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Investigation of preparation methods on surface/bulk structural relaxation and glass fragility of amorphous solid dispersions

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ABSTRACT

The objective of this study was to investigate the effect of preparation methods on the surface/bulk molecular mobility and glass fragility of solid dispersions. Solid dispersions containing indometacin and PVP K30 were chosen as the model system. An inverse gas chromatography method was used to determine the surface structural relaxation of the solid dispersions and these data were compared to those for bulk relaxation obtained by DSC. The values of τ^{β} for the surface relaxation were 4.6, 7.1 and 1.8 h for melt quenched, ball milled and spray dried solid dispersions respectively, compared to 15.6, 7.9 and 9.8 h of the bulk. In all systems, the surface had higher molecular mobility than the bulk. The glass fragility of the solid dispersions was also influenced by the preparation methods with the most fragile system showing the best stability. The zero mobility temperature (T_0) was used to correlate with the physical stability of the solid dispersions. Despite having similar T_g (65 °C), the T_0 of the melt quenched, ball milled and spray dried samples were 21.6, −4.2 and 16.7 °C respectively which correlated well with their physical stability results. Therefore, T_0 appears to be a better indicator than T_g for predicting stability of amorphous materials.

1. Introduction

The difficulty in delivery of poorly soluble drug substances can be addressed by use of amorphous forms, but there are concerns with respect to the stability of such systems, with a risk of crystallisation causing a slowing of dissolution rate as a function of storage time. Physical stability testing of amorphous forms is problematic as storage at stressed conditions can be misleading as the sample can move to the rubbery rather than glassy state, making extrapolation difficult. Real time storage is more reliable, but obviously it is time consuming. Therefore, some alternative methods have been used to try to predict the stability of amorphous materials. Among these methods, relaxation assessment has been conventionally used since it can provide useful information about the molecular mobility of the product and therefore its shelf-life.

Some studies on polymers have shown that the molecular mobility at the surface should be differentiated from the bulk (Tanaka et al., 1996; DeMaggio et al., 1997; Kajiyama et al., 1997), since surface mobility of polymers has important implications for friction, lubrication, adhesion and any applications involving polymer modification by way of coatings (Fakhraai and Forrest, 2008). The study of surface molecular mobility for pharmaceutical materials is also of importance because the surface properties can affect the surface wetting, diffusion and interaction between different materials. A number of studies have indicated the necessity of studying surface crystallisation of amorphous materials. For example, Wu and Yu (2006) found that the surface of indometacin crystallised at a faster rate than the bulk. Wu et al. (2007) investigated a method of using nano-coating to inhibit surface crystallisation of indometacin. Zhu et al. (2010) studied the crystal growth rates of amorphous griseofulvin below its glass transition temperature (T_g) and it was found that its surface crystallisation dominated the overall crystallisation kinetics of the amorphous powders. It was concluded by Zhu et al. (2010) that surface crystallisation should be distinguished from the bulk.

Relaxation studies may become a fast and useful way by which to predict the crystallisation tendency of amorphous materials and as such provide valuable information for use during formulation design and product manufacturing. There are several techniques that have been used for measurement of bulk relaxation such as dielectric relaxation spectroscopy, isothermal calorimetry, and differential scanning calorimetry (DSC) (Caron et al., 2010); however, none of these techniques can be used to study surface relaxation. In the pharmaceutical field, the lack of an efficient technique for fast determination of surface relaxation has limited the understanding of the molecular mobility at the surface. Inverse gas

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chromatography (IGC) has been widely used to measure isotherms, surface free energy, heat of sorption and surface heterogeneity (Newell et al., 2001; Roubani-Kalantzopoulou, 2004). IGC can also be used for some specific applications such as differentiating small but functionally significant levels of amorphous content between samples and measuring glass transition temperature as a function of relative humidity or temperature (Surana et al., 2003; Buckton et al., 2004). In a previous study, the authors have developed an inverse gas chromatography method using the retention volume of decane to study the structural relaxation at the surface of an amorphous solid dispersion system and it was found that IGC can be a potential powerful technique for surface molecular mobility measurement (Hasegawa et al., 2009).

The decane retention volume method was therefore applied in this study to investigate the surface relaxation of amorphous polyvinylpyrrolidone (PVP) and indometacin solid dispersions prepared using different methods (ball milling, spray drying and melt quenching). Previous studies have shown that the physical properties of an amorphous material could be greatly affected by the way it was prepared (Surana et al., 2004), but the understanding of the effect of preparation methods on solid dispersions is limited (Patterson et al., 2007). Moreover, the effect of preparation methods on the surface molecular mobility is not known. It is understood that amorphous materials can have varying amounts of molecular order, but that they lack the long range packing order that is a characteristic of a crystal. The hypothesis in this study is that since different preparation methods can generate amorphous materials of different structure, surface and bulk properties of the amorphous forms will vary independently to each other as a function of preparation method. The aim was to compare the surface relaxation, measured using IGC, with the relaxation of the bulk measured using DSC, and to see to what extent these two relaxation rates predicted the long term stability of otherwise identical amorphous materials made using different methods.

Apart from molecular mobility, other parameters, such as T_g are often used to attempt prediction of the physical stability of an amorphous solid. In order for an amorphous form to have good stability it is necessary for it to have a high T_g. When the storage temperature is too close to or even higher than the T_g, the glassy sample will transform into the rubbery state which gives rise to physical collapse and crystallisation (te Booy et al., 1992). Although a high T_g is important, it is still difficult to predict the stability of amorphous materials using T_g alone. Many studies have been conducted in the past by different researchers to find out some other useful predictors for good amorphous stability. Apart from molecular mobility which is considered as the main factor governing physical stability (Andronis and Zografi, 1997; DiMartino et al., 2000), the relationship of thermodynamic factors such as entropy, enthalpy and Gibbs free energy to amorphous stability was studied in some other cases (Zhou et al., 2002; Marsac et al., 2006). Zhou et al. (2002) found that together with molecular mobility, configurational entropy could help to predict the physical stability of amorphous pharmaceuticals. In another study, Marsac et al. (2006) found that nifedipine which had a larger enthalpic driving force for crystallisation and lower activation energy for nucleation crystallised more readily than felodipine. Graeser et al. (2009) studied configuration entropy in relation to amorphous stability above T_g, however due to the non-equilibrium nature of the glassy state, thermodynamic considerations cannot be easily applied below the T_g. As the name implies, the zero mobility temperature (T_0) is the temperature at which molecular mobility would effectively stop in an amorphous sample, and is the point where the temperature has been decreased sufficiently below T_g, that the configuration entropy will reach zero (Hatley, 1997). Therefore, T_0 would be the highest storage temperature for amorphous materials at which the crystallisation tendency would be minimised. In this study, the glass fragility of the solid dispersion system prepared by different methods was measured and the fragility values were used to determine T_0. The extent to which T_0 was able to predict the stability of the amorphous form was assessed by comparison to long term stability storage tests.

2. Material and methods

2.1. Material

γ-indometacin was obtained from Tokyo Kasei. PVP K30 was purchased from BASF Corporation. All reagents used were of analytical grades.

2.2. Methods

2.2.1. Preparation of solid dispersion by ball milling

A Fritsch Pulverisette 5 planetary mill (Fritsch, Idar-Oberstein, Germany) was used for preparing ball milled solid dispersions. 5 g of indometacin and PVP powders with a ratio of 70:30 (w:w) was weighed carefully into a milling pot. The weighing process was conducted in a glove bag with N_2 flowing through to keep the relative humidity (RH) below 10% and the pot was wrapped with parafilm before moving it out from the glove bag to prevent moisture getting in during milling. The powders were then milled for 18 h at 300 rpm to achieve complete amorphous state conversion. The milled powders were removed from the pot (in the dry glove bag) and passed through a 90 μm sieve to break down any lumps (also in the glove bag) and then kept in a vacuumed desiccator over phosphorus pentoxide (P_2O_5) at room temperature.

2.2.2. Preparation of solid dispersion by spray drying

Indometacin and PVP (70:30, w:w) was spray dried using a GEA Niro SD MICRO™ spray dryer (Niro, Soeborg, Denmark) equipped with a nitrogen generator (Dominick Hunter, Gateshead, UK). 200 mL of ethanol was used to dissolve indometacin and PVP. The feed concentration in the solvent was 1.5% (w/v) and 30 min were allowed for the drug and carrier to dissolve completely into the solvent. The solution was then spray dried using the following parameters: atomiser gas flow 2.5 kg/h; chamber inlet flow 30.0 kg/h; inlet temperature 80 °C; and feeding rate 20%. The spray dried samples collected were passed through a 90 μm sieve and then dried in a vacuumed desiccator over P_2O_5 at room temperature for at least 2 h before any further study.

2.2.3. Preparation of solid dispersion by melt quenching

3 g of indometacin and PVP (70:30, w:w) physical mixtures were weighed into a crucible and then placed in an oven which was set at 175 °C. The physical mixtures were heated for 15 min to allow complete melting of the ingredients. In the time points of 5 and 10 min, the crucible was taken out and the melted liquid was stirred gently using a small spatula. This was to help the components to mix properly and prevent phase separation. After heating, the crucible was immediately placed on liquid N_2 for quench cooling. A glassy amorphous solid (appeared as a hard cake) was formed and it was kept in a vacuumed desiccator over P_2O_5 at room temperature for 1 h for drying and to allow the cooled sample to recover to room temperature. The sample was ground using a pestle and mortar and sieved through a 90 μm sieve in a glove bag and the powders was dried in the desiccator (0% RH and room temperature) for another 1 h.

2.2.4. Inverse gas chromatography for surface relaxation measurement

The IGC instrument used for this study was made by Surface Measurement Systems (London, UK). 500–800 mg of powder samples were weighed accurately and loaded into a pre-silanised glass

column followed by 15 min of tapping. Columns filled with this mass achieved infinite dilution conditions when probe vapour was injected. The packed column was placed in the column oven and conditioned at 25 °C and 0% RH for 10 h in order to eliminate any moisture (helium was used as the carrier gas at a flow rate of 20 mL/min). Then decane with a concentration of $0.03p/p^0$ (p^0 represents the saturated vapour pressure of the liquid probe at the experimental temperature) was repeatedly injected for up to 24 or 48 h with the column oven temperature set at 50 °C. Methane was injected in between of decane injections as an internal reference. The signal recording time for decane was 30 min while the one for methane was 15 min. The net retention volume of decane can be calculated according to the following equation:

$$V_n = \frac{j}{M} F(t_r - t_m)\frac{T}{273.15}$$

where V_n is the net retention volume, t_r and t_m are the retention time of decane and methane, T is the column temperature, M is the sample mass, F is the exit flow rate of the carrier gas at 1 atm and 273.15 K, and j is the James–Martin compressibility correction factor for correction of the retention time affected by the pressure drop in the column. V_n is proportional to the surface partition coefficient between mobile and stationary phase, K_S, which is essentially an equilibrium constant and it is related to the standard free energy of adsorption, ΔG_a. Therefore, V_n can also be related to ΔG_a, by:

$$-\Delta G_a = RT \log K_S = RT \log V_n + c$$

where R is the gas constant and c is a constant related to the surface area of solid phase and the reference state for the adsorbed molecule. The IGC experiment was controlled by software SMS IGC controller V1.5 and data were analyzed using a SMS IGC analysis macros V1.2 (Surface Measurement Systems, London, UK).

2.2.5. Differential scanning calorimetry for glass transition temperature characterisation

A Pyris 1 DSC (PerkinElmer Instruments, Beaconsfield, UK) which was connected to an Intracooler IIP unit (PerkinElmer Instruments, Beaconsfield, UK) was used for the study. Calibration was carried out using pure indium (T_m = 156.6 °C). Measurements were performed under a N_2 gas purge at a flow rate of 20 mL/min. Samples were heated using the step-scan mode: starting temperature: 0 °C, heating rate: 10 °C/min, step: 2 °C, isothermal time per step: 1 min and repeats: 100 times. The onset temperature of the glass transition was used through out this study.

2.2.6. Enthalpy recovery measurement of the solid dispersions

About 5 mg of solid dispersion was loaded in a non-hermetically sealed aluminium pan and stored in a desiccator over P_2O_5 at 50 °C. After different periods of aging time (0, 2, 4, 8, 16/24 and 48 h), the pans were taken out and their enthalpy of relaxation was determined using the Pyris 1 DSC with step-scan mode as stated above. For each aging time point, 3 sample pans were prepared and measured. Indium was used as the reference for DSC calibration. The enthalpy of relaxation was then fitted into the Kohlrausch–Williams–Watts (KWW) equation to obtain relaxation parameters τ (the relaxation time constant) and β (distribution of the relaxation time constant, $0 < \beta \leq 1$). Origin version 7.0 was used for this fitting.

2.2.7. Fragility measurement of the solid dispersions

The glass fragility of the samples was obtained using the dependence of glass transition temperature on heating rate. The Pyris 1 DSC was used for this study. Dry, high purity N_2 gas with a flow rate of 40 mL/min was purged through the sample. A two-point temperature calibration was performed at each heating rate (2, 5, 10, 20 and 40 °C/min) using the extrapolated onset of melting temperature (T_m) and fusion of melting (ΔH_m) of indium and n-decane (T_m = −29.7 °C). Frequent calibration checks were conducted during the experiment. About 5–6 mg of samples were accurately weighed into non-hermetically sealed pans. The samples were first heated to 20 °C over its T_g in order to remove any moisture sorbed and thermal history and then cooled to at least 50 °C below T_g at a cooling rate that equalled the subsequent heating rate. The sample was then heated at different heating rate and the onsets of T_g were recorded. All T_g obtained were an average of three measurements.

2.2.8. X-ray powder diffraction (XRPD)

An X-ray diffractometer (Philip PW3710, Holland) was used for the characterisation of the amorphous samples using copper radiation $K_{\alpha1}$ and $K_{\alpha2}$ with tube power of 45 kV voltage and 30 mA current. The powder sample was loaded and flattened on a copper plate and placed into the detection chamber of the XRPD. The X-ray patterns were obtained using a step of 0.02° in a 2θ range of 5–40°, with a rate of one second per step.

2.2.9. Scanning electron microscopy (SEM)

All samples tested were manually dispersed onto a carbon tab adhered to an aluminium stub using a micro-brush. Samples were gold-coated prior to viewing using a sputter coater (Emitech K550X, Texas, USA) and scanned using a Phillips SEM (XL30, Cambridge, UK) to study their morphology, with magnifications of 5 and 10 μm. The acceleration voltage was 10–12 kV.

2.2.10. Thermal gravimetric analysis (TGA)

A TGA (PerkinElmer Instruments, Beaconfield, UK) was used to detect the moisture level of the samples. About 10–20 mg of sample was weighed and scanned from 30 to 200 °C at a heating rate of 20 °C/min. Nitrogen purge was applied at a flow rate of 20 mL/min.

2.2.11. Evaluation of the physical stability of the solid dispersions

All three solid dispersion systems were stored in a desiccator over saturated NaCl solution to achieve an RH of 75% at room temperature for a certain period of time. The physical stability of these samples was monitored by XRPD using parameters stated above.

3. Data analysis

In order to estimate the minimum (convergent) retention volume after infinite aging time, a modified Kohlrausch–Williams–Watts equation was applied:

$$V_n = V_{min} + A \exp\left(-\left(\frac{t}{\tau}\right)^{\beta}\right)$$

where t is the aging time, and A is the pre-exponential factor. When t becomes infinite, $A \exp(-(t/\tau)^{\beta})$ approaches zero which leads to the convergent retention volume V_{min}. The decane retention volumes obtained were then normalised using the equation below and fitted to the KWW equation:

$$\phi(t) = 1 - \frac{(V_n - V_{min})}{(V_{max} - V_{min})}$$

where V_{max} is the maximum retention volume of decane obtained. Origin version 7.0 was used for this fitting.

The T_g of the samples obtained under different heating rate can be used to calculate the activation enthalpy of structural relaxation ΔE_{T_g} (which can be obtained from the slope of a plot of $1/T_g$ against $\log q$) according to an equation applied by Moynihan et al. (1974):

$$-\frac{\Delta E_{T_g}}{R} = \frac{d(\log q)}{d(1/T_g)}$$

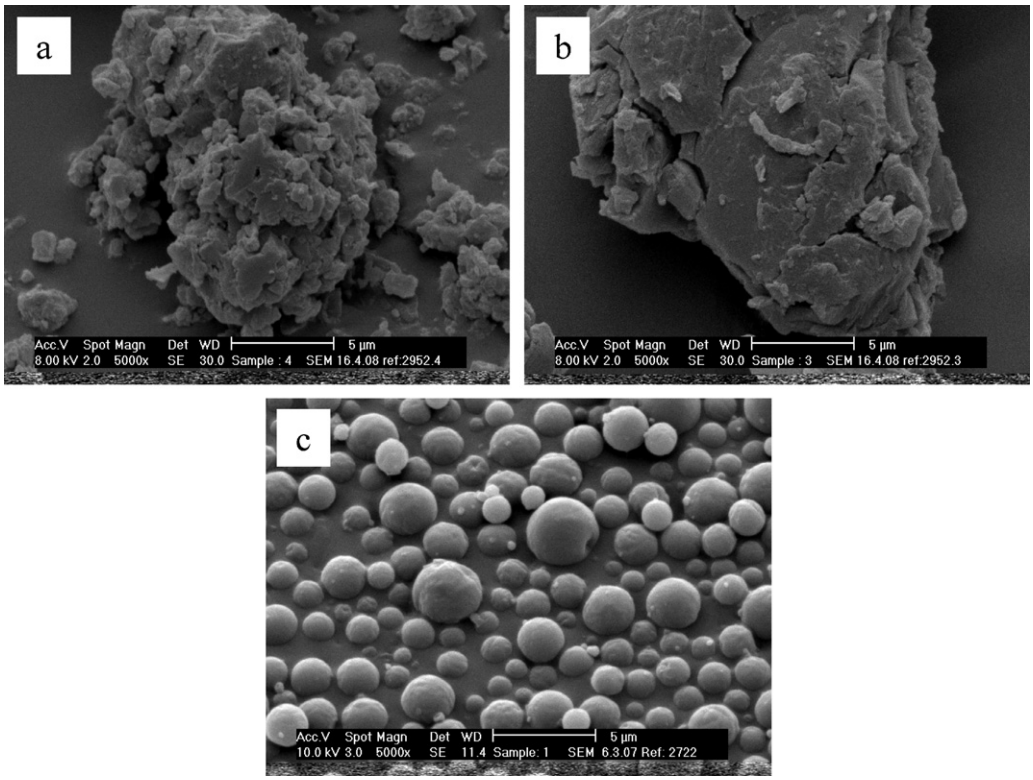

Fig. 1. SEM images of (a) ball milled, (b) melt quenched and (c) spray dried solid dispersions.

where R is the gas constant ($R = 8.3145\,\mathrm{J\,K^{-1}\,mol^{-1}}$) and q is the heating/cooling rate. Fragile glasses which display non-Arrhenius behaviour usually have a large ΔE_{T_g} close to T_g and therefore a less significant effect of heating rate on T_g (Crowley and Zografi, 2001).

The fragility parameter, m, defined as the slope of the $\log_{10}\tau$ versus T_g/T line at the glass transition temperature ($T = T_g$), can be expressed in the equation below:

$$m = \left[\frac{d\log_{10}\tau}{d(T_g/T)}\right]_{T=T_g}$$

where τ is the relaxation time constant and it would slow down to 100 s at T_g according to a previous study (Zallen, 1983). The equation above can also be expressed in terms of ΔE_{T_g}:

$$m = \frac{\Delta E_{T_g}}{(\log_{10})RT_g}$$

A large value of m indicates a fragile glass and a small value indicates a strong one. According to m, T_0 can be calculated using the following equation (Yoshioka and Aso, 2005):

$$T_0 = T_g\left(1 - \frac{m_{\min}}{m}\right)$$

where $m_{\min}$ is the minimum value of m and it is defined as $m_{\min} = \log(\tau_{Tg}/\tau_0)$. Because τ_{Tg} is approximate 100 s, with τ_0 which is a constant that represents the lifetime of atomic vibrations being 10^{-14} s, $m_{\min}$ can be calculated to be 16.

4. Results and discussion

4.1. Physical characterisation of solid dispersions

Scanning electron microscopy was used to study the morphology of the solid dispersions (Fig. 1). The spray dried particles were spherical in shape with a size of less than 5 μm. The ball milled and melt quenched samples appeared to be of irregular shape with a particle size of around 20 μm. Different preparation methods generated different particle surface. Spray dried particles were relatively smooth without any obvious defects while ball milled particles were visually the roughest. This was due to the progressive milling, in which mechanical energy from the colliding balls generates defects and destruction to the particles.

XRPD measurements were carried out to confirm the amorphous content of the solid dispersions prepared by different methods. All systems were completely amorphous according to the XRPD (Fig. 2). Moisture content or any residual organic solvent would affect the relaxation behaviour of a sample greatly because they can act as a plasticiser to reduce the T_g of the sample and increase its molecular mobility. Therefore, before the freshly prepared solid dispersions were examined, they were allowed to dry in a vacuumed desiccator over P_2O_5 to minimise any moisture or organic solvent residual (in the case of spray drying). Thermal gravimetric analysis results of the solid dispersions after drying

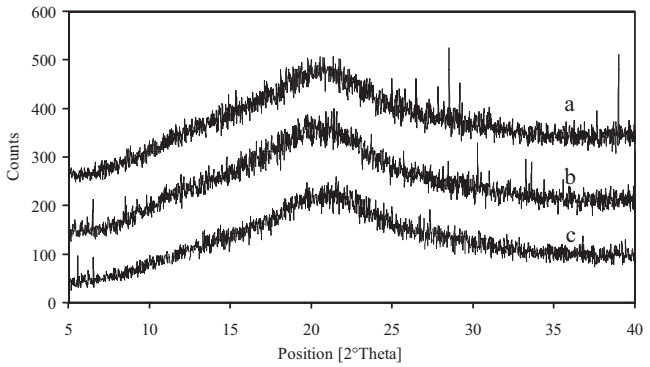

Fig. 2. XRPD pattern of (a) ball milled, (b) melt quenched and (c) spray dried solid dispersions.

Table 1
Glass transition temperature and change of heat capacity of the solid dispersions determined by step-scan DSC and the loss on drying determined by TGA ($n = 3$).

Preparation method	T_g (onset)	ΔC_p (J/g°C)	Loss on drying (% w/w)
Ball milling	64.0 ± 1.47	0.26 ± 0.03	0.44 ± 0.04
Melt quenching	67.3 ± 0.58	0.25 ± 0.01	0.35 ± 0.05
Spray drying	64.7 ± 1.81	0.29 ± 0.05	0.63 ± 0.11

are shown in Table 1. All systems showed a low loss on drying. The samples were also tested by step-scan DSC. For all systems, a single T_g was noticed and no melting of indometacin was observed (Fig. 3). The T_g values for all the samples were around 65 °C, although the melt quenched sample had the highest value and the ball milled one had the lowest (Table 1).

4.2. Determination of bulk structural relaxation using differential scanning calorimetry

The enthalpies of recovery of solid dispersions prepared by ball milling, melt quenching and spray drying respectively after aging for different periods of time are shown in Fig. 4. In order to eliminate the "frequency effect" and "temperature scan effect", the raw endotherm traces of samples aged for different times were subtracted by the one obtained from the time zero samples. As shown in Fig. 4, the solid dispersions have all shown a gradual increase in the enthalpy of recovery as aging time increased. This indicated structural rearrangement of the glassy sample towards the equilibrium state. The enthalpy relaxation data of the solid dispersions were normalised and fitted to the KWW equation in order to obtain the τ and β values. The solid dispersions prepared by different methods have shown different relaxation behaviours (Table 2). The relaxation time constant τ^{β} was used to evaluate the relaxation rate of these three systems because of its lower sensitivity to experimental error (Liu et al., 2002). The τ^{β} of the spray dried solid dispersion is in good agreement with that obtained by Matsumoto and Zografi (1999), which was 10.0 h compared to 9.8 h in the current study. According to the relaxation parameter, the molecular mobility of the systems was in the order of melt quenched, spray dried and ball milled from low to high. During structural relaxation, a sample starts to deviate from its initial glassy state, where the configurations were "frozen in" during processing, towards the equilibrium supercooled liquid state (Liu et al., 2002). Hence the relaxation can be expected to be dependent on the preparation methods.

The β values of the solid dispersions were compared and found to be different for the samples prepared by different methods, with the melt quenched sample having the most homogeneous distribution of relaxation and the ball milled one the least. This large distribution in relaxation of the ball milled sample indicates that it is heterogeneous at a molecular level. During milling, strong mechanical forces occur which can help to facilitate the incorporation of drug and carrier (Gupta et al., 2003). Heat might be generated in the local collision region between the balls and the wall of the pot, which could help to dissolve the drug into a carrier with good miscibility. However, ball milling does not generate the same heat as that used for melt quenching so it is unlikely that there is complete melting of indometacin and PVP, and certain that there is no dissolution into a solvent (which is what occurs prior to spray drying). Therefore a one-phase system with complete miscibility of the drug and carrier is difficult to achieve by milling, but more understandable by processes of melt quenching and spray drying. Patterson et al. (2007) studied the effect of different preparation methods on the physical properties of some drugs compounded with PVP and it was found that the ball milled carbamazepine and PVP was less homogenous than the melt quenched and spray dried ones. Though modulated-temperature DSC only detected a single T_g on the ball milled carbamazepine and PVP sample suggesting a one-phase system, Raman mapping data had indicated that there was evidence for small clusters of carbamazepine rich areas in the sample, therefore, complete glass solution formation had not occurred (Patterson et al., 2007). In the current study, small clusters of drug or PVP rich areas might appear in the ball milled solid dispersion leading to a less homogeneity compared to the other two systems.

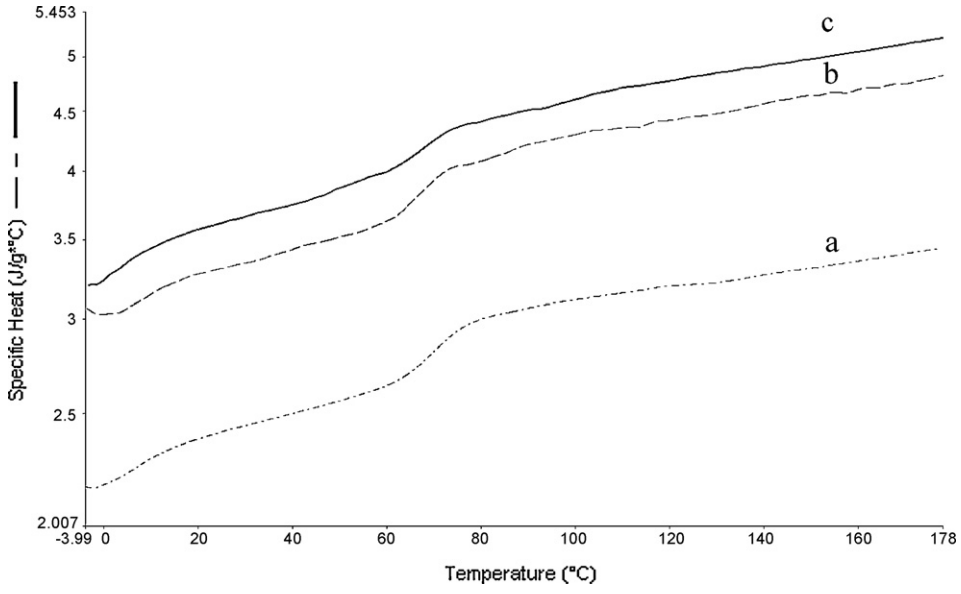

Fig. 3. Step-scan DSC traces of the (a) ball milled, (b) melt quenched and (c) spray dried solid dispersions.

Table 2
A comparison of the surface (IGC) and bulk (DSC) relaxation (R^2, coefficient of determination).

Preparation method	IGC (surface)				SSDSC (bulk)			
	τ (h)	β	τ^{β} (h)	R^2	τ (h)	β	τ^{β} (h)	R^2
Melt quenching	13.1	0.60	4.6	0.9904	47.7	0.71	15.6	0.9733
Ball milling	50.8	0.50	7.1	0.9575	59.6	0.50	7.9	0.9865
Spray drying	2.8	0.60	1.8	0.9756	39.9	0.62	9.8	0.9785

4.3. Determination of surface structural relaxation using inverse gas chromatography

IGC is an inverse version of the gas chromatography technique. In conventional gas chromatography the solid phase is the material with known physicochemical properties and the vapour phase is the sample to be investigated, with IGC the solid is the unknown and the injected vapours are known. IGC has been increasingly used to characterise the surface energy of solids (Thielmann, 2004). Since the structural relaxation might be defined as a loss of energy during aging (Liu et al., 2002; Kawakami and Pikal, 2005), measuring the decrease of dispersive surface energy of an amorphous solid during aging by IGC should be able to provide information regarding its surface structural relaxation. The dispersive surface energy of a solid can be obtained by measuring the V_n of a series of alkanes purging through the column. In a previous study, the authors found that the surface energy of an amorphous system decreased during aging which confirmed the decrease of surface energy during relaxation (Hasegawa et al., 2009). However, error was associated with variability in the measurement of the rapid clearance of the lower alkanes from the IGC column. Considering that V_n of a known probe can also be related to the energy state of the surface of a solid, it should be able to reflect surface structural relaxation. Therefore, decane was chosen as the only probe to be injected for the acquisition of the relaxation profile because of its longer retention time, i.e. higher interaction potential with the solid and accordingly higher sensitivity.

The V_n values of decane for the solid dispersions as a function of the aging time are shown in Fig. 5. Although, there was slight difference in the absolute value of the retention volume for each batch of the solid dispersions prepared using the same method, which might be due to a difference in the surface area and/or the morphology, the general trend was similar. For all samples, V_n of decane decreased as the aging time increased. The spray dried solid dispersion displayed a steep drop of V_n in the first 3–5 h and reached a plateau very quickly. In the case of ball milled and melt quenched solid dispersions, the decrease of V_n was slower. In order to have a clear view of the relaxation behaviours, the V_n data obtained were normalised to perform a KWW fitting as described. Once the surface relaxation parameters were acquired, they were compared to that of the bulk relaxation obtained from the DSC study. The comparison of the KWW fitting obtained using IGC and DSC data is shown in Fig. 6. For all solid dispersions, the surface showed higher molecular mobility than the bulk. In polymer science, Fakhraai and Forrest (2008) studied the surface relaxation of polystyrene using atomic force microscopy and the surface relaxation was observed at all temperatures studied from 4 to 96 °C with enhanced surface mobility relative to the bulk. A previous study showed that the surface crystallisation of amorphous nifedipine was found to be an order of magnitude faster than the bulk when below T_g and a thin coating

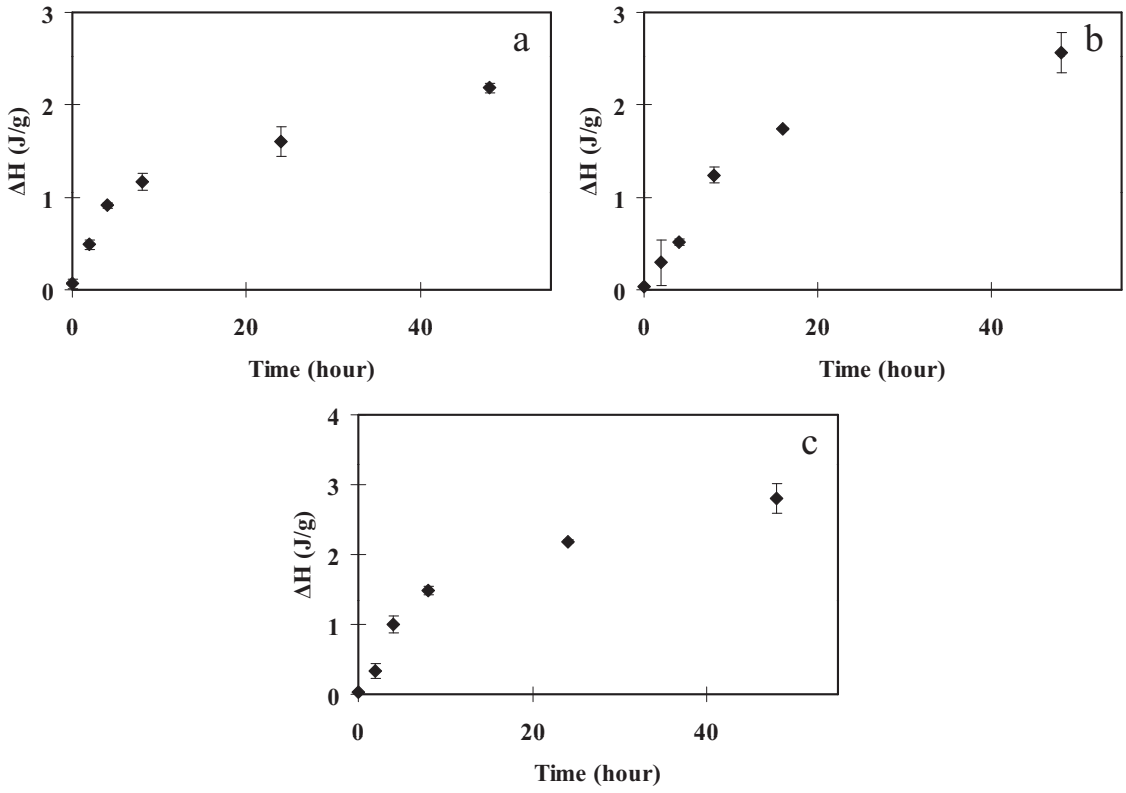

Fig. 4. Enthalpy recovery of (a) ball milled, (b) melt quenched and (c) spray dried solid dispersions aged at 50 °C as a function of time, determined by SSDSC ($n = 3$).

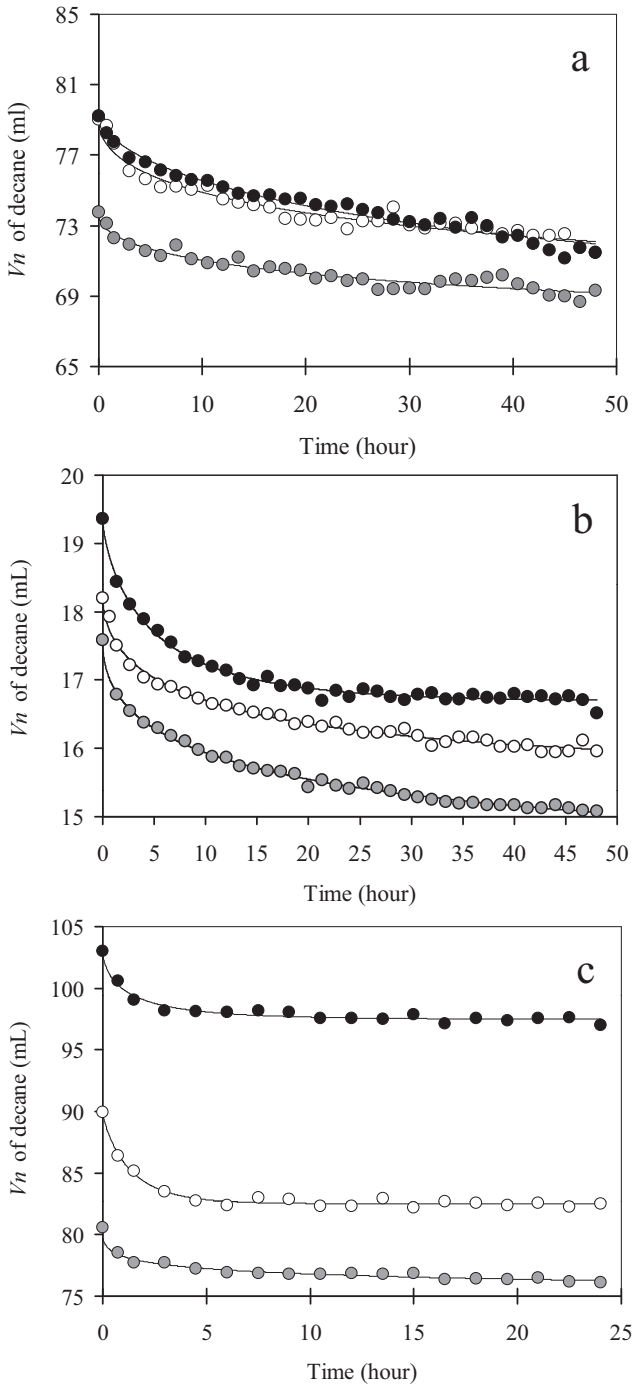

Fig. 5. Change of V_n of decane at 50 °C as a function of aging time: (a) ball milled, (b) melt quenched and (c) spray dried solid dispersions.

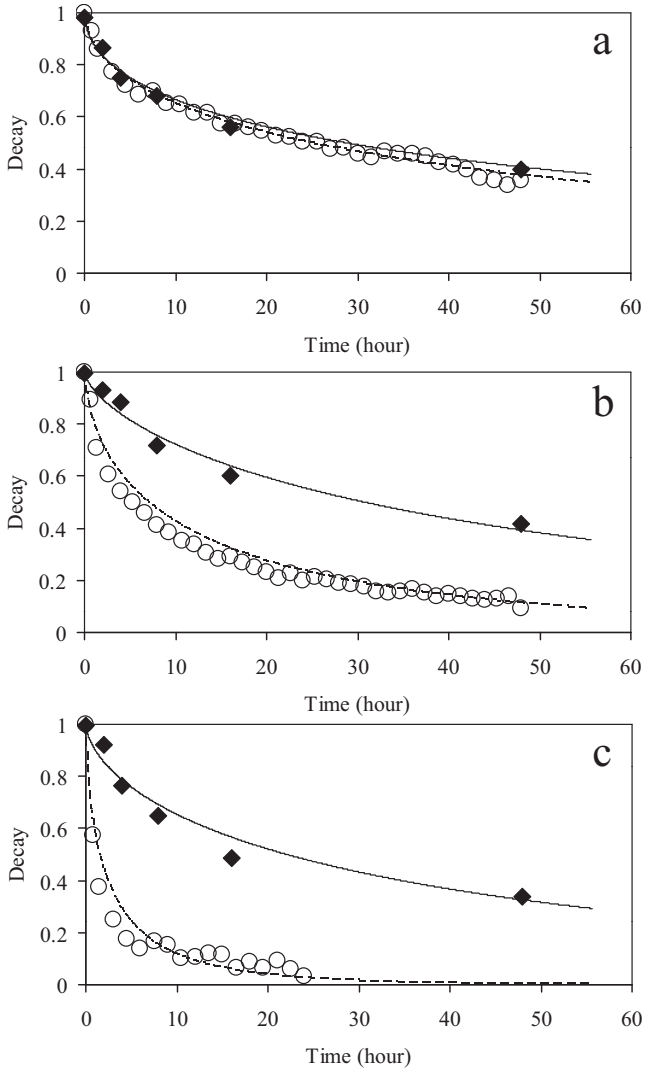

Fig. 6. KWW fitting of the IGC and DSC data of the (a) ball milled, (b) melt quenched and (c) spray dried solid dispersions aged at 50 °C. "♦" represents the DSC data and "—" indicates the KWW fitting; "○" represents the IGC data and "- - -" indicates the KWW fitting.

of gold (10 nm) could reduce the surface crystallisation rate to that of the bulk (Zhu et al., 2008). A faster crystallisation at the surface might be related to a higher surface molecular mobility compared to the bulk, and this might be a result of the temperature and humidity effects at the surface. The preparation methods resulted in different surface relaxation which confirmed the hypothesis of this study. The surface of the ball milled sample showed the slowest relaxation but the spray dried sample relaxed the fastest. The difference between the surface and bulk relaxation is obvious in melt quenched and spray dried samples. However, in the case of the ball milled sample, the difference was not as significant. It was expected that the ball milled sample should have the fastest surface relaxation, since strong mechanical stress was applied on the particle surface. The surface of sample might absorb the excess free energy leading to a higher molecular mobility at the surface. However, this slow relaxation of the ball milled sample, which is in keeping with its bulk relaxation, indicates that although this sample is the most heterogeneous overall, the surface and bulk are not readily discriminated (essentially being equally heterogeneous) Fig. 7.

4.4. Fragility, zero mobility temperature and their relationship with long time amorphous stability

It is important to understand how molecular mobility of amorphous materials changes with temperature, because this can help one to decide a suitable storage condition that can reduce the rates of any physical or chemical degradation of these materials to an acceptable range (Crowley and Zografi, 2001). The strong/fragile classification system developed by Angell (1995) can help to predict the behaviours of molecular mobility of amorphous materials around their T_g. For a solid solution system in which two solids are ideally mixed, there should be only one fixed fragility value, however, in reality, this is difficult to achieve. Therefore, the fragility

Table 3
A table of fragility and other related values of the solid dispersions prepared by different methods (T_g values are mean ± s.d., $n = 3$).

Preparation method	T_g ($q = 10$ °C/min)	ΔE_{T_g} (kJ/mol)	m	D	T_0 (°C)	$T_g - T_0$ (°C)
Ball milling	66.4 ± 0.4	498.8	77	9.7	−4.2	70.6
Melt quenching	65.2 ± 0.7	804.3	124	5.5	21.6	43.6
Spray drying	66.5 ± 1.1	708.1	109	6.3	16.7	49.8

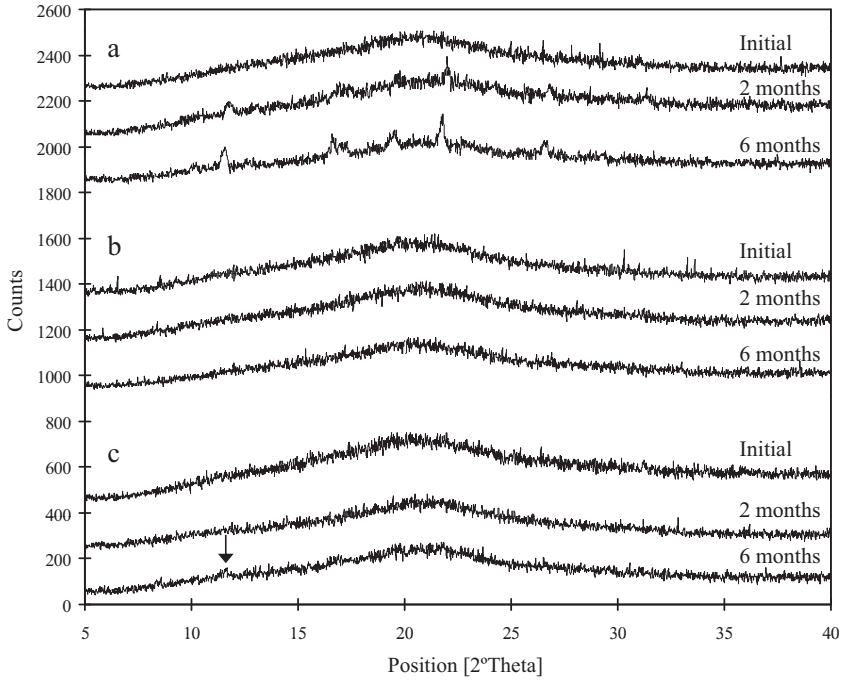

Fig. 7. XRPD patterns of the (a) ball milled, (b) melt quenched and (c) spray dried solid dispersions stored at room temperature and 75% RH for 0, 2 and 6 months.

value might vary depending on the status of the mixture and in this case, how the mixture is prepared. The fragility parameters of the solid dispersions are shown in Table 3. The fragility parameters indicate that all three systems were fragile with the melt quenched sample being the most fragile glass and the ball milled being the least fragile. Different preparation methods therefore have different impacts on the fragility of the solid dispersions. While the ball milled, melt quenched and spray dried samples have similar T_g, at the same aging temperature, the fragile sample would appear to be more stable than the strong one, because the viscosity of a fragile glass decreases more drastically as a function of temperature decrease below T_g. Pikal et al. (1995) also suggested that a higher fragility might provide a better stability if the glass transition temperatures are the same.

The glass transition temperature is often considered to be an important factor relating to the stability of a glass, and the higher the T_g value the more stable the glass would be at a particular storage temperature. However, some studies have shown that this is not necessary the case (Tarelli et al., 1994; Hatley and Colaco, 1997). Zero mobility temperature, T_0, instead can be a better measure of stability than T_g. T_0 is a hypothetical temperature representing infinite viscosity (zero mobility). If the T_0 is low, the storage temperature required for minimising crystallisation is also low. Therefore, theoretically, T_0 should be the highest storage temperature to be confident of physical stability for amorphous solids. Despite the solid dispersions have similar T_g, their T_0 are different to each other as shown in Table 3, hence, these samples should have different shelf life at the same storage temperature (above T_0). To confirm this, a long term stability study was conducted to differentiate the stability of the solid dispersions. The ball milled sample had partially recrystallised after 2 months, followed by the spray dried one which partially recrystallised after 6 months as characteristic peaks of crystalline indometacin were observed. The XRPD patterns of the melt quenched solid dispersion did not show any significant change after storage for 6 months indicating the sample still remained in its amorphous form. This result correlates well with the rank order of the T_0 value. The T_0 values were also found to be in good correlation with the rank order of the bulk molecular mobility of the solid dispersions (Table 2), and molecular mobility has been widely used for prediction of the stability of amorphous materials. Therefore T_0 can be a very useful indicator for the prediction of stability of amorphous materials. In addition, though the components are the same, the technique used for preparation of solid dispersions can greatly affect the stability of the final products.

5. Conclusions

The IGC decane retention volume method was applied to evaluate the surface molecular mobility of the PVP–indometacin solid dispersions prepared by ball milling, melt quenching, and spray drying. The surface relaxation was then compared to the bulk relaxation obtained from the enthalpy relaxation detected by step-scan DSC and it was found that the surface relaxed faster than the bulk, especially for spray dried and melt quenched samples. The ball milled sample was more heterogeneous than the spray dried and melt quenched samples, but its surface and bulk relaxation behaviour were more similar. The glass fragility of the solid dispersions was measured using the heating rate dependence of the glass transition temperature. From the fragility parameter, the zero mobility temperature of the samples was obtained. Samples prepared using different methods were shown to have different fragility and zero mobility temperatures. Physical stability data

were obtained by storing the solid dispersions at 25 °C 75% RH, and the stability profiles of the samples were seen to be related to their fragility, zero mobility temperature and molecular mobility. The most fragile system presented the best stability. Zero mobility temperature was shown to be very useful in predicting the physical stability of the amorphous samples made by different methods. Though the T_g of the solid dispersions were close to each other, their T_0 were very different, and the rank order of T_0 matched well with the physical stability data. This study showed that the preparation methods can significantly affect the physical stability of amorphous solid dispersions. Therefore, the effect of preparation method should be taken into account when preparing a stable amorphous solid dispersion. In this instance bulk mobility was different to surface mobility, but it was bulk mobility that correlated most closely to the long term storage stability of the amorphous dispersions made by different methods. It is not necessarily the case that it will always be bulk relaxation that is the best predictor of stability, as other samples, unlike the model system used here, may well undergo surface crystallisation.

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