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A novel powder sample holder for the determination of glass transition temperatures by DMA

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ABSTRACT

The use of a new sample holder for dynamic mechanical analysis (DMA) as a means to characterise the T_g of powdered hydroxypropyl methyl cellulose (HPMC) has been investigated. A sample holder was constructed consisting of a rectangular stainless steel container and a lid engineered to fit exactly within the walls of the container when clamped within a TA instruments Q800 DMA in dual cantilever configuration. Physical mixtures of HPMC (E4M) and aluminium oxide powders were placed in the holder and subjected to oscillating strains (1 Hz, 10 Hz and 100 Hz) whilst heated at 3 °C/min. The storage and loss modulus signals showed a large reduction in the mechanical strength above 150 °C which was attributed to a glass transition. Optimal experimental parameters were determined using a design of experiment procedure and by analysing the frequency dependence of T_g in Arrhenius plots. The parameters were a clamping pressure of 62 kPa, a mass ratio of 0.2 HPMC in aluminium oxide, and a loading mass of either 120 mg or 180 mg. At 1 Hz, a T_g of 177 ± 1.2 °C ($n = 6$) for powdered HPMC was obtained. In conclusion, the new powder holder was capable of measuring the T_g of pharmaceutical powders and a simple optimization protocol was established, useful in further applications of the DMA powder holder.

1. Introduction

The solid state characterisation of novel pharmaceuticals and polymeric materials frequently involves the measurement of a glass transition temperature (T_g) (Craig et al., 1999; Pijpers et al., 2002). The T_g is a vitally important feature of a pharmaceutical material, because it marks a dramatic change in viscoelastic properties which has implications not only for the material's mechanical behaviour but also for its stability (Angell, 1995; Debenedetti and Stillinger, 2001). Dynamic mechanical analysis (DMA) is used to characterise solid materials by monitoring their mechanical properties, storage modulus (G') and loss modulus (G''), during heating (Menard, 1999; Price, 2002). DMA is highly sensitive to the decline in mechanical strength over the glass transition region of amorphous or partially amorphous solids. However, the application of DMA is restricted to self-supporting systems, for example bars, films or fibres (Menard, 1999; Price, 2002; Bandi and Schiraldi, 2006), and the literature reports of the use of conventional DMA to characterise the T_g of a powdered pharmaceutical are rare (Royall et al., 2005). Nevertheless the analysis of T_g associated with powdered materials is essential for the development of amorphous drugs and pharmaceuticals, for example amorphous solid solutions of drugs and polymers, milled or spray dried particles and stabilised protein formulations (Fragiadakis et al., 2005; Mao et al., 2006).

The primary method for analysing the T_g of powders is differential scanning calorimetry (DSC), whereby the step change in the heat capacity, as the sample is heated, indicates the glass transition region (Craig et al., 1999). A large proportion of pharmaceutical polymers and macromolecular protein and peptide materials are classified as strong glass formers, thus having relatively small changes in their heat capacity over T_g (McPhillips et al., 1999; Huang and McKenna, 2001). Therefore, when analysing strong glass formers or when the amount of amorphous content is low, DSC encounters difficulties detecting T_g (McPhillips et al., 1999). DMA's high sensitivity towards the glass transition (Kararli et al., 1990) indicates that it is an interesting alternative for the detection and measurement of T_g for powdered samples when other techniques fail. Thus the aim of this study was to evaluate a new DMA sample holder designed to measure glass transition temperatures associated with powders and to determine the experimental parameters that will provide accurate and repeatable values of T_g.

Dynamic mechanical analysis applies a sinusoidal deformation to a material. In the instrumental setup used, the oscillating deformation is controlled to a fixed maximum amplitude which is often

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referred to as strain. The strain is determined from a ratio of dimensions, i.e. the changed dimensions divided by the original dimensions and so is a dimensionless quantity. The oscillating force per unit area required to maintain the set maximum deformation amplitude or fixed maximum strain is measured. Therefore, the primary signals measured are the stress, measured as a force per unit area (Pa), and the phase angle between strain and stress phases (δ).

These are converted to the analysed parameters storage modulus (G'), loss modulus (G'') and $\tan\delta$ (G''/G').

The frequency of deformation is normally fixed at a single frequency or varied across a frequency range to explore the time dependant nature of the sample's transitions. Typically, the sample is heated in a controlled linear manner, in the range of 1–5 °C/min. The range of the glass transition is frequency dependent and will increase as the measurement frequency increases because it is time dependent in nature (Menard, 1999). The storage modulus is a measure of a material's resistance to deformation and indicates its elastic nature. In simple terms it is an indication of how much mechanical energy is stored in the material during deformation that will be recovered when the stress is released. Conversely, loss modulus reflects the material's viscous nature, i.e. how much mechanical energy is lost during deformation. This can be thought of as how much energy is converted to heat through molecular movements to release stress in the material whilst under deformation. The ratio G''/G' is equal to $\tan\delta$, the value of which gives an indication of the viscoelastic nature of the material. For instance, a $\tan\delta$ lower than unity implies an elastic nature of the material whereas when the ratio is above unity the material is more viscous.

2. Materials and methods

2.1. Sample preparation

2.1.1. Materials

Hydroxypropyl methyl cellulose (HPMC) was selected for its stability, film forming properties and its very small step change in heat capacity over the glass transition region (Kararli et al., 1990; Huang and McKenna, 2001). Thus this material was a good test for our new powder sample holder. HPMC-Methocel E4M premium USP/EP IF10200 Batch No.: SL09012N01 was kindly donated by Colorcon Limited UK, and was used as received. (HPMC E4M has an average molecular mass of 95,000, a methoxyl and hydroxypropyl content of 29.3% and 8.4% respectively.) Aluminium oxide (Al_2O_3, mesh < 100 μm, 99.9%) was obtained from Sigma–Aldrich, UK and used as received.

2.1.2. Powder mix preparation

HPMC and aluminium oxide were mixed in appropriate proportions (for details see Section 2.2.3) by weighing into glass vials which were sealed and rotated and tapped by hand repeatedly (at least 50 times) to make a homogenous mixture and to avoid either of the components sticking to the glass wall or the cap.

2.1.3. HPMC film preparation

For reference measurements in a conventional clamp, films of pure HPMC were produced by pouring a 2% (w/v) water solution of the HPMC (McPhillips et al., 1999) onto a levelled glass plate. After overnight drying at room temperature the film that formed was removed from the plate and stored in an evacuated desiccator over silica gel for at least 24 h.

2.2. DMA

2.2.1. Instrumentation

A TA instruments Q800 Dynamic Mechanical Analyser in conjunction with a liquid nitrogen cooling system was used throughout the study. All measurements were performed using a heating rate of 3 °C/min from either 0 °C or 80 °C to 240 °C. The DMA was operated by the application of a sinusoidal deformation to the powder sample holder (details see below) at a fixed strain. The amplitude was 20 μm and the frequency of deformation (oscillating frequency) was alternated between 100 Hz, 10 Hz and 1 Hz, as the temperature was increased.

2.2.2. Powder sample holder

The new powder sample holder was designed and custom made to generate a defined geometry to contain powder. The sample holder consisted of a rectangular stainless steel open container with inner dimensions of 60 mm × 11 mm × 1 mm (Fig. 1) and a lid. A preweighed mass of powder was evenly spread within this shallow container, and the upper plate (lid) was then placed onto the top surface of the powder. The dimensions of the lid were engineered to allow an exact fit within the walls of the container. This configuration was then loaded into the dual cantilever configuration and the clamps tightened to the required pressure. The clamps apply pressure to the sample via the three raised blocks on the upper tray. Adjustment of the clamping pressure using a torque wrench enabled control and even distribution of the pressure exerted by the lid on the powder bed within the holder. The sample holder was mounted in the instrument in a dual cantilever clamp so that during measurement the DMA oscillated the sample perpendicular to the base plane of the sample holder by a vertical motion of the middle clamp (Fig. 1).

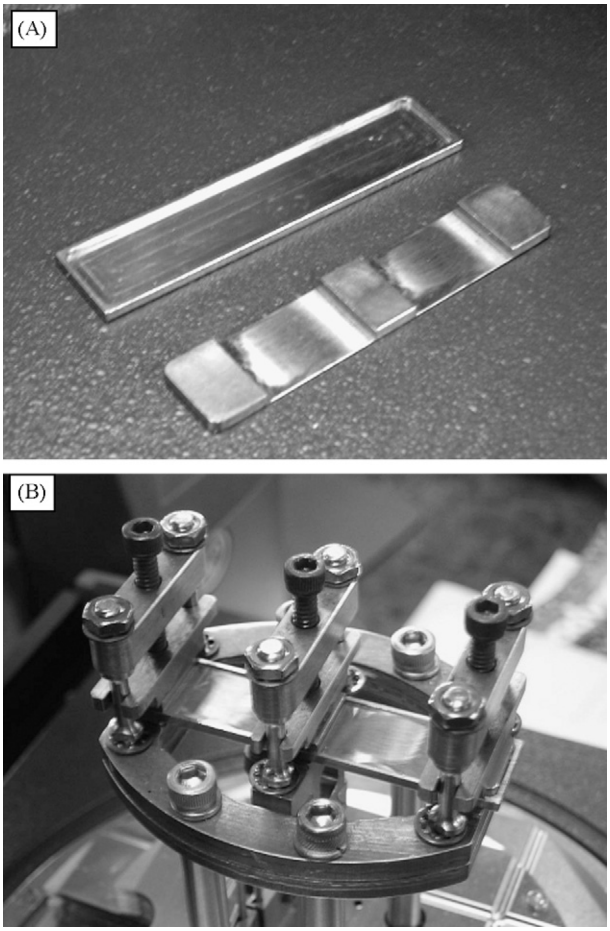

Fig. 1. (A) The new powder DMA sample holder, which consists of a rectangular stainless steel open container with inner dimensions of 60 mm × 11 mm × 1 mm into which the powder mix was placed. (B) Holder clamped into the DMA with the powdered sample sandwiched between the bottom of the holder and the detachable lid.

Table 1
Parameter values chosen in high/low design of experiment.

Parameters	Low	High
Total loading mass	120 mg	180 mg
Clamping pressure	14 kPa	62 kPa
Weight fraction HPMC in powder mixture	0.2	0.5

2.2.3. *Design of experiment*

After some preliminary experiments using small amounts of HPMC alone (1–10 mg) and in ~30% mixture with aluminium oxide (100–200 mg) three experimental parameters were picked to be varied systematically to determine the optimum conditions for the powder holder; total loading mass, mass fraction (w/w) of HPMC diluted by aluminium oxide and clamping pressure. Two values were chosen, one high and one low on a scale within the operational range of each parameter (Table 1). Measurements on all possible combinations of these parameters were performed in triplicate.

2.2.4. *Data analysis*

The T_g was determined from plots of storage modulus, G', loss modulus, G'', and $\tan\delta$ as a function of temperature using the software provided with the instrument (Universal Analysis, TA Instruments). T_g was taken as the mid-point of the step change on the G' curve and temperature at signal peak max for the G'' curve and $\tan\delta$ curves.

2.3. *Modulated temperature differential scanning calorimetry (MDSC)*

MDSC performed on TA Instruments Q2920 was also used to determine the T_g of powder samples of the HPMC. 7–11 mg of powder was weighed into 50 μl pin-holed aluminium pans and then analysed by applying a temperature programme where the oscillating amplitude was 0.5 °C and each oscillation period 40 s. The underlying heating rate was 3 °C/min going from 0 °C to 240 °C. The runs were performed under a dry nitrogen purge. T_g was determined from the mid-point in the step transition of the reversing heat flow signal.

3. Results and discussion

3.1. *Powder holder*

Initial DMA runs on 1–10 mg of pure HPMC gave results as those shown in Fig. 2. The low sample mass range was used to reduce the risk of overflow of de-vitrified HPMC post T_g. For all the samples a loss of mechanical strength was observed above 160 °C, indicated by the drop in G' which reflects the occurrence of a glass transition (Menard, 1999). This event is seen as a peak in G'' and $\tan\delta$. The response of the HPMC powder to the thermal ramping was similar to what was observed for the HPMC films when clamped into conventional tensile clamp. Furthermore, the T_g showed the frequency dependence which is normally seen in the DMA analysis of glass transitions associated with self-supporting materials (Menard, 1999).

In some experiments after the heating cycle was complete, it was difficult to remove the lid from the holder because the polymer effectively served as glue. To minimize the possible effect of interactions between the powder and holder and also to attain an even distribution of the powder in the sample holder, we introduced the procedure of using a diluent. The sample powder was mixed with an inert and free-flowing powder of aluminium oxide before being loaded into the sample holder. The use of a diluent enabled convenient reuse of the holder by easy removal of the lid and washing of the parts. Fig. 3 shows that the magnitude and posi-

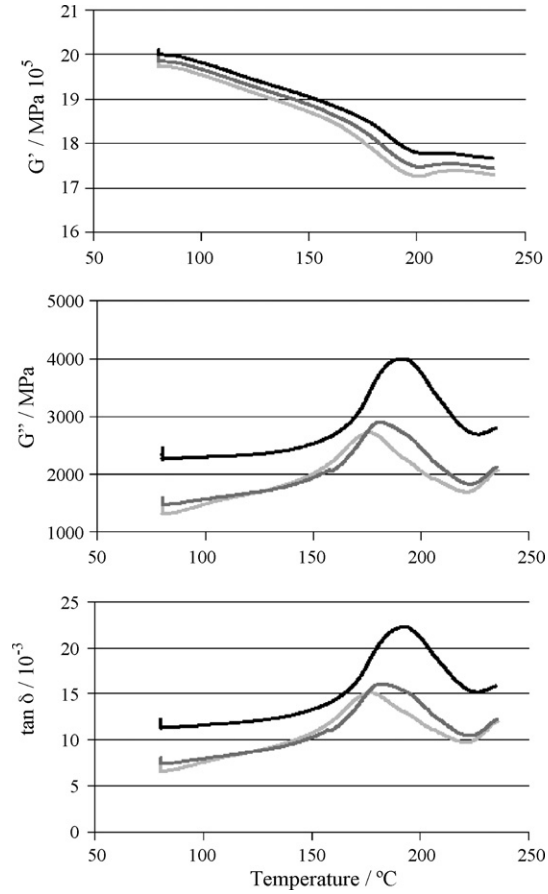

Fig. 2. Mechanical response of 1.8 mg pure HPMC to increasing temperature in the powder sample holder. From top to bottom, storage modulus, loss modulus and $\tan\delta$. Heating rate 3 °C/min, data recorded at oscillation frequencies of 1 (light grey), 10 (dark grey) and 100 Hz (black).

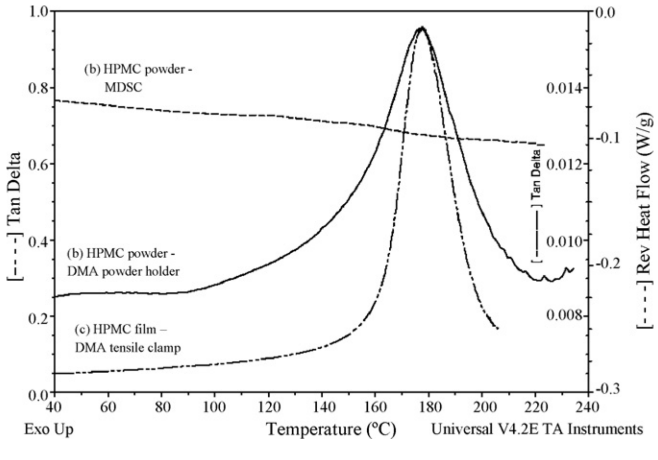

Fig. 3. Signals from thermal analysis of the HPMC by MDSC and DMA. (a) Reversing heat flow signal of MDSC on 10 mg of HPMC powder in a pin-holed Al pan, run on a TA instruments Q2920. Modulation amplitude was set to 0.5 °C, the period to 40 s, and the heating rate 3 °C/min. (b) 1 Hz $\tan\delta$ signal from DMA using powder sample holder. 180 mg of a physical mix of HPMC with Al_2O_3, weight fraction of HPMC 0.2 mg, 36 mg of HPMC in total 62 kPa clamping pressure. (c) 1 Hz $\tan\delta$ signal from conventional DMA using standard tensile film clamp on a HPMC film prepared from the evaporation of a 2% (w/w) solution. The signal associated with the glass transition is much stronger when detected by DMA. The peak maximum temperature obtained by powder DMA overlaps the one from conventional DMA.

tion of the peak in the tan δ signal is preserved when the diluent is introduced. It can be clearly seen that the response of the HPMC powder to heating corresponds closely to the response for HPMC films when clamped into conventional tensile clamp and that their peak maxima overlap. Furthermore, the appearance and location of the storage modulus step transition and loss modulus peak at T_g were very similar to the results without diluent (data not shown). Also in Fig. 3 for comparison, the reversed heat signal from the MDSC analysis of the HPMC is shown. It highlights the difficulties to determine the T_g with DSC, due to the very small change in the heat capacity of HPMC.

It should be noted that all of the DMA signals reflect the mechanical response of the holder, the diluent and the sample powder combined. However, the holder and the diluent alone showed a flat, transitionless response when heated and therefore any peaks or step transitions can be attributed to the transitions of the sample.

3.2. Optimization of experimental parameters

A design of experiment procedure was applied in order to find the optimum conditions for using the powder holder to analyse HPMC powders. Three experimental parameters were considered to be important to evaluate; the total weight of powder mix used, the ratio between the sample powder (HPMC) and the diluent, and the clamping pressure. Two values, one high and one low on a scale judged to be within the operational range of each parameter, were picked (2^3 design) in order to efficiently explore the design-space of interest with a practical number of experiments. By keeping within the operational range of each parameter, and guided by the prelim-

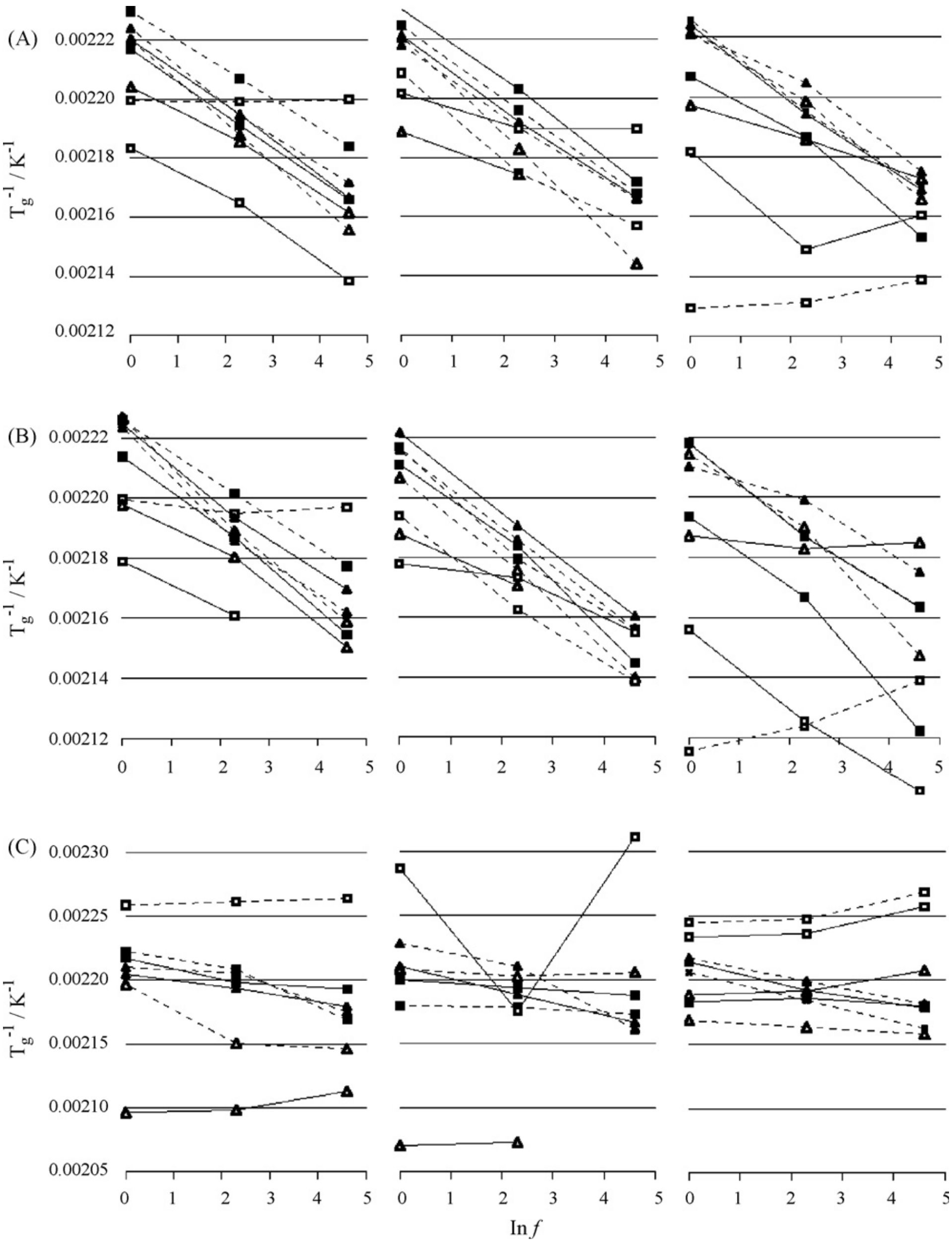

Fig. 4. Reciprocal T_g plotted against the natural logarithm of frequency (ln f). T_gs were determined from peaks in (A) loss modulus, (B) tan δ and (C) mid-point of the storage modulus step change. Each line with connected data point markers corresponds to a single set of parameters: 120 mg (dashed line) and 180 mg (solid line) sample weight, 14 kPa (hollow markers) and 62 kPa (solid markers), 0.2 weight fraction (triangle markers) and 0.5 weight fraction (square markers) of HPMC sample in powder mixture with aluminium oxide. Reproducibility was evaluated by comparing the position of the data points on the y-axis between the repeats (left, mid and right column being first, second and third repeat respectively). Linearity of the plots was used as the second evaluation criteria for optimal parameter setup.

inary results, we judged that the response was likely to be either monotonic or nearly so within these limits. The rationale for specific selections were as follows; the weight of powder mix loaded was limited, on the lower end, by the need to attain an even distribution of the powder mix in the holder and, on the upper end, by the need to avoid overfilling and thus overflow of material above T_g. The high and low values for the ratio between the sample powder (HPMC) to the diluent were dictated by the balance between good powder flow, provided by the diluent, and enough amorphous material to be detected. The clamping pressure value was chosen to avoid spikes and noise in the data which would result from excessive movement of the powder within the holder. Hence, in the optimization experiment, the total weight of powder mix used was either 120 mg or 180 mg, the weight fraction between the sample powder (HPMC) in the diluent (alumina oxide) either 0.2 or 0.5, and the clamping pressure either 14 kPa or 62 kPa.

The data analysis involved two stages. Firstly, parameter combinations that did not produce reproducible peak maximum temperatures (T_gs) in the tan δ and G'' signals were considered sub-optimal. Secondly, the frequency dependence of T_g was used as an indicator of the optimal parameters. HPMC is a strong glass former, and as such displays Arrhenius behaviour whereby T_g increases when the frequency of oscillation is raised (Huang and McKenna, 2001). This Arrhenius behaviour was confirmed when the reciprocal of T_g was plotted against the natural logarithm of oscillation frequency, because linear relationships were observed for nearly all of the parameter combinations (Fig. 4). Thus the parameter combinations which produced linear regression coefficients, R^2 values, closest to 1 in the Arrhenius plots were considered optimal. In Fig. 4 this is evaluated by comparing the reproducibility of the data values between the repeats, i.e. the value consistency between plots within each row of diagrams, and by looking at the linearity of the plots for each setup. For example, many of the samples run at low clamping pressure (unfilled markers) could be excluded since they were being both inconsistent upon repetition and non-linear in the plots. Further exclusion of sub-optimal data sets left two parameters settings to be the most favourable. A pressure of 62 kPa, a mass ratio of 0.2 and a loading mass of both 120 mg and 180 mg showed a low variation between repeats and yielded best linearity of the combinations tried. These two sets of parameters were run for a further six repeats in order to establish the true optimum set. In Fig. 5 an Arrhenius plot of these two are shown. Using a sample size of 120 mg gave a slightly better fit of straight line ($R^2 = 0.953$) compared to the 180 mg sample ($R^2 = 0.913$). Both setups gave a T_g of 177 ± 1.2 °C at 1 Hz and activation energy of 704 kJ mol^{-1} and 707 kJ mol^{-1} respectively. The T_g values are comparable to the values determined on a HPMC film in conventional DMA tensile clamp (178 ± 0.5 °C).

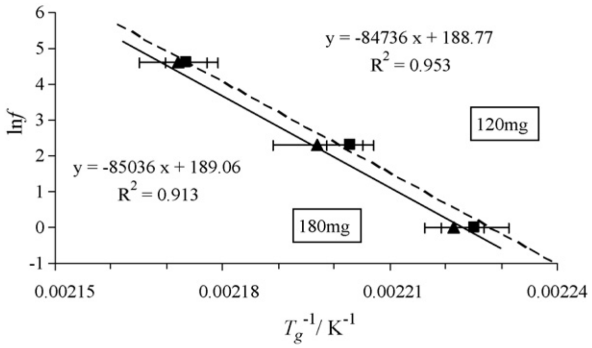

Fig. 5. Arrhenius plot of HPMC powders run in the DMA powder holder at optimized conditions and at two different loaded weights, 120 mg (dashed line) and 180 mg (solid line). Plotted points showing average values ($n = 6$) and error bars the standard deviation. Straight lines fitted to individual data values.

The common features of the two best setups are high proportion of the diluent (a weight fraction of 0.8) in the powder mix and a high clamping pressure. A possible explanation for this combination of parameters to be superior may be that a large proportion of diluent in the powder mix probably gives good flow properties which, together with a high enough clamping pressure, assured a good packing of the powder in the holder. This would also indicate that the optimum parameters will depend on the flow properties of the examined powder. As evident from the data a free-flowing diluent can reduce such influences and in this way make possible to arrive at values overlapping those of non-granular forms of the material. At a weight fraction of 0.8 of the diluent the powder properties seems to dominate the properties of the powder mix. However, the results also suggest that parameters may have to be optimized for each separate powder analysed. The optimization here presented may serve as a simple and straightforward protocol for this purpose.

Ideally the T_g values obtained with the new sample holder should be compared with data obtained for untreated powder on a well-established method. Hence, in this study we included reference measurements on the HPMC E4M using MDSC. However, as mentioned previously, the T_g of HPMC is inherently difficult to detect using MDSC. After some difficulty, a weak step change in the reversing heat flow signal could be detected giving a T_g value of 165 ± 0.5 °C close to 162 °C determined by (McPhillips et al., 1999). This value is slightly lower than the one obtained by DMA. However, at very low oscillation frequencies DMA would produce T_g values more similar to the ones from DSC measurements. If the linear relationship between ln f and $1/T_g$ shown in Fig. 5 were to be extrapolated, the oscillation frequency required to give a T_g similar to the value determined by DSC measurements can be estimated. For instance, assuming a timescale of a minute, which corresponds to an oscillation frequency of around 0.01 Hz, gives a T_g of 165 °C or 166 °C, depending on which of the two Arrhenius plots from Fig. 5 are used. On the basis of this and the very close similarity to the data obtained on films analysed by conventional DMA (Fig. 3) we conclude that the powder holder produced accurate T_g values.

4. Conclusion

It is apparent that the novel powder holder together with a diluent powder allows DMA to measure the T_g of pharmaceutical powders. A set of parameters were determined that gave an accurate and repeatable value for the T_g of HPMC. Hence, this publication demonstrates a simple optimization protocol, making use of the Arrhenius behaviour associated with strong glass formers, which may be used for other powders to be analysed by DMA. As the T_g of an amorphous material is accompanied by a large change in its mechanical properties the newly developed DMA powder holder has the potential to detect very small amounts of amorphous content in powders and characterise the glass transitional behaviour of strong glass formers which are difficult to analysis by non-mechanical approaches.

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