An Evaluation of the Use of Modulated Temperature DSC as a Means of Assessing the Relaxation Behaviour of Amorphous Lactose

Duncan Q. M. Craig,[1,3] Merete Barsnes,[2] Paul G. Royall,[1] and Vicky L. Kett[1]

Received February 22, 2000; accepted March 8, 2000

Purpose. To evaluate the use of Modulated Temperature DSC (MTDSC) as a means of assessing the relaxation behaviour of amorphous lactose via measurement of the heat capacity, glass transition (*Tg*) and relaxation endotherm.

Methods. Samples of amorphous lactose were prepared by freeze drying. MTDSC was conducted using a TA Instruments 2920 MDSC using a heating rate of 2°C/minute, a modulation amplitude of ±0.3°C and a period of 60 seconds. Samples were cycled by heating to 140°C and cooling to a range of annealing temperatures between 80°C and 100°C, followed by reheating through the *Tg* region. Systems were then recooled to allow for correction of the *Tg* shift effect.

Results. MTDSC enabled separation of the glass transition from the relaxation endotherm, thereby facilitating calculation of the relaxation time as a function of temperature. The relative merits of using MTDSC for the assessment of relaxation processes are discussed. In addition, the use of the fictive temperature rather than the experimentally derived *Tg* is outlined.

Conclusions. MTDSC allows assessment of the glass transition temperature, the magnitude of the relaxation endotherm and the value of the heat capacity, thus facilitating calculation of relaxation times. Limitations identified with the approach include the slow scanning speed, the need for careful choice of experimental parameters and the *Tg* shift effect.

KEY WORDS: amorphous; freeze drying; glass transition; lactose; relaxation time; modulated temperature differential scanning calorimetry.

INTRODUCTION

There has been considerable interest in developing means by which not only the glass transition but also the relaxation behaviour of amorphous pharmaceutical systems may be characterised (1–3). Such information is of importance not only in terms of characterising molecular mobility, which may be related to physical and chemical stability, but also in understanding changes in macroscopic properties such as mechanical strength with time (4,5). One method by which measurement of the relaxation time below the glass transition temperature may be achieved is via assessment of the enthalpy relaxation behaviour on storage (6–8). Figure 1 indicates the enthalpic processes involved. The system is initially in the liquid state and forms a glass on rapid cooling, whereby the system departs from the equilibrium liquid enthalpy curve.[4] At point T_S the system is in a non-equilibrium state and time-dependent relaxation takes place. The magnitude of the enthalpy change on relaxation to the extrapolated liquid state at T_S is given by $\Delta H_{\infty(TS)}$. This value may be estimated via

$$\Delta H_{\infty(TS)} = (Tg - T_S)\Delta C_p \quad (1)$$

where *Tg* is the (fictive) glass transition temperature and ΔC_p is the change in heat capacity between the glass and the liquid at *Tg*. The measured enthalpic recovery ΔH at temperature (T_S) and time (t_S) is then given by the empirical equation

$$\Delta H(t_S T_S) = \Delta H_\infty(T_S)[1 - \Phi(t_S)] \quad (2)$$

where $\Phi(t)$ is the relaxation function which may be related to the relaxation time via the Williams-Watt expression

$$\Phi(t) = \exp[-(t/t_c)^\beta] \quad (3)$$

where β is a power law function which is associated with the distribution of relaxation times and t_c is a characteristic time which is usually considered to be equivalent to the average relaxation time τ.

Recently, Hancock *et al.* (2) used differential scanning calorimetry (DSC) to characterise relaxation parameters for a range of pharmaceutically relevant glasses, deriving the relaxation times and corresponding activation energies for these materials. While this approach is undoubtedly of considerable interest for the characterisation of pharmaceuticals, there are experimental difficulties associated with these measurements. To perform the above calculation, the operator must know the glass transition temperature *Tg*, the magnitude of the enthalpic relaxation and the change in heat capacity through the glass transition. It is inevitably necessary to use one of a range of estimation techniques to quantify the experimental glass transition and relaxation endotherm using conventional DSC, while accurately measuring the heat capacity is a laborious process requiring heat flux measurements to be made at a range of scanning speeds.

Modulated Temperature DSC (MTDSC) is a recently introduced development of conventional DSC whereby a modulation is superimposed on the underlying heating or cooling signal, thereby facilitating measurement of the experimental glass transition, the relaxation endotherm and the heat capacity. In this study, we examine the use of MTDSC as a means of characterising the relaxation behaviour of amorphous lactose with the twin objectives of identifying the strengths and weaknesses of the use of the technique in this application and also as a means of providing information on the relaxation characteristics of a pharmaceutically important material.

[1] The School of Pharmacy, The Queen's University of Belfast, Belfast, UK.

[2] The School of Pharmacy, University of Oslo, Oslo, Norway.

[3] To whom correspondence should be addressed. (e-mail: duncan.craig@qub.ac.uk)

[4] For completeness, it should be noted that the equilibrium liquid curve will not decrease with lowering temperature indefinitely as otherwise the curve would cross the solidus line (the Kauzmann paradox). The following argument is therefore valid only above the thermodynamic glass transition temperature that may be regarded as the *Tg* value obtained at an infinitesimally slow cooling rate.

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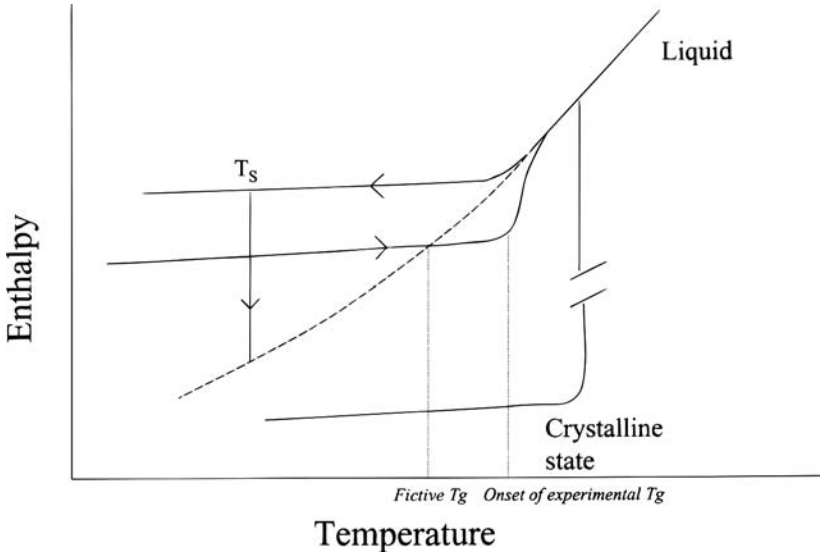

Fig. 1. Schematic representation of the temperature dependence of the enthalpy for a glass forming system.

MATERIALS AND METHODS

Materials and Sample Preparation

Samples of α-lactose monohydrate (BDH) were prepared as 10% w/v solutions in 2 ml aliquots and frozen (−18°C). Samples were then freeze dried in an Edward Modulyo Drier with RV8 rotary vacuum pump. The condenser was preset with a shelf temperature of −60°C and the drying time used was 21 hours followed by 5 hours secondary drying. Water contents were measured as being <3% w/w using thermogravimetric analysis.

Methods

MTDSC studies were performed using a TA Instruments 2920 DSC with refrigerated cooling system using a heating rate of 2°C/min, a modulation amplitude of ±0.3°C and a period of 60 seconds. Temperature calibration was performed using n-decane, cyclohexane and indium, while C_p calibration was performed using a one-point method at the glass transition temperature as outlined by Hill *et al.* (9) using powdered sapphire of known mass (c.10 mg) as a calibrant.

Samples of 4 to 5 mg lactose were weighed into matched pinholed pans (Perkin Elmer) and heated to 140°C (approximately 25°C above *Tg*), held for five minutes and then cooled through the glass transition to one of a range of storage temperatures (80°C–100°C). This protocol also served to drive off the excess water associated with the sample (10). The samples were annealed for up to 16 hours at each temperature before heating back to 140°C and recooling back to the annealing temperature. Nitrogen was used as the purge gas with a flow rate of 40 cm^3/min through the DSC cell.

RESULTS

The MTDSC approach was found to allow separation of the total heat flow signal into the reversing and non-reversing signals, as shown for a specimen sample in Fig. 2. These two signals are related to the heat capacity and kinetically hindered components of the response according to

$$dQ/dt = Cp.dT/dt + f(t, T) \quad (4)$$

where dQ/dt is the total heat flow, dT/dt is the temperature scanning rate with $Cp.dT/dt$ representing the reversing signal and $f(t, T)$ is a function of time and temperature representing kinetically controlled thermal events such as the enthalpic relaxation process which appears in the non-reversing signal (11,12). The heat capacity obtained from Eq. (4) is a complex quantity, hence it is possible to resolve this parameter into real and imaginary components (13). In practice, the phase angle tends to be extremely small in the glassy region; indeed, this has been found to be the case for amorphous lactose (10) and hence this issue is not considered further in this study. It is appreciated, however, that there is undoubtedly further information to be

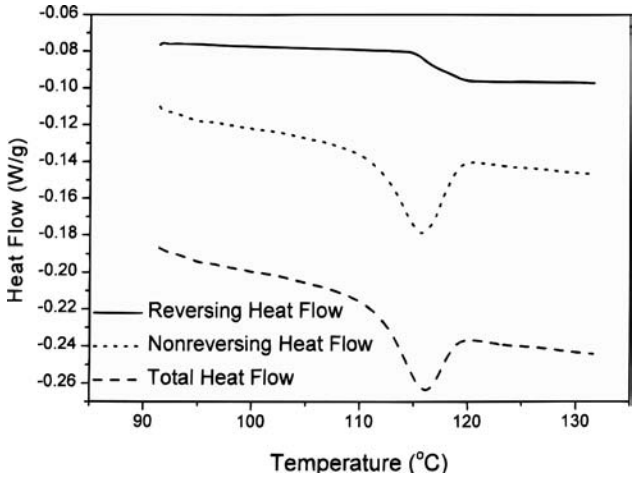

Fig. 2. MTDSC response for amorphous lactose, showing the total, reversing and non-reversing heat flow signals.

gained from this parameter, although at present the physical significance of *Cp″* is not fully understood.

Inspection of Fig. 2 indicates the primary advantage of the use of MTDSC, namely the separation of the signal into real and imaginary components, thereby allowing clear visualisation (and, at least theoretically, quantification) of the glass transition and relaxation endotherm. These signals were then obtained for lactose systems annealed at temperature between 80°C and 100°C for up to 16 hours. Typical responses for systems held at 90°C are shown in Fig. 3 for the reversing and non-reversing signals. There are, however, also disadvantages associated with the technique, some of which have been outlined in previous communications (10,11). These include the necessity of using slow scan speeds in order to maintain steady state through the required number of oscillations, resulting in longer experimental running times and the possibility of annealing during the cycling process. In addition, there is a need to consider more experimental parameters than is the case for conventional DSC and also to account for the artefact generated in the non-reversing signal. This last consideration is particularly pertinent to these studies. In essence, the reversing signal will yield an experimental glass transition that is slightly higher than that obtained from the underlying (linear) heating signal due to the *Tg* being obtained from the response to the oscillation rather than the baseline signal *per se*. Consequently, the *Tg* will be slightly higher in the reversing signal, hence on subtraction from the total heat flow this will result in an apparent contribution to the non-reversing heat flow (the *Tg* shift effect, (12)). This must be corrected for when quantifying the relaxation endotherm, hence the samples were cooled back through the *Tg* in order to quantify and hence correct for this artefact. The same separation procedure was applied to systems held at a range of annealing temperatures for up to 16 hours. A very consistent value of 0.59J/g was found for the magnitude of the non-reversing enthalpy on cooling which was then subtracted from the value on reheating.

Calculation of the relaxation parameters has been performed in the standard manner using Eqs. (1)–(3), with the value of β set to 1 as given the magnitude of the enthalpic relaxation peaks it was not possible to precisely determine non-unity values for this parameter with confidence. Specimen data is given for the 90°C samples in Table 1, while Fig. 4 gives the corresponding values for the relaxation function against time at 90°C. The relaxation times at the various annealing temperatures are shown in Fig. 5, yielding values that are of the same order of magnitude as those reported previously [e.g., 2].

Table 1. Measured Parameters for Freeze Dried Lactose Annealed at 90°C

Annealing time	Tg (°C)	Fictive Temperature (°C)	Enthalpy (J/g)	Δ Cp (J/g/°C)
10 minutes	117.2	115.2	2.75	0.49
1 hour	116.8	115.3	3.19	0.49
2 hours	117.2	115.5	3.16	0.46
4 hours	116.8	115.4	4.12	0.49
8 hours	117.6	115.8	4.69	0.50
16 hours	116.0	115.8	5.69	0.52

Note. Tg refers to the experimentally derived glass transition temperature derived from the reversing heat flow signal. The enthalpy values are derived from the non-reversing heat flow signal and have been corrected for the *Tg* shift effect. Data represent the mean of at least four measurements with coefficients of variation <1% for *Tg* values, <5% for enthalpy values and <8% for heat capacity values.

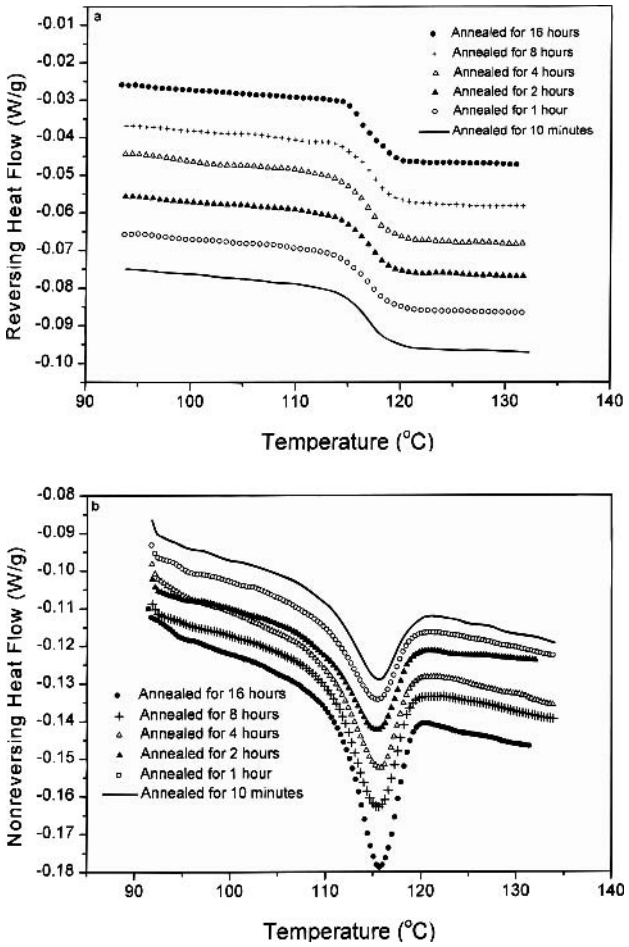

Fig. 3. MTDSC response for amorphous lactose annealed at 90°C, showing the (a) reversing and (b) non-reversing heat flow signals.

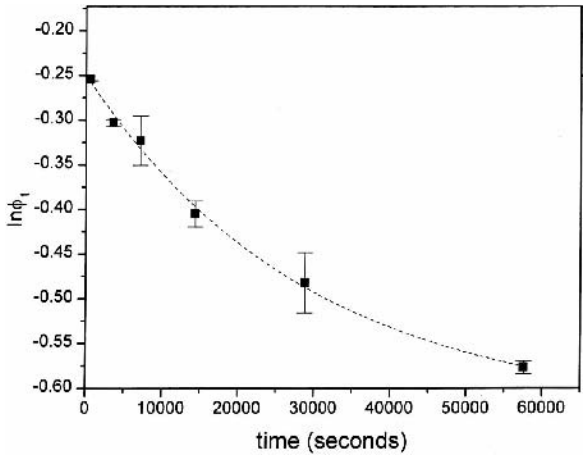

Fig. 4. Relaxation function for amorphous lactose against annealing time at 90°C.

DISCUSSION

As discussed previously, the principal perceived advantage of the use of MTDSC for the measurement of relaxation parameters is the facilitation of the measurement of *Tg*, ΔH (relaxation) and ΔCp at *Tg*. The instrumental artefact associated with relaxation enthalpy measurements has been outlined above, hence in theory one may now simply use Eqs. (1)–(3) to calculate the relaxation times at each temperature. However, there is a further consideration that is not intrinsic to MTDSC measurements but is highlighted by the separation of the heat flow into the reversing and non-reversing signals. Examination of Fig. 1 indicates that the experimental *Tg* on heating for the annealed sample may be greater than that expected from consideration of the enthalpy of the liquid state. Increases in the apparent *Tg* on storage may be interpreted in terms of the dynamic nature of the transition (14,15). In essence, the material is not able to respond to the heating signal instantaneously and superheats through the transition, in the same manner as has been described for the effect of heating rate on the apparent *Tg*. This therefore demonstrates the difficulty associated with measuring *Tg* on the heating cycle, which is unavoidable when using DSC or MTDSC to measure relaxation endotherms.

One way in which this kinetic effect can be avoided is the use of the fictive temperature. This may be defined as the temperature at which the enthalpies of the glassy and liquid state are equal (14,15), thereby removing the dependence of the measurement on experimental detection parameters; this value is represented in Fig. 1. The fictive temperature may be calculated from the values of ΔH and the heat capacity before and after the thermal event and is therefore not dependent on direct observation of the glass transition. The method of Richardson and Savill (14,15) may be summarised as follows. The temperature-dependent heat capacities of the glass (*Cp(g)*) and liquid (*Cp(l)*) may to a first approximation be given by;

$$Cp(g) = a + bT \tag{5}$$

$$Cp(l) = A + BT \tag{6}$$

where *a*, *b*, *A* and *B* are constants which may be easily obtained from the heat capacity signal before and after the glass transition.

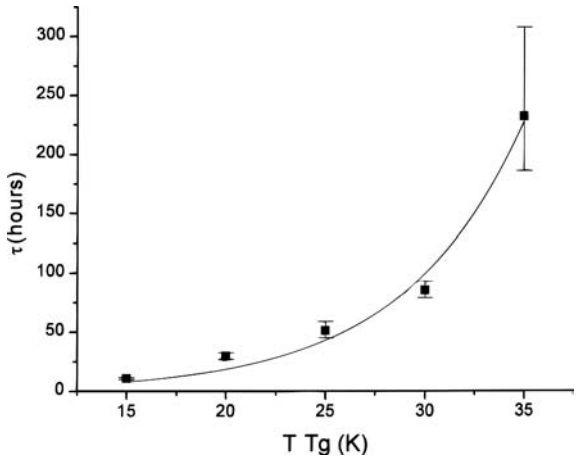

Fig. 5. Relationship between the relaxation time and annealing temperature for amorphous lactose.

Integration of the above expression with respect to temperature gives;

$$H_g(T) = aT + 1/2bT^2 + P \tag{7}$$

and

$$H_l(T) = AT + 1/2BT^2 + Q \tag{8}$$

with *P* and *Q* being integration constants. The value of *P*-*Q* is obtained from the enthalpy change between two temperature points before and after the relaxation endotherm, hence it is a simple task to calculate *T* when $H_g = H_l$, this value being the fictive temperature. It should be noted, therefore, that if one adopts this approach the advantage of the use of MTDSC is not so much the direct observation of *Tg* but the facilitation of heat capacity measurements.

The mean of the experimentally derived values of *Tg* at 90°C was 116.9 ± 0.5°C (calculated from the midpoint of the extrapolated reversing heat flow curves above and below *Tg* using Origin), with no clear trend seen with annealing time. The fictive temperature gave very consistent values of 115.5 ± 0.2°C. Theoretically one would expect a small decrease in the fictive *Tg* with annealing time (Fig. 1) but in this case the trend was too slight to be detected. Clearly, the error involved in the use of the *Tg* derived directly from the reversing signal is small in this case, hence given the approximations involved in the Williams-Watts model it is probably unnecessary to use the fictive value for all but the most accurate work. However, the true benefit of using the fictive temperature almost certainly lies with the use of conventional DSC, whereby clear visualisation of the change in heat capacity through *Tg* is often not possible due to superimposition of the relaxation endotherm. It should, however, be emphasised again that the approach is only of use if adequate heat capacity calibration has been performed.

CONCLUSIONS

The study has served to provide an evaluation of the advantages and disadvantages of using MTDSC as a means of obtaining relaxation data for an important amorphous pharmaceutical system. The advantages of the technique include clear visualisation of the parameters associated with the relaxation (*Tg*, relaxation endotherm, heat capacity), thus greatly facilitating accurate assessment of the relaxation process. The disadvantages include the standard considerations of low scan speed and the necessity to carefully control the experimental variables, while the *Tg* shift effect requires particular attention in this application. A further consideration is the facilitation of the calculation of the fictive temperature via direct measurement of the heat capacity using MTDSC. This parameter is not currently widely used within the pharmaceutical sciences but may prove to be of considerable use as a well defined and scanning rate independent measure of the glass transition temperature.

ACKNOWLEDGMENTS

We wish to thank the EPSRC for provision of funding for Dr. Paul Royall and Professor Jan Karlsen for facilitating the visit of Merete Barsnes from the University of Oslo.

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