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Quantifying the rates of relaxation of binary mixtures of amorphous pharmaceuticals with isothermal calorimetry

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ABSTRACT

While the use of isothermal calorimetry to quantify the rate of relaxation of one-phase amorphous pharmaceuticals, through application of models, is well documented, the resolution of the models to detect and quantify relaxation in systems containing two independent amorphous phases is not known. Addressing this knowledge gap is the focus of this work. Two fitting models were tested; the Kohlrausch–Williams–Watts model (KWW) and the modified-stretch exponential (MSE). The ability of each model to resolve relaxation processes in binary systems was determined with simulated calorimetric data. It was found that as long as the relaxation time constants of the relaxation processes were with 10^3 of each other, the models could determine that two events were occurring and could quantify the correct reaction parameters of each. With greater differences in the time constants, the faster process always dominates the data and the resolving power of the models is lost. Real calorimetric data were then obtained for two binary amorphous systems (sucrose–lactose and sucrose–indomethacin mixtures). The relaxation behaviour of all the single components was characterised as they relaxed individually to provide reference data. The ability of the KWW model to recover the expected relaxation parameters for two component data was impaired because of their inherently noisy nature. The MSE model reasonably recovered the expected parameters for each component for the sucrose–indomethacin system but not for the sucrose–lactose system, which may indicate a possible interaction in that case.

1. Introduction

The increasing prevalence of BCS (Biopharmaceutics Classification System) Class II drugs (i.e. those with poor aqueous solubility) presents a considerable formulation challenge. An attractive strategy is formulation in an amorphous form (Hancock and Parks, 2000) since the absence of any structural order and crystal lattice energy mean dissolution of amorphous materials is usually rapid (and often results in generation of a supersaturated concentration). However, the amorphous form is thermodynamically unstable and the material will relax with time, leading eventually (at least if it is a small molecular weight organic) to a crystal form. Quantifying the rate of relaxation is thus critical for formulation of a successful medicine (Hancock and Zografi, 1997; Hilden and Morris, 2004; Kaushal et al., 2004; Bhugra and Pikal, 2008) and is underpinned by the need for analytical methodologies capable of quantifying relaxation rates.

The majority of the stability studies in the literature have dealt with single-phase amorphous pharmaceutical systems. Examples include either pure, amorphous, active pharmaceutical ingredients (APIs) and excipients (Hancock et al., 1995; Haque et al., 2006; Liu et al., 2002; Kawakami and Pikal, 2005; Van den Mooter et al., 1999) or amorphous solid solutions (in which the API is molecularly dispersed within an inert matrix) (Aso et al., 2004; Hasegawa et al., 2009; Korhonen et al., 2008; Matsumoto and Zografi, 1999; Shamblin and Zografi, 1998). A formulation could, however, consist of more than one amorphous phase (for instance, if an amorphous excipient is added to a formulation already containing an amorphous API). Amorphous solid suspensions are another good example. Methods of quantifying relaxation in two-phase amorphous systems have not been widely discussed and are the topic of this work.

Using isothermal microcalorimetry (IMC) as the method of analysis, we show how simulated data can be used to define the experimental limits within which classical models of amorphous relaxation (Kohlrausch–Williams–Watts (KWW) and modified-stretch exponential (MSE) functions) can discriminate between relaxation of two discrete phases. We then apply the models to two real co-formulated amorphous systems; sucrose–lactose and sucrose–indomethacin.

2. Materials and methods

Crystalline sucrose (HPLC grade, ≥99.5%) was purchased from Fluka. α-Lactose monohydrate was supplied by Merck Sharp and Dohme Laboratories (Hoddesdon, UK). Crystalline indomethacin

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(>99%) was purchased from Molekula Ltd; acetone (>99%) was purchased from Fisher Scientific. Materials were used as received.

Two binary amorphous systems were prepared: sucrose–lactose and sucrose–indomethacin. Amorphous sucrose and lactose were prepared by spray drying. A 12% (w/w) solution was prepared by dissolving the appropriate sugar in a distilled water:acetone (3:2) solvent system; the solution was then spray-dried using an SD Niro (GEA Niro, Denmark) spray-dryer, employing the following spray-drying parameters: inlet temperature – 90 °C, outlet temperature – 56 °C, chamber gas flow – 30 kg/h, atomising gas flow – 2.5 kg/h.

The amorphicity of the spray-dried samples was confirmed with X-ray powder diffraction (XRPD). Gravimetric analysis revealed that the sucrose and lactose samples had 1.7 (±0.1)% and 2.5 (±0.1)% moisture content, respectively. Samples were sieved and stored at −20 °C until use.

Amorphous indomethacin was prepared by melt-cooling. Crystalline indomethacin, pre-weighed and sealed in air-tight glass ampoules, was melted at 175 °C for 5 min. The molten material was then spread around the inner walls of the ampoule and immediately cooled under tap water. XRPD analysis showed production of amorphous indomethacin. The advantage of adopting this preparation method was that the sample was not exposed to any mechanical stress (usually exerted by liquid nitrogen in quench-cooled samples) that can affect sample behaviour (Bhugra et al., 2008). Amorphous indomethacin samples were analysed gravimetrically and were found to contain less than 0.2% moisture.

Sucrose–lactose binary systems were prepared by directly loading 300 mg of each sugar in glass ampoules (3 mL volume). The powders were dry-blended by mixing with a small spatula. Ampoules were sealed with a crimped metal cap. A rubber sealing disc ensured an air-tight seal. The process was conducted inside a nitrogen-filled glove bag where the relative humidity was maintained below 10% to ensure samples did not absorb additional water from the atmosphere.

The sucrose–indomethacin system was prepared by directly placing amorphous sucrose (500 mg) into glass ampoules (3 mL volume) in which amorphous indomethacin (200 mg) had been quench-cooled. Mixing the two components was not possible because amorphous indomethacin formed a thin layer around the ampoule and any attempt to scratch the solid could introduce some mechanical stress, which as noted above was intentionally avoided. Ampoules were loaded and sealed as above.

Calorimetric measurements were conducted with a 2277 Thermal Activity Monitor (TAM, TA Instruments Ltd) at 25 °C. Ampoules were left in the equilibration position for 30 min before being lowered to the measuring position. Data capture was subsequently initiated with the dedicated software package Digitam 4.1. All measurements were conducted in triplicate. The instrument was calibrated prior to use with the electrical substitution method and operated on an amplifier range of 100 μW.

2.1. Data analysis

An isothermal microcalorimeter measures the total heat output resulting from any processes occurring in the sample. This heat output is recorded in the form of power–time data; fitting such data to a suitable model (written to account for the reaction events) can resolve the reaction steps and thus predict the behaviour of the system under investigation (O'Neill et al., 2007). Relaxation of an amorphous matrix will initiate and progress through molecular rearrangement and hence can be considered as the sum of all the configurational changes that must occur in a sample for it to change from its 'frozen' glassy state to its equilibrium glassy state at a given annealing temperature (T_a). Commonly used equations to describe relaxation are the time-derivatives of the Kohlrausch–Williams–Watts (KWW) equation (Eq. (1)) and the modified stretch exponential (MSE) equation (Eq. (2)) (Kawakami and Pikal, 2005; Liu et al., 2002):

$$P = m \cdot \Delta H_\infty \cdot \left(\frac{\beta}{\tau}\right) \cdot \left(\frac{t}{\tau}\right)^{\beta-1} \exp\left[-\left(\frac{t}{\tau}\right)^{\beta}\right] \quad (1)$$

$$P = m \cdot \frac{\Delta H_\infty}{\tau_0} \cdot \left(1 + \frac{\beta t}{\tau_1}\right) \cdot \left(1 + \frac{t}{\tau_1}\right)^{\beta-2} \exp\left[-\left(\frac{t}{\tau_0}\right)\left(1 + \frac{t}{\tau_1}\right)^{\beta-1}\right] \quad (2)$$

where P, t, m and ΔH_∞ represent respectively power, time, sample mass and the total enthalpy available for relaxation. In the KWW equation, structural relaxation is characterised by the relaxation time, τ, and the stretch power, β. The MSE equation is a modified version of the KWW equation written to account for the inability of the KWW to describe data as time approaches zero (Liu et al., 2002). β holds the same meaning in the MSE equation as in the KWW equation, whereas the equivalent parameter to τ, known as τ_D, is calculated from β and time constants τ_0 and τ_1 as follows (Kawakami and Pikal, 2005):

$$\tau_D = (\tau_0 \tau_1{}^{\beta-1})^{1/\beta} \quad (3)$$

The development of Eq. (2) and its application to the study of the relaxation of amorphous pharmaceuticals has been demonstrated on a number of systems, including a series of disaccharides (Kawakami and Pikal, 2005; Liu et al., 2002) and an amorphous maltose formulation (Kawakami and Ida, 2003)

The focus of the current work is to determine whether IMC data has sufficient resolution to identify the relaxation of discrete amorphous phases. The power–time data resulting from relaxation of two co-existing, but independent, amorphous phases should be the linear sum of the power–time data resulting from the two components as they relax separately under the same conditions. The calorimetric data for a two-phase amorphous system can thus be described by the sum of two relaxation models i.e. $KWW_1 + KWW_2$ (2-KWW, Eq. (4)) or $MSE_1 + MSE_2$ (2-MSE, Eq. (5));

$$P = m_i \cdot \Delta H_{\infty i} \cdot \left(\frac{\beta_i}{\tau_i}\right) \cdot \left(\frac{t}{\tau_i}\right)^{\beta_i-1} \exp\left[-\left(\frac{t}{\tau_i}\right)^{\beta_i}\right] + m_{ii} \cdot \Delta H_{\infty ii} \left(\frac{\beta_{ii}}{\tau_{ii}}\right) \cdot \left(\frac{t}{\tau_{ii}}\right)^{\beta_{ii}-1} \exp\left[-\left(\frac{t}{\tau_{ii}}\right)^{\beta_{ii}}\right] \quad (4)$$

$$P = m_i \cdot \frac{\Delta_r H_\infty}{\tau_{0i}} \cdot \left(1 + \frac{\beta_i t}{\tau_{1i}}\right) \cdot \left(1 + \frac{t}{\tau_{1i}}\right)^{\beta_i-2} \times \exp\left[-\left(\frac{t}{\tau_{0i}}\right) \cdot \left(1 + \frac{t}{\tau_{1i}}\right)^{\beta_i-1}\right] + m_{ii} \cdot \frac{\Delta_r H_{\infty ii}}{\tau_{0ii}} \cdot \left(1 + \frac{\beta_{ii} t}{\tau_{1ii}}\right) \cdot \left(1 + \frac{t}{\tau_{1ii}}\right)^{\beta_{ii}-2} \exp\left[-\left(\frac{t}{\tau_{0ii}}\right)\left(1 + \frac{t}{\tau_{1ii}}\right)^{\beta_{ii}-1}\right] \quad (5)$$

where the subscripts i and ii correspond to the two relaxing components of the system.

Eqs. (4) and (5) contain numerous variables and fitting to the data is achieved through least-squares minimisation. One concern with fitting data to a model with so many variables is that by adjustment of the variables it is always possible to achieve a satisfactory fit to the data. We have argued in the past that while this is true to some extent, the approach to be adopted when fitting data originating from an unknown process is to select the simplest model that satisfactorily describes the data (Beezer et al., 1998; Gaisford et al., 1999). Here, since the process undergone by the sample is known to be relaxation, Eqs. (4) and (5) contain the fewest parameters

Table 1
Initial values for the reaction parameters entered into the fitting program.

	Component 1	Component 2
ΔH_∞ (J/g)	7	12
β	0.4	0.7
τ (s)	7×10^5	2×10^5

needed to describe the data. Secondly, when the fitting model has many variables, there are usually many mathematically consistent sets of values that describe the data being fitted. Our experience of analysing with kinetic models is that the rate constant is usually determined correctly (in this case, this value would be τ), while an experimentally determined value for ΔH increases confidence in the other values (Skaria et al., 2005). Here, one aim is to define the design space in which the model can recover correct values, so it is necessary to have some idea of the values of β, τ and ΔH. These values can be determined by experimental analysis of the relaxation of the individual phases prior to analysis of the binary mixtures, in the case of real systems, and/or by the construction of simulated data.

2.1.1. Data simulation

Data for one-component systems were generated using the time derivative of the KWW model (Eq. (1)) with Mathcad (Mathsoft Inc). All data sets for single-component systems were produced using the same values for ΔH (1 J/g), β (0.8) and m (1 g) and only τ values were varied (between 10^5 and 10^8 s). These values were chosen based on previous studies reported in the literature for real amorphous systems (Kawakami and Pikal, 2005; Liu et al., 2002). The KWW model was used for data simulation since the relaxation time constant (τ) in the KWW model can be readily varied unlike the τ_D parameter in the MSE model.

Data for two-component systems were produced by summing single-component system data, generated as above. A range of two-phase system data sets were generated in which the difference between the relaxation time constants for the two phases varied up to three orders of magnitude.

2.1.2. Simulated data analysis

Two-component simulated data were fitted to the 2-KWW equation (Eq. (4)) by least-squares minimisation. This method requires entering initial estimations for all the unknown parameters. The same input values were entered for all systems (summarised in Table 1). Values for m_i and m_{ii} were fixed to 1 g as these would be known experimentally.

2.1.3. Microcalorimetric data analysis

Power–time data from the first 2 h were discarded from each data set to ensure all data used for analysis were free from disturbances that result from lowering the ampoules. The time axis was adjusted by adding the time period from sample preparation to commencement of data capture (30 min).

Data were fitted to the models (Eqs. (1), (2), (4) and (5)) with least-squares minimisation. Power–time data for single-component systems were fitted to the KWW and MSE equations to obtain the 'true' relaxation parameters for each component. These values were set as the initial values in the fitting of two-component data. The goodness of fit was determined with the χ^2 function (a lower number indicating a better fit).

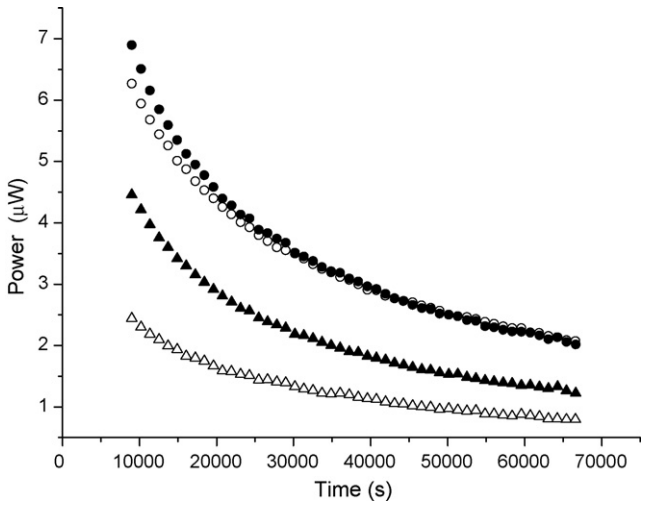

Fig. 1. Power–time traces resulting from relaxation of sucrose (▲), lactose (△), experimental sucrose–lactose binary system (○) and theoretical sucrose–lactose binary system (●).

3. Results

3.1. Simulated data

The reaction variables, determined by fitting 2-component simulated data to the 2-KWW model are summarised in Table 2. All data were well fitted by the model as seen from the very small values of χ^2 and by visual observation of the fit lines (data not shown). The values of the reaction variables agreed reasonably with the correct values when the relaxation time constants of the two phases were of the same order of magnitude, Table 2, column 1. The fit values started to deviate from the correct values as the difference between the two time constants increased. Once the difference increased to three orders of magnitude, non-physical values for ΔH and β were obtained for the component with the slowest τ value, while the correct values for the component with larger τ value were fully recovered. This is because data from the faster relaxing component dominate the observed power–time data and the fitting model does not have the resolution to detect the contribution from the minor component.

3.2. Experimental calorimetric data

3.2.1. Amorphous sucrose–lactose

The amorphous sucrose and lactose batches used to prepare the binary system were annealed separately in the TAM to determine their relaxation rates. Typical power–time traces for the two sugars are shown in Fig. 1. Both the KWW and MSE models resulted in a good fit for the resulting power–time data as indicated by very small values for χ^2. The fit values for the relaxation parameters

Table 2
Fit values obtained by fitting simulated data to the 2-KWW model.

Time constant ratio (s)	$\tau_1 = 2\tau_2 = 2E+05$		$\tau_1 = 10\tau_2 = 1E+06$		$\tau_1 = 100\tau_2 = 1E+07$		$\tau_1 = 1000\tau_2 = 1E+08$	
	Comp. 1	Comp. 2	Comp. 1	Comp. 2	Comp. 1	Comp. 2	Comp. 1	Comp. 2
ΔH_∞ (J/g)	0.63	1.30	0.84	1.12	0.36	1.01	−0.90	1.00
β	0.82	0.79	0.96	0.79	1.01	0.79	−0.10	0.79
τ (s)	2.6E+05	1.0E+05	1.1E+06	1.0E+05	2.2E+06	1.0E+05	3.4E+09	1.00E+05

Table 3
Relaxation parameters for individual sucrose and lactose samples obtained by fitting power–time data to the KWW and MSE models.

	KWW				MSE			
	τ (h)	β	τ^{β}	ΔH_{∞} (J/g)	τ_D (h)	β	$\tau_D{}^{\beta}$	ΔH_{∞} (J/g)
Sucrose	25.03 (2.37)	0.63 (0.01)	7.77 (0.46)	1.13 (0.05)	41.7 (7.2)	0.56 (0.02)	8.3 (0.65)	1.29 (0.1)
Lactose	36.08 (3.24)	0.67 (0.01)	11.22 (0.76)	0.74 (0.31)	45.93 (19.7)	0.66 (0.04)	11.98 (1.42)	0.79 (0.13)

Standard deviation values in parentheses, $n = 3$.

are summarised in Table 3. Note that τ and β are combined in one parameter, τ^{β}, since this parameter is supposed to give a better representation of the relaxation rate (Liu et al., 2002) and can be used as a more comprehensive tool to compare the relaxation behaviour of different materials (Kawakami and Pikal, 2005).

Fig. 1 also shows the power–time data resulting from the relaxation of the binary mixture of amorphous sucrose and lactose (denoted as experimental binary system). The expected heat flow trace of the binary mixture is also depicted in the same figure (referred to as theoretical binary system). The latter was obtained by summing the power–time data for sucrose and for lactose as they relaxed individually in the TAM. It can be seen that the trace for summed data does not totally superimpose the experimental trace, indicating some interaction between the components, an outcome discussed further below.

The experimental power–time data for the sucrose–lactose binary mixtures were fitted to the 2-KWW and 2-MSE models. As mentioned earlier, the iteration process requires the provision of preliminary estimates of the parameters. In this case, the mean relaxation parameters identified earlier for individual components (summarised in Table 3) were employed for this purpose. The resulting fit values are summarised in Table 4. By comparing the relaxation parameters for sucrose and lactose (Table 3) with the fit values summarised in Table 4, it can be seen that the 2-KWW model reasonably recovered the expected relaxation parameters for sucrose (component 1), whereas the fit values for lactose (component 2), besides their great variability, clearly differ from those of lactose. The fit values obtained from the 2-MSE equation seemed to be more variable and the parameters for the two components did not match any of those for sucrose or lactose.

3.2.2. Sucrose–indomethacin

The mean relaxation parameters for sucrose alone and indomethacin alone were obtained by fitting the power–time data for each material to the KWW and MSE models (Table 5). Both models fitted the data for the two materials very well as indicated by the very small values of χ^2.

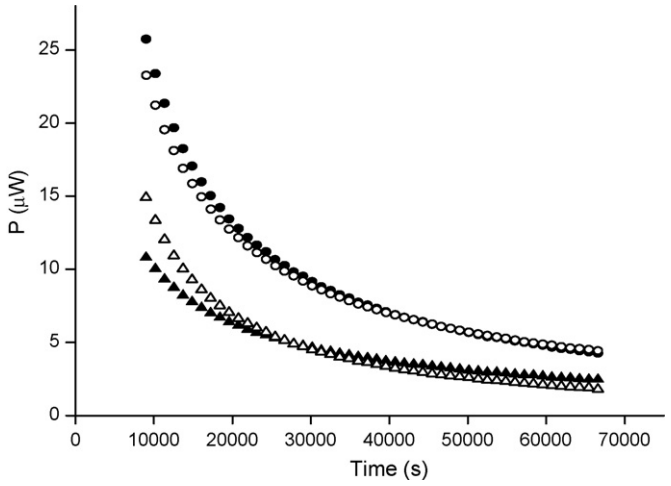

Fig. 2. Power–time traces resulting from relaxation of sucrose (▲), indomethacin (△), experimental sucrose–indomethacin binary system (○) and theoretical sucrose–indomethacin binary system (●).

Power–time data for the individual components and experimental and theoretical binary sucrose–indomethacin systems are shown in Fig. 2. Similar to the sucrose–lactose system, the trace for the theoretical sucrose–indomethacin system did not superimpose that for the experimental system.

Isothermal microcalorimetric data for the real binary system were then fitted to 2-KWW and 2-MSE equations using the identified mean relaxation parameters for each material to carry out the iteration process. Results are illustrated in Table 6.

Unlike the sucrose–lactose binary system, the 2-MSE model reasonably recovered the expected values of τ^{β} and ΔH_{∞} for both components (Table 5) and with tight variability. The 2-KWW model, conversely, only recovered the expected relaxation time constant τ^{β} for component 2 (indomethacin, Table 6) but not for component 1 (sucrose, Table 6). ΔH_{∞} values were reasonably recovered for both components.

Table 4
Fit values for relaxation parameters returned by the 2-KWW and 2-MSE models for binary sucrose–lactose samples.

	KWW				MSE			
	τ (h)	β	τ^{β}	ΔH_{∞} (J/g)	τ_D (h)	β	$\tau_D{}^{\beta}$	ΔH_{∞} (J/g)
Comp. 1 (sucrose)	20.27 (2.70)	0.683 (0.020)	7.79 (0.34)	1.22 (0.02)	37.82 (20.28)	0.717 (0.166)	13.48 (7.87)	0.98 (0.23)
Comp. 2 (lactose)	116.67 (43.33)	0.907 (0.163)	106.79 (96.12)	1.11 (0.23)	130.97 (26.59)	0.517 (0.131)	14.53 (10.2)	1.590 (0.22)

Standard deviation values in parentheses, $n = 3$.

Table 5
Relaxation parameters for individual sucrose and indomethacin samples obtained by fitting power–time data to KWW and MSE equations.

	KWW				MSE			
	τ (h)	β	τ^{β}	ΔH_{∞} (J/g)	τ_D (h)	β	$\tau_D{}^{\beta}$	ΔH_{∞} (J/g)
Sucrose	35.91 (3.07)	0.483 (0.011)	5.64 (0.18)	1.92 (0.14)	43.48 (1.98)	0.506 (0.003)	6.74 (0.22)	1.81 (0.08)
Indomethacin	5.31 (1.16)	0.352 (0.023)	1.80 (0.21)	5.40 (0.55)	7.89 (0.92)	0.422 (0.016)	2.40 (0.20)	4.14 (0.26)

Standard deviation values in parentheses, $n = 3$.

Table 6
Fit values for relaxation parameters returned by the 2-KWW and 2-MSE models for binary sucrose–indomethacin samples.

	KWW				MSE			
	τ (h)	β	τ^{β}	ΔH_{∞} (J/g)	τ_D (h)	β	$\tau_D{}^{\beta}$	ΔH_{∞} (J/g)
Comp.1 (Sucrose)	111.86 (30.60)	0.529 (0.126)	14.85 (11.64)	2.10 (0.13)	90.83 (6.68)	0.436 (0.032)	7.16 (0.80)	2.09 (0.10)
Comp. 2 (Indomethacin)	9.48 (3.73)	0.426 (0.026)	2.53 (0.31)	5.34 (0.16)	25.50 (9.28)	0.354 (0.026)	3.11 (0.49)	45.23 (0.26)

Standard deviation values in parentheses, $n = 3$.

4. Discussion

There are two main requirements for the data fitting approach to be successful. First, there should exist prior knowledge about the processes being recorded by the calorimeter. Second, these processes should be describable by a model which can be manipulated to fit microcalorimetric data. The fitting process is usually carried out iteratively; as the complexity (i.e. number of variables) of the model increases the more likely it is that the model will fit (if not describe) the data. Knowledge of the reaction process ensures the fitting model has the fewest variables.

Based on the results in Table 2, the 2-KWW model appeared to be able to recover reasonably the correct parameters for both components in a binary mixture as long as the relaxation time constants differed by no more than three orders of magnitude. This in effect reflects the influence of the ratio between the two components in terms of their contribution to the total power signal (this assumes roughly equal reaction enthalpies). This becomes clear when the data are plotted (Fig. 3), which shows how this ratio increases in favour of the component with lower relaxation time constant until this latter predominates and the 2-KWW model fails to "see" the minor component.

In both the binary amorphous systems used in this study, the two components contributed significantly to the total calorimetric system (Figs. 1 and 2) and thus were analysable by the models. However, the models performed differently with each of the real binary mixtures. For both systems, the 2-KWW model recovered the expected τ^{β} value for the component with lower τ^{β} value (see Tables 3 and 4). Simulating the data based on the fit values obtained for each measurement provides a better comprehension of the results. The fit values for a representative sucrose–lactose binary sample were used for this purpose; the plots are depicted in Fig. 4 along with the average experimental traces for the two sugars as they relaxed individually. It is clear that the component with higher τ^{β}, which contributes less to the total signal (i.e. lactose), deviates from the expected behaviour. The same observations were noted for the sucrose–indomethacin system (data not shown).

When the same analysis was carried out on the results obtained with the 2-MSE model (Tables 4 and 6), the traces obtained for the sucrose–lactose system were scattered and no correlation could be observed between the simulated and experimental traces (data not shown). On the other hand, the simulated traces for the sucrose–indomethacin system were in very good agreement with expected (experimental) traces (Fig. 5).

When summed data for sucrose and lactose were fitted to the 2-MSE model, recovery of the correct relaxation parameters depended greatly upon how closely the iteration parameters related to the 'correct' values (data not shown). This implies that the failure of the 2-MSE model to recover the expected parameters for real sucrose–lactose systems most likely results from the two components (or one of them) not behaving as expected. A number of likely explanations for this present themselves; the first is simply variability in relaxation behaviour between different samples from the same batch. The variability in τ^{β} value within individual sucrose and lactose batches used to construct the binary system is clearly greater than those for sucrose and indomethacin batches constituting the sucrose–indomethacin system (see Tables 3 and 5).

Alternatively, there could be a possible interaction between the two constituting sugars. The most likely interaction between sucrose and lactose, which both had at least 1.5% moisture content, is moisture redistribution within the solid mixture. When materials are mixed together in a closed container, the total moisture content is likely to redistribute between the different components via the vapour phase (Ahlneck, 1990; Zografi et al., 1998). Water is a potent plasticizer for amorphous materials (Hancock and Zografi, 1994) and changing the moisture content can greatly affect the molecular mobility and hence the structural relaxation (Liu et al., 2002). Water exchange between the sugars would also result a heat effect,

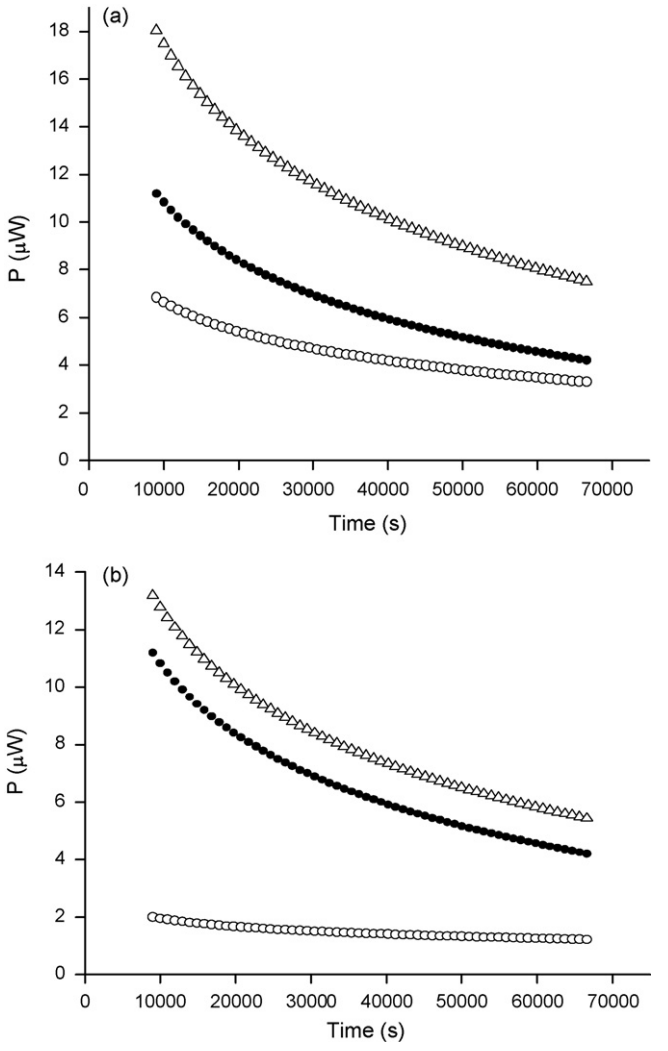

Fig. 3. Simulated calorimetric data for relaxation of a binary system (△) produced by summing data for two single-component systems (● major component; ○ minor component) having time constants of the same order of magnitude (a) and different by one order of magnitude (b).

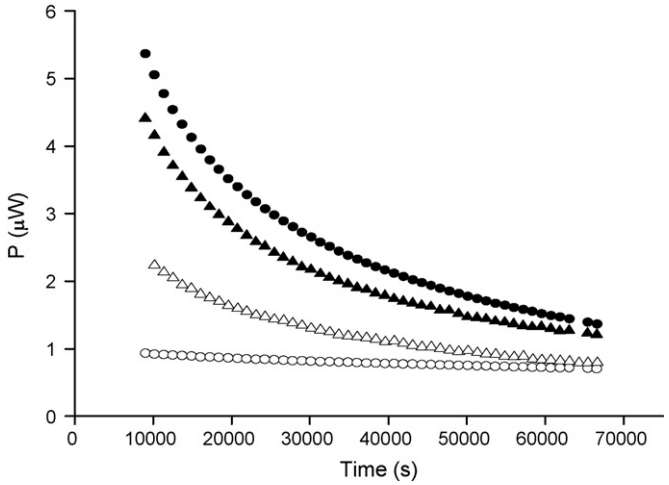

Fig. 4. Deconvoluted calorimetric signal for the sucrose–lactose mixture as obtained from 2-KWW fit (● component 1; ○ component 2) compared with calorimetric data for relaxation of individual sucrose (▲) and lactose (△) samples.

which would contribute to the observed data and adversely affect the fitting process. In the sucrose–indomethacin system such an interaction seems unlikely since the water contents of both components were so low.

When comparing the outcomes obtained from the two different models (2-KWW model versus 2-MSE model) based on the previous discussion, the 2-MSE model seems to be more robust than the 2-KWW model. This is based on the outcome for the sucrose–indomethacin system since neither of the two models offered satisfactory results for the sucrose–lactose system. A similar observation was made by Liu et al. (2002) regarding the difference between the two models but in the single form; and it was speculated that the superiority of the MSE equation might stem from the fact that it contains more parameters that appear to be less interdependent. This makes the 2-MSE model less sensitive to the inherent noise in the data unlike the 2-KWW model, which explains the contradiction between the outcome from the latter model with simulated and real calorimetric data. This was confirmed by the fact that the 2-KWW model was found to recover the correct parameters for simulated sucrose–lactose relaxation data. Inherent noise in microcalorimetric data has been reported previously to affect the analysis using iterative least squares regression (Skaria et al., 2005).

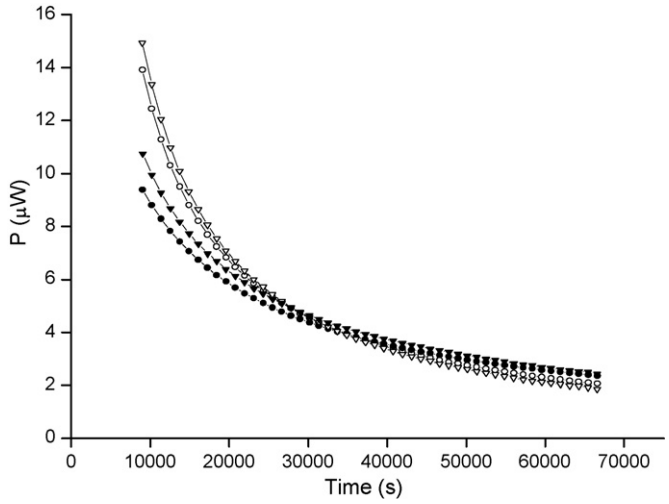

Fig. 5. Deconvoluted calorimetric data for the sucrose–indomethacin mixture as obtained from 2-MSE fit (● component 1; ○ component 2) compared with calorimetric data for relaxation of individual sucrose (▲) and indomethacin (△) samples.

5. Summary

Structural relaxation of two-phase amorphous systems has not been explored using thermal methods. In this work, the feasibility of using isothermal microcalorimetry for this purpose was investigated using a model fitting approach. It was found using simulated data that the 2-KWW model had the resolution to deconvolute the total signal into its constituting components. Satisfactory resolution was dependent upon the time constants of the relaxations not being more than three orders of magnitude different; if outside these limits the signal from one component dominated the total calorimetric signal. Noise in real calorimetric data was another factor that compromised the resolution of the 2-KWW equation. The 2-MSE model, on the other hand, was found to be less sensitive to the effect of noise and successfully recovered the expected relaxation parameters for the individual components of an amorphous sucrose–indomethacin system. This could be attributed to the lower inter-dependent nature of 2-MSE model parameters. The failure of the 2-MSE model to recover the expected relaxation parameters of the constituting components of an amorphous sucrose–lactose system could be considered as a sign of change in the behaviour of the components. This could have resulted from a possible interaction between the two sugars when present together or from greater variability in their relaxation behaviour compared to the components of the sucrose–indomethacin system. The work shows that isothermal microcalorimetric data can be used to quantify the relaxation of two co-existing amorphous phases and that the 2-MSE model performs best with real data.

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