# The development of DMA for the detection of amorphous content in pharmaceutical powdered materials

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## Abstract

The aim of this short study was to develop a novel method of sample presentation that will allow currently available DMA apparatus designed for the testing of self-supporting materials to detect amorphous content in controlled mixtures of amorphous and crystalline powders. The preparation of amorphous lactose was carried out by spraying drying, using a Büchi mini spray drier. Controlled mixtures of amorphous and crystalline lactose were produced to give eight samples ranging between 2% and 75% (w/w) amorphous content. These powdered mixtures were loaded into the DMA using a novel powder-pocket device, which consisted of folded sheet of stainless steel. The pocket was clamped directly into the DMA using a single cantilever configuration, and subjected to oscillating displacement, forcing horizontal shearing of the powder between the two plates of the pocket. Typical experimental parameters were a dynamic displacement of 0.05 mm with a frequency of 1 Hz and a heating rate of 5 °C/min, from 25 °C to 250 °C. Over the glass transition region of amorphous lactose, the storage modulus decreased rapidly and a peak was observed in the tan $\delta$ signal, which are typical DMA responses for self-supporting glassy materials over their glass transition region. In both the storage modulus and tan $\delta$ signals, contributions from both plasticized and non-plasticized amorphous lactose were demonstrated. Such an observation was caused by the powder pocket restricting the loss of the 2.5% (w/w) water present in the spray-dried lactose within the time scale of the first heating cycle. The tan $\delta$ peak for the non-plasticized amorphous lactose showed Arrhenius behaviour as function of oscillation frequency. The relationship between the increase in the tan $\delta$ peak with increasing frequency allowed the determination of an activation energy that was comparable to the literature values for similar compounds. The height of the tan $\delta$ peak for the non-plasticized material was directly proportional to the amount of amorphous lactose present in the mixtures. The glass transition response was still detectable in mixtures containing as little as 2% (w/w) amorphous content, however the theoretical limit of detection was higher than that determined for the same mixtures using solution calorimetry. The results demonstrate that the novel powder pocket allows the use of conventional DMA instruments for the analysis of pharmaceutical powders, however the technique requires more development to further reduce its theoretical limit of detection.
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*Keywords:* DMA; Amorphous powders; Glass transition; Powder pocket; Lactose

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## 1. Introduction

Preparation of the amorphous form of a drug is often beneficial in terms of an increased dissolution rate and thus bioavailability (Yu, 2001; Craig et al., 1999). However, accidental production of amorphous material during particle size reduction processing is an important issue as small amounts, 0.5%–1% (w/w), can cause agglomeration of a previously free flowing powder (Ward and Schultz, 1995). There are many techniques available for the detection of amorphous content in processed powders, including modulated DSC (Saklatvala et al., 1999), high-speed DSC (Saunders et al., 2004), gravimetric vapour sorption (Hogan and Buckton, 2001), isothermal microcalorimetry (Briggner et al., 1994), solution calorimetry (Hogan and Buckton, 2000), inverse gas chromatography (Newell et al., 2001) and Raman spectroscopy (Taylor and Zografi, 1998). The application of these techniques is based on the measurement of an extensive property associated with the amorphous phase. For a particular technique, if the measurement of the extensive property is obscured by impurities or by the presence of other components within the powder then the technique cannot be used. Many of the extensive properties, for example the heat released or absorbed upon the formation of a solution, the extent of re-crystallisation, or the intensity of a Raman peak, are dependent on the molecular nature of the sample. Thus for all techniques, the limit of detection for amorphous content will vary. The issues of resolution and sensitivity imply that no single technique will have the potential for universal application to the problem of amorphous content detection. Therefore, there is a continuing need for the development of techniques for the detection of amorphous content.

Dynamic mechanical analysis (DMA) measures the mechanical properties of a sample as a function of temperature (Price, 2002; Jones, 1999). The solid or semi-solid sample is held within the instrument and subjected to an oscillating stress, measured as a force per unit area, Pa (Jones, 1999). The applied oscillating stress results in an observable oscillating strain (deformation) within the sample. DMA instruments are configured such that the force applied to the sample together with the amplitude and phase of the resultant displacement are measured. For most DMA instruments the oscillating stress can be described by Eq. (1) (Price, 2002)

$$\sigma(t) = \alpha_{\max} \sin \omega t \qquad (1)$$

The stress at time $t$ is given by $\sigma(t)$, $\alpha_{\max}$ is the maximum stress applied, $\omega$ is the angular frequency of oscillation, such that $\omega$ equals $2\pi f$, with $f$ being the frequency (Hz). The ratio of the applied stress and the deformation or strain, is defined as the modulus in the case of elastic, usually solid, materials. Deformation (strain) is the ratio of the change in the sample's dimensions and the sample's original dimensions, so it is a dimensionless quantity. Furthermore, as strain is dimensionless, the modulus will have units of force per unit area (Pa), and can be thought of as the resistance of the sample to deformation (Jones, 1999).

Most materials behave visoelastically to an applied stress. Therefore, in DMA experiments, the oscillating strain lags behind the applied oscillating stress by a phase difference defined as $\delta$. Thus, the modulus is complex, with an in-phase (storage modulus) component corresponding to the sample's elastic response and an out of phase (loss modulus) viscous component. The ratio between these parameters ($E''/E'$), gives the damping parameter tan $\delta$, which is proportional to the ratio of dissipated mechanical energy (primarily as heat)/stored mechanical energy for each cycle.

The glass transition of an amorphous material is accompanied by a large change in its mechanical properties. Thus DMA is very a sensitive technique for the identification and characterisation of glass transitions (Ward, 1984). It is currently only possible to use this technique with self-supporting materials, usually polymers (Price, 2002; Jones, 1999). However, as most pharmaceutical amorphous or semi-amorphous systems of therapeutic interest are powders, e.g. micronised, spray or freeze dried materials, DMA's pharmaceutical applications have been limited. Therefore, the aim of this short study was to develop a novel method of sample presentation that will allow the currently available DMA apparatus designed for the testing of self-supporting materials to detect amorphous content in controlled mixtures of amorphous and crystalline powders.

## 2. Materials

Crystalline α-lactose monohydrate (Lactochem®, Borculo Whey, Chester, UK), Tris(hydroxymethyl)

Table 1
Target and actual experimental masses of amorphous and crystalline lactose tumble turbula mixed to form the set of samples run in the Sol Cal and DMA

| Target | | | Experimental | | |
|---|---|---|---|---|---|
| Amount of amorphous lactose (mg) | Total amount: amorphous and crystalline (mg) | Amorphous content % (w/w) | Amount of amorphous lactose (mg) | Total amount: amorphous and crystalline (mg) | Amorphous content % (w/w) |
| 375 | 500 | 75 | 378.32 | 504.88 | 74.93 |
| 250 | 500 | 50 | 249.41 | 500.23 | 49.86 |
| 125 | 500 | 25 | 126.05 | 502.58 | 25.08 |
| 50 | 500 | 10 | 50.34 | 513.27 | 9.81 |
| 40 | 500 | 8 | 40.18 | 500.91 | 8.02 |
| 30 | 500 | 6 | 30.80 | 500.46 | 6.15 |
| 20 | 500 | 4 | 20.71 | 500.70 | 4.14 |
| 10 | 500 | 2 | 10.27 | 500.57 | 2.05 |

amino-methane (supplied by Aldrich, UK), and sucrose (supplied by Tate & Lyle, Thames Refinery, Silvertown, London, UK, in the form of commercial cane sugar) were used as received. Lactose was chosen for this study because it is a commonly used test material for the development of new techniques associated with the detection of amorphous content (Newell et al., 2001; Saunders et al., 2004). Distilled water (Option 3 Elga water purification), was used to prepare solutions of lactose and as the solvent in the solution calorimetry experiments.

Preparation of amorphous lactose was carried out by spray drying, following the method described by Hogan and Buckton (2000) using a Model 190 Büchi mini spray drier (Büchi Laboratoriums-Technik AG, Switzerland). The resulting material was collected immediately and dried in a vacuum tray drier held at 50 °C for 3 days (Heraeus Instruments Vacutherm).

Quantities of amorphous and crystalline lactose were combined to produce 500 mg powder mixes (Turbula mixer, Basel, Switzerland, for 20 min) of different amorphous content: 2%–75% (w/w), respectively. Details of the actual masses are given in Table 1. These samples were stored in a desiccator over silica gel at room temperature prior to analysis.

## 3. Methods

### 3.1. DMA

Experiments were run using a Tritec 2000 DMA (Triton Technology Ltd., Nottinghamshire, UK) run-

ning Tritec 2000 DMA version 1.43.00 software. Approximately 50 mg of powdered sample were loaded into a metal pocket fabricated from a sheet of stainless steel, following the procedure outlined below.

Initially the powder pocket was formed by folding the sheet along a pre-scored line to form an angle of approximately 60° between the inner faces of the pocket (Fig. 1). This was weighed and then powder
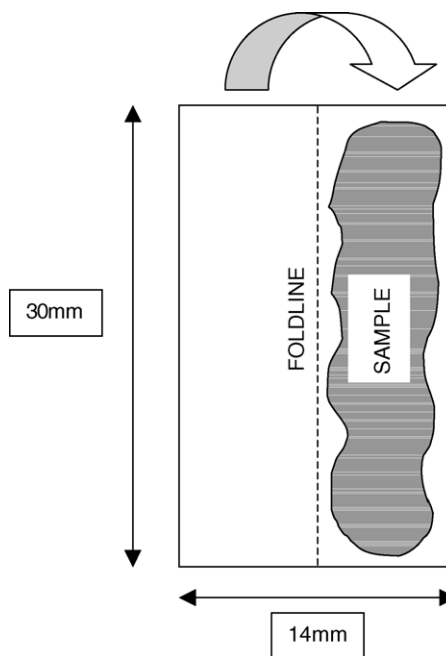


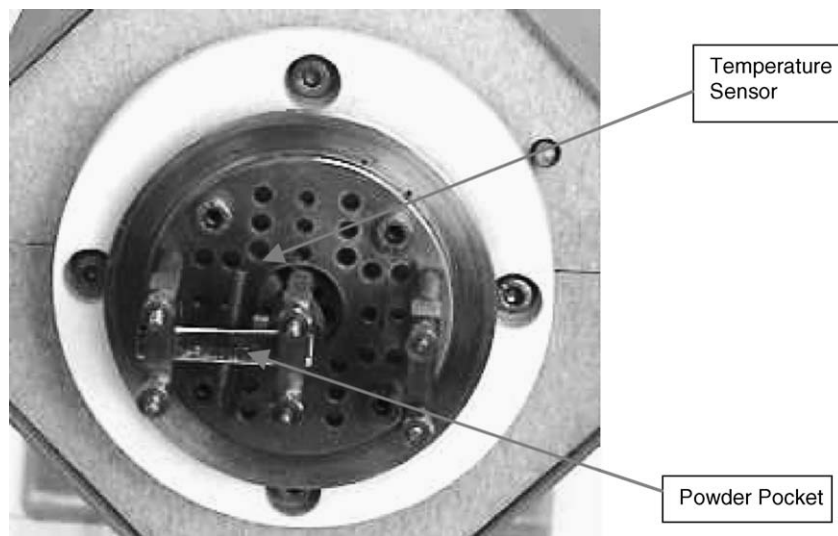Fig. 1. Fabrication of the powder pocket; vertical profile during filling.

Fig. 2. A clamped powder pocket in the DMA (note the furnace cover is removed).

added to the horizontal inner face to form a uniform layer. The pocket was then crimped closed to form a thin sandwich of approximately 0.4 mm of powder encased in the pocket. Once tightly compressed, the pocket was re-weighed to determine the sample mass. The dimensions and pressing procedure of the pocket determine the precise sample mass that must be employed in the testing procedure. For this study, the dimensions are shown in Fig. 1.

The pocket was then clamped directly into the instrument. Fig. 2 shows how the two ends of the pocket were supported with one end clamped to the rigid frame, the other end being attached to the moving driveshaft. The experimental geometry used to determine the force data in the software was a rectangular cross-section in a single cantilever bending using a single frequency in deformation mode (Fig. 2). This involved clamping the left-hand side of the pocket stationary, and applying the oscillating displacement through the central driveshaft clamp (the right-hand clamp is empty). The pocket was subjected to a bending oscillatory motion in and out of the plane, forcing horizontal shearing of the powder between the two plates of the pocket.

The DMA furnace, which encased the clamping area completely, was used to apply the temperature program. A small tube, positioned close to the sample (Fig. 2) behind the middle of the pocket, contained the platinum resistor sensor used to record the temperature of the sample. The experimental parameters employed in this study were a dynamic displacement of 0.05 mm under a frequency of 1 Hz and a heating rate of 5 °C/min, from 25 °C to 250 °C. The force was automatically controlled between 1 N and 10 N to achieve the target displacement, in this case 0.05 mm. The modulus was calculated from the actual measured dynamic displacement amplitude. The instrument was calibrated for temperature by using the melting point of indium (156.6 °C) and the force calibration was conducted following the manufacture's manual (Triton Technology Ltd., 2000), and consisted of placing a known weight of approximately 100 g on the driveshaft.

### 3.2. Solution calorimetry

A Thermometric 2225 Precision Solution Calorimeter with a 100 mL vessel (Thermometric AB, Sweden), in a Heto precision water bath, at 25 °C was used to measure the enthalpies of solution. Between 50 mg and 200 mg samples were prepared the glass crushing ampoules using a standard protocol (Hogan and Buckton, 2000). All experiments were performed in distilled water with a stirrer rate of 500 rpm. Conditions were semi-adiabatic and the enthalpies of solution were determined by the dynamics of calibrations calculation model run on the accompanying software. The

performance of the solution calorimeter was validated chemically by running crystalline sucrose in water and Tris in 0.1 M HCl.

### 3.3. TMDSC

Temperature modulated differential scanning calorimetry was used to measure the glass transition temperature of the spray-dried lactose. The experiments were conducted using a DSC 2920 Modulated DSC (TA Instruments, Leatherhead, UK), using aluminium hermetic DSC pans with a pinhole in the lid, which contained approximately 3 mg of sample for each run. TMDSC experiments were performed with a modulation amplitude of $\pm 0.3\,^\circ$C and a 60-s period with a $2\,^\circ$C/min underlying heating rate. The TMDSC was calibrated, and the value for the glass transition determined following a previously reported protocol (Hill et al., 1998; Royall et al., 1998).

### 3.4. TGA

Thermogravimetric analysis was used to determine the water content of the spray-dried lactose. The experiments were conducted using a TGA 2950 (TA Instruments, Leatherhead, UK), using a heating rate of $10\,^\circ$C/min from $25\,^\circ$C to $220\,^\circ$C and with the sample placed in an open DSC pan. The sample mass was $7 \pm 0.5$ mg. Both temperature and mass had been previously calibrated using the manufacturer's recommended methods.

## 4. Results and discussion

Solution calorimetry was used to validate the amorphous content of the spray-dried amorphous lactose, the crystalline lactose and the mixed samples. Chemical calibrations were within literature parameters (Yff et al., 2004): Tris in 0.1 M HCl, $\Delta_{sol}H = -245.4 \pm 0.8$ J/g, $n = 4$; sucrose: $\Delta_{sol}H = 17.8 \pm 0.4$ J/g, $n = 6$. It should be noted that all of the experimental results given in this paper are mean values with their associated standard deviations given as the $\pm$error. The enthalpy of solution for amorphous and crystalline lactose was determined to be $-55.8 \pm 0.2$ J/g ($n = 6$) and $56.2 \pm 0.7$ J/g ($n = 6$), respectively. These values correlated well with the

literature, as the corresponding enthalpies determined Hogan and Buckton (2001) were within the standard deviations of the enthalpies determined in this study. The results obtained from TMDSC and TGA studies did not show the presence of any crystalline material in the spray-dried lactose. The glass transition temperature, $117.5 \pm 0.9\,^\circ$C ($n = 4$), and water content $2.5 \pm 0.3\%$ (w/w) ($n = 3$) were comparable to the literature (Saunders et al., 2004; Hill et al., 1998). It can be assumed that the Buchi spray drier produced material that was 100% (w/w) amorphous.

The batch of crystalline lactose used was USP grade material and was thus certified by TMDSC & DSC, with a single melting peak close to the literature value for the $\alpha$ form (Hill et al., 1998) and by the absence of the peak associated with the melting of the $\beta$ optical isomer. Further indication that the crystalline material used in this study was wholly the monohydrate $\alpha$ isomer, was the similarity of its enthalpy of solution with the literature where lactose samples were validated using powder X-ray diffraction which confirmed the absence of the $\beta$ form (Saunders et al., 2004; Hill et al., 1998).

The exact percentage isomeric composition of amorphous lactose is currently unknown, however in this study it was assumed to be predominantly amorphous $\alpha$-anhydrous lactose. The spray-dried lactose produced in this study has been shown to have a similar composition to the validated material produced by previous studies using a Buchi spray drier (Saunders et al., 2004; Hill et al., 1998). In these studies the spray-dried material gave a diffuse halo in response from the PXRD analysis, indicating the absence of detectable crystallinity. The aim of the current study was to develop a novel approach to detect amorphous content in controlled mixtures of amorphous and crystalline material, and not to determine the isomeric composition of amorphous lactose. The results from the present study show that TMDSC and DMA did not discriminate between the different isomeric forms, as only a single transition was observed. Thus, the possible influence of the, as yet undetermined, isomeric composition of amorphous lactose should not diminish the outcomes and conclusions of this paper.

Typical responses from the DMA are shown in Fig. 3a and b, respectively. A dramatic change in both the storage modulus and tan $\delta$ signals of the amorphous samples can be seen between $80\,^\circ$C and $140\,^\circ$C, this
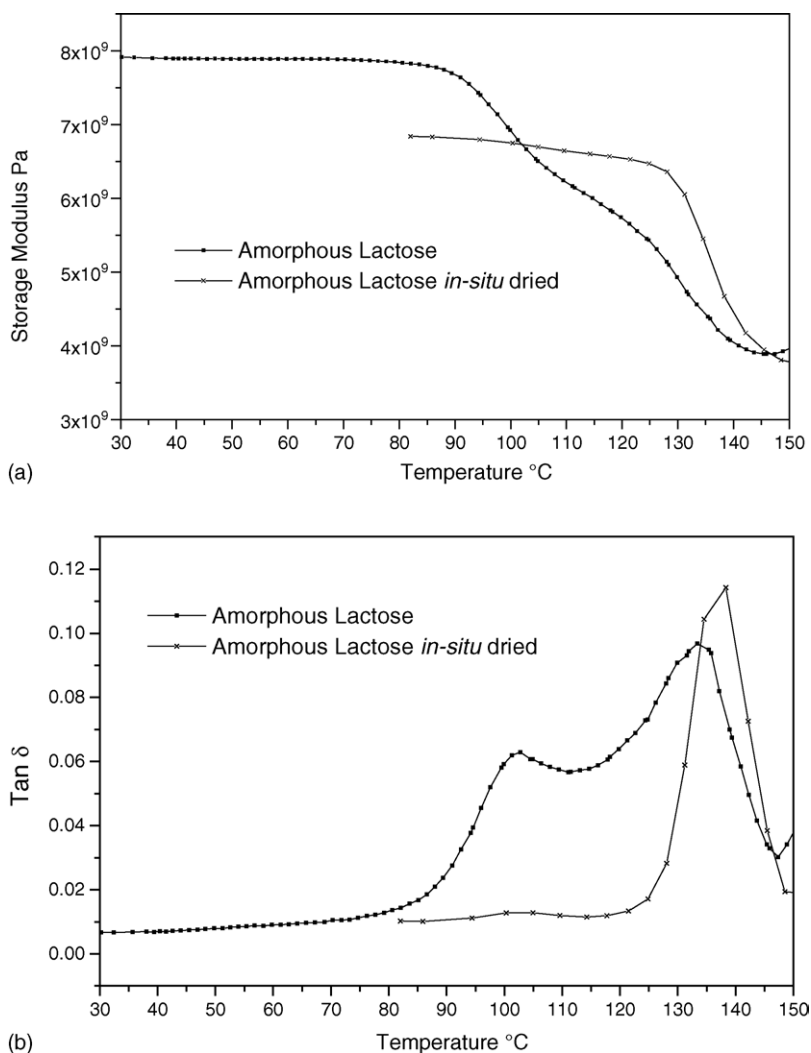
Fig. 3. (a) A typical powder-pocket DMA response for spray-dried amorphous lactose showing a comparison between the modulus signals of spray-dried amorphous lactose, and in situ dried amorphous lactose (in situ drying consisted of heating to 110 °C then cooling to 80 °C and then re-heating to 250 °C, all with a temperature scan rate of 5 °C/min). (b) A typical powder-pocket DMA response for spray-dried lactose showing a comparison between the tan δ signals of spray-dried amorphous lactose, and in situ dried amorphous lactose (in situ drying consisted of heating to 110 °C then cooling to 80 °C and then re-heating to 250 °C, all with a temperature scan rate of 5 °C/min).

range falls over the glass transition of amorphous lactose (Saunders et al., 2004; Hill et al., 1998). The glass transition can be described as a relaxation process, whereby the solid glass becomes less rigid over this region (Price, 2002; Jones, 1999). This is due to the molecules undergoing a transition from a totally vitrified state (with long relaxation times) to one where they are mobile (having short relaxation times). The DMA literature of self-supporting samples describes the glass transition as a decrease in the storage modulus, caused by the decrease in resistance of the material to deformation and a peak in the damping component (tan δ) due to the increased loss of energy as heat during the transition process (Jones, 1999). The storage modulus signal of the spray-dried samples showed a sharp inflection corresponding to a sudden loss in the samples elastic behaviour (Fig. 3a) and a corresponding peak in the tan δ signal (Fig. 3b). However the onset of

this glass transition like behaviour was approximately 80 °C, which is much lower than the glass transition measured by the TMDSC experiments. To investigate this difference, the normal heating cycle was interrupted at 110 °C, with the sample then cooled to 80 °C and subsequently re-heated to 250 °C at the usual scan rate of 5 °C/min. The affect of this in situ drying on the modulus and tan δ signals is shown in Fig. 3a and b.

It can be clearly seen that the shoulder on the tan δ peak and the depressed onset temperature of the decrease in storage modulus are removed by the temperature cycle. The hypothesis that the temperature cycle is in effect a drying step was supported by the TMDSC experiments. No depression of the glass transition was observed in these experiments on the first and only heating cycle because the pin holed pans allowed the 2.5% (w/w) of water present in the spray-dried lactose to evaporate before the glass transition was reached. In the case of the DMA experiments the powder pockets allowed the water to only partially evaporate during the original heating cycle, so the observed response had a contribution from both plasticized and non-plasticized amorphous lactose. This produced the two-step profile in the storage modulus and the double peaks in the tan δ signal. The plasticization effect of water is well known to dramatically depress the glass transition of lactose (Hill et al., 1998).

In order to confirm that a glass transition is still observed in the second heating cycle from 80 °C to 250 °C, the storage modulus and tan δ were recorded as a function of frequency, as well as temperature. Fig. 4a and b show that the onset and peak temperatures for the transition are promoted as the frequency is increased. This is typical of a glass transition, and is a consequence of the glass transition being a relaxation process (Talja and Roos, 2001). In simple terms, when a glass is heated in a DMA, the glass transition region is observed when the molecules of the glass have sufficient mobility that their relaxation times approach the frequency of the oscillating stress. If a higher frequency is imposed, more thermal energy is required to reach this point and the glass transition region falls at a slightly higher temperature. Thus the rate of oscillation has a corresponding influence on the temperature at which the glass transition is activated. This concept has been used by many authors to model, as a first approximation, the frequency dependence shown in Fig. 4a and b using a modified Arrhenius equation given in Eq. (2)

(Talja and Roos, 2001; Weuts et al., 2003).

$$\ln f = \ln A - \left[ \frac{E_a}{RT} \right] \qquad (2)$$

where $f$ is the applied frequency, $A$ a constant, $R$ the gas constant, $T$ the peak maximum temperature, in Kelvin, of the tan δ peak over the glass transition. Plotting the natural logarithm of the frequency against the inverse of the observed peak temperature gave a linear relationship with a regression coefficient of 0.98 (data not shown). This linear relationship indicated Arrhenius behaviour, which allowed an activation energy to be determined from the slope of the linear regression line of approximately 580 kJ/mol. An Arrhenius relationship between the instrumental time scale, either heating rate or measurement frequency, and the glass transition temperature has been observed for many of the amorphous forms of small organic molecules. For example, activation energies for sorbitol and ketoconazole have been determined using dielectric analysis and differential scanning calorimetry of 402 kJ/mol and 731 kJ/mol, respectively (Talja and Roos, 2001; Weuts et al., 2003). These values represent the activation energy for the transition from the glassy state to the super-cooled liquid, and are the energy barrier to the relaxation process observed at the glass transition. Ranking the activation energies for a series of amorphous materials has been used to indicate the relative stabilities and molecular mobilities of the glassy materials within a series. However, it should be noted that activation energies associated with glass transitions are only apparent values, because glassy materials are meta-stable, and possess a range of different properties and structural relaxation times.

The Arrhenius behaviour exhibited by the tan δ peak between 130 °C and 150 °C, and similarity of the magnitude of the activation energy with the literature offers further support that the DMA response reported here is a result of the glass transition of lactose. However the peak in the tan δ signal and the onset for the reduction in storage modulus for the non-plasticized amorphous lactose was higher than the glass transition observed for lactose by the TMDSC experiments. The DMA experiments were carried out using a frequency of 1 Hz. The glass transition is a relaxation process, thus it is expected to have a high dependency on the frequency of measurement, which is illustrated in Fig. 4a and b
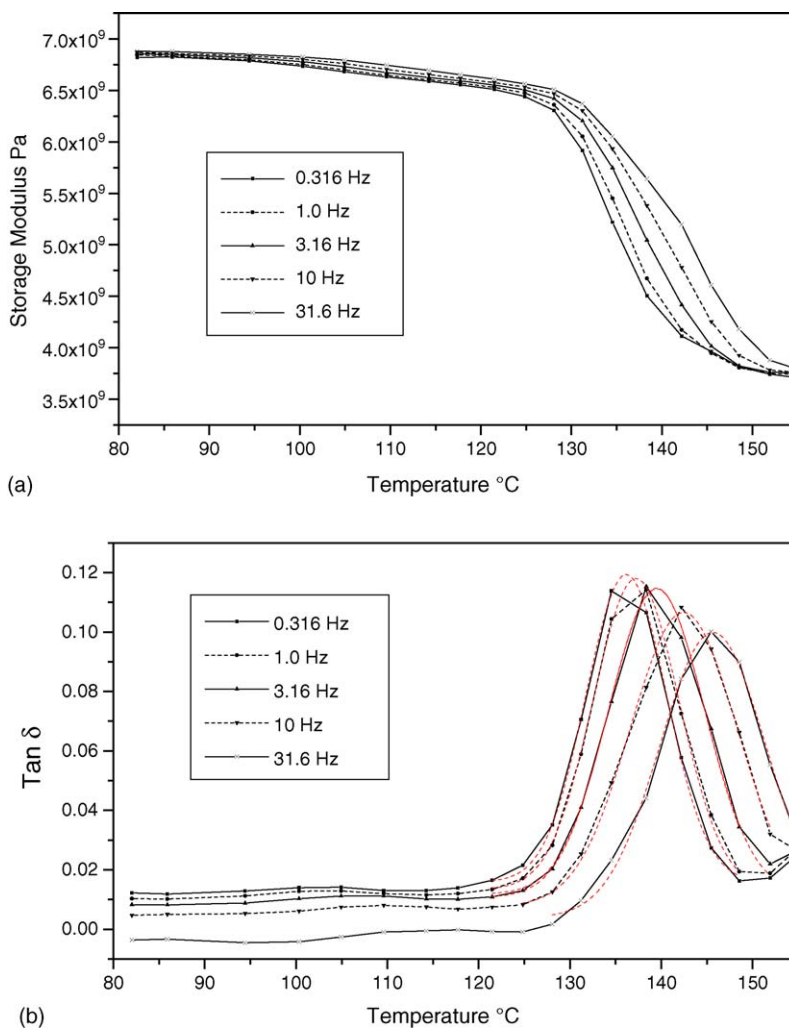
Fig. 4. (a) Modulus signal for in situ dried amorphous lactose as a function of frequency. (b) The tan $\delta$ signal for in situ dried amorphous lactose as a function of frequency. The dashed smooth curves represent a Gaussian equation fitted to the experimental data. The peak maximums of these Gaussian fits were used to give the peak temperatures, used in the determination of the activation energy.

and by the Arrhenius behaviour described above. It is a very common observation that the glass transition determined by conventional DMA using the tan $\delta$ peak response is many degrees higher than the glass transition determined by calorimetric techniques (Talja and Roos, 2001). The relationship between frequency and peak temperature must be extrapolated to lower frequencies in order to determine the frequency that will give a glass transition temperature that coincides with the value observed by DSC. For the case of sorbitol this frequency is 0.08 Hz (Talja and Roos, 2001). Therefore

the data presented here conforms to the literature concerning conventionally operated DMAs, whereby the glass transition temperature increases as a function of frequency and very low frequencies, often outside the working range of the DMA, are required to give glass transition temperatures comparable to the values determined by differential scanning calorimetry.

The typical tan $\delta$ signals for the mixtures of amorphous and crystalline material are shown in Fig. 5. However, these experiments did not include a drying cycle. It can be clearly seen that both the plasticized
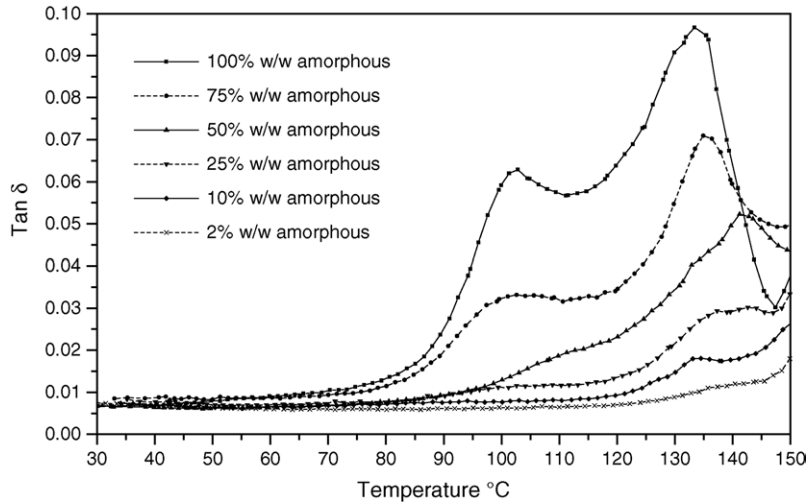
Fig. 5. The tan $\delta$ signal for the mixed amorphous and crystalline samples.

and non-plasticized glass transition peaks fall in intensity as the amount of amorphous material is reduced in the controlled mixtures. In order to determine the theoretical limits of detection, the DMA strength was determined and plotted against amorphous content. The DMA strength was calculated by subtracting the base line response from the peak height in the tan $\delta$ signal for the non-plasticized glass transition (the second peak in Fig. 5). This normalised value was then subtracted

from 1 to give the parameter "DMA strength". This calculation served two purposes, it normalised the signal, removing the influence of base line shifts (the baseline signal was simply the tan $\delta$ signal between 30 °C and 40 °C for each experiment) and it allowed a visual comparison with the enthalpies of solution, also included in Fig. 6. It can be easily seen that the relationship between amorphous content and DMA strength and enthalpy of solution is linear. The equations for the linear regres-
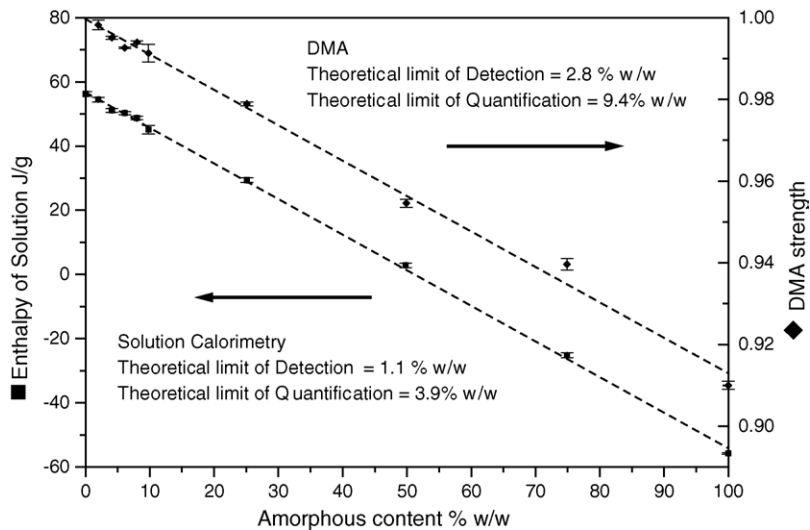


Fig. 6. Relationship between amorphous content and both the enthalpy of solution and DMA strength. Each data point is the mean of $n = 3$, and the error bars represent $\pm$ the standard deviation (DMA strength determined from the normalised tan $\delta$ peak heights subtracted from 1).

sions are given below:

DMA strength

$$= 0.999 - 8.49 \times 10^{-4}$$
$$\times (\% \text{w/w amorphous content}); \quad r^2 = 0.994$$

Enthalpy of solution

$$= 56.7 - 1.11$$
$$\times (\% \text{w/w amorphous content}); \quad r^2 = 0.999$$

These linear regression equations were used to determine the theoretical limits of detection and quantification for DMA and solution calorimetry, respectively. The method used was based on the recommendations of the United States Pharmacopoeia, and is described in detail by Miller and Miller (1993). This approach uses the standard deviation of the blank response, which in terms of the present study, was given by the standard deviation of the *y*-intercepts from both of the linear regressions shown in Fig. 6. This method is regularly applied to HPLC data, but has also been used recently on calorimetric data generated from controlled mixes of amorphous and crystalline lactose (Saunders et al., 2004). The definitions used in the calculation were as follows: the limit of detection was the analyte concentration giving a signal equal to the blank response plus three standard deviations of this value; whereas the limit of quantification was the analyte concentration giving a signal equal to the blank response plus 10 standard deviations of this value (Miller and Miller, 1993). Applying this analysis, gave a theoretical limit of detection (t-LOD) and a theoretical limit of quantification (t-LOQ) of 2.8% (w/w) amorphous content and 9.4% (w/w) amorphous content, respectively, for powder-pocket DMA. In the case of solution calorimetry lower values were obtained, with t-LOD and t-LOQ values of 1.2% and 3.9% (w/w) amorphous content, respectively.

The values of t-LOD and t-LOQ determined here were specific to amorphous lactose whereas for different materials, alternate values for these parameters are to be expected. For both techniques, detection and quantification limits will have a strong correlation with the molecular structure of the material under investigation. Specifically for lactose, solution calorimetry provides a theoretical limit of detection which is lower

than the value determined for DMA. Solution calorimetry is an established technique, however powder-pocket DMA is currently being developed, and may provide lower values for t-LOD and t-LOQ for materials with a higher response in the tan $\delta$, or when suitable solvents that will provide large enthalpies of solution are not available. Therefore, the current disadvantage of powder-pocket DMA is the relatively high levels for the detection and quantification limits when compared to other techniques using lactose as a model material (Saunders et al., 2004; Hogan and Buckton, 2000), and to the solution calorimetry data given in this study. However, it should be noted that unlike solution calorimetry, where the enthalpy of solution for a mixed sample has a contribution from both the crystalline and amorphous phases, the DMA approach measures the amorphous phase directly, independent of the response from the crystalline phase. Therefore theoretically, DMA should yield a greater sensitivity towards the amorphous material present in milled crystalline powders, and this hypothesis encourages further development of powder-pocket DMA.

## 5. Conclusions

The provision of a new analytical tool allowing DMA to characterise the phase behaviour pharmaceutical powders, and the ability to measure activation energies within the same experiment are the clear advantages of the powder-pocket DMA, and should encourage further development of this technique. Indeed, the authors are currently investigating the potential of this technique to characterise amorphous content in milled powders, and this will form the basis of a forthcoming paper. However, this first study was required in order to establish the feasibility of powder-pocket DMA. This study has shown that amorphous powders held in the powder-pocket respond in a similar fashion to self-supporting glassy materials.

The study has fulfilled its aims by illustrating the ability of powder-pocket DMA to detect small amounts of amorphous material in predominantly crystalline pharmaceutical powders. This is a completely novel application of DMA, with no previous references in the literature, and will allow conventional DMA instruments to characterise the glass transition of amorphous pharmaceutical powders. However, the design

and application of this simple device has yet to be optimised. Thus, the on going development of the powder pocket will involve pocket design, the effect of loading capacity and its application to a range of different compounds present as both milled and micronised powders.

## Acknowledgments

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