quad (2)$$

If one assumes complete dispersion of the drug in the polymer, the calculated T_g values are 46.2 °C and 43.4 °C for the 10% and 20%, respectively. The experimental values are somewhat lower than this (33.3 °C and 28.0 °C, respectively), besides which it is proposed that not all the drug is molecularly dispersed in the polymer in any case. However, these expressions are approximations only, besides which the possibility of densification differences and minor levels of water sorption may also contribute to the observed effects. The key point remains that a single, lower T_g is seen for the drug dispersions compared to the extruded polymer which in turn clearly implies some degree of molecular dispersion.

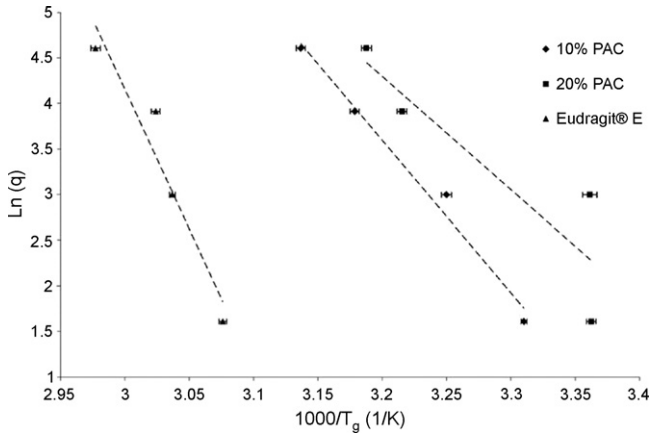

Fig. 7. Plots of ln(q) against inverse glass transition (1000/K) of HME EUDRAGIT® E, 10% paracetamol in EUDRAGIT® E extrudates, and 20% paracetamol in EUDRAGIT® E extrudates.

The scanning rates were also varied, allowing assessment of the effect of scanning speed on the T_g. It is possible to approximate the activation energy of the glass transition for the two dispersions using Eq. (3), as follows:

$$\frac{d\ln|q|}{d(1/T_f)} = -\frac{E_a^*}{R} \quad (3)$$

where E_a^* is the activation energy, R is the gas constant, q as cooling/heating rate, and T_f is the fictive temperature. As seen in Eq. (3), $-E_a^*/R$ is the slope of the plot $1/T_f$ against ln(q). 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. In most cases, T_f values are around 1 °C different to the T_g values (Hancock and Zografi, 1997; Claudy et al., 1997; Badrinarayanan et al., 2007), hence in this study T_f was replaced by the experimental T_g as a reasonable approximation. Fig. 7 shows the plots of ln(q) against inverse T_g (plotted as $1000/T_g$ for clarity) from which the values of E_a^* are calculated as 254.6 kJ/mol for HME EUDRAGIT® E, 139.2 kJ/mol and 103.3 kJ/mol for the 10% and 20% systems, respectively. The fragility index (m) of the extrudates then can be calculated using Eq. (4), as expressed below:

$$m = \frac{d\log_{10}(\tau)}{d(T_g/T)} = \frac{E_a^*}{2.303RT_g} \quad (T = T_g) \quad (4)$$

Fragility is a measure of the rate at which properties such as viscosity and relaxation time change as the glassy state is approached. The fragility index has been commonly used for characterising glassy materials, with strong and fragile (weak) glasses having values of $m < 100$ and $100 < m < 200$, respectively (Borde et al., 2002). Fragile systems are typically held together by weak isotropic bonds such as van der Waals interactions, while strong glasses are typically composed of stronger, often

covalent bonds that form three dimensional networks. The calculated fragility index values are 41.3 for HME EUDRAGIT® E, 23.7 for 10% paracetamol-loaded systems and 17.9 for 20% systems. The fragility index of amorphous paracetamol has been previously reported as 86.7 (Qi et al., accepted for publication).

The conventional and fast DSC studies yielded evidence for the presence of crystalline paracetamol in the dispersions and also allowed calculation of the approximate proportion in the crystalline form. The presence of crystalline drug, at least in the 20% systems, was further supported by the FTIR and μ-TA studies, with both indicating a much greater preponderance of the drug in the centre rather than the surface of the polymeric extrudates.

Taken together the study has both indicated the complexity of the nature of the dispersion, despite it being a binary system, as well as the absolute necessity of using several techniques to study these systems. Evidence has been presented for the drug simultaneously existing as both a molecular dispersion and as a crystalline phase. This in not in itself counterintuitive (an aqueous suspension may contain both solid and dissolved drug, for example) but this type of combined dispersion has not been extensively described or identified. The techniques used all appeared to have strengths and limitations which were largely complimentary. MTDSC is an excellent method for studying glass transitions but the slow scanning speeds render it susceptible to kinetic processes occurring during the experimental run due to the scanning rate limit of circa 2 °C/min. Conventional and faster DSC progressively overcome the difficulty of kinetic effects but at the possible expense of baseline stability. FTIR was not able to clearly discern crystalline paracetamol in the 10% dispersions but was able to identify the drug in the higher concentration systems, as well as indicating a greater concentration in the centre of the strands. The latter was also indicated using MTA, although the poor resolution of the Wollaston probes (circa 10 μm^2) is almost certainly a serious drawback for studying such disperse systems; the use of the recently introduced nanoprobes (Harding et al., 2007) should address this issue in the future.

5. Conclusion

The study has highlighted the remarkable complexity that an apparently simple two-component system may exhibit in terms of the distribution of the drug in the polymeric matrix. There are three key findings to the present investigation. Firstly, thermal analysis indicated evidence for both the 10% and 20% systems containing drug dispersed on both a molecular and particulate (crystalline) basis. While it is widely recognized that drugs may be dispersed in polymers on either a molecular or particulate basis, there is very little information available that addresses the possibility of the drug being present in both forms simultaneously. Secondly, evidence has been presented for the drug being concentrated preferentially in the centre of the extrudate. Both of these findings may be of profound importance in understanding physical stability and dissolution kinetics. Finally, the study has demonstrated the advisability of using a range of characterisation techniques (thermal, spectroscopic, microscopic) as each provides information that is complimentary to the others. In particular we describe the use of microthermal analysis as a means of performing site-specific studies on the extruded materials, an approach that may prove to be of increasing importance given the finding that drug distribution may not be automatically assumed to be homogeneous.

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