ELSEVIER

International Journal of Pharmaceutics 161 (1998) 95–107

international journal of pharmaceutics

Characterisation of spray-dried lactose using modulated differential scanning calorimetry

Vivienne L. Hill [a], Duncan Q.M. Craig [a,*], Liam C. Feely [b]

[a] *Centre for Materials Science, School of Pharmacy, University of London, 29–39 Brunswick Square, London WC1N 1AX, UK*
[b] *International Development Centre, Abbott Laboratories Ltd., Queenborough, Kent ME11 5EL, UK*

Received 21 July 1997; received in revised form 22 September 1997; accepted 1 October 1997

Abstract

Modulated differential scanning calorimetry, a recent development to differential scanning calorimetry, has been investigated as a tool for the characterisation of low moisture content spray-dried lactose. Particular attention was paid to evaluating the effect of experimental parameters, such as pan type, period of modulation, sample mass and calibration method, on the results obtained. The quality of the sine wave oscillation was assessed by plotting the modulated data in the form of a Lissajous figure. It was found that the MDSC technique could be of benefit in the investigation of the amorphous lactose sample by allowing the change in heat capacity at the glass transition to be measured separately from the associated endotherm. © 1998 Elsevier Science B.V.

Keywords: Lactose; Glass transition; Heat capacity; Modulated differential scanning calorimetry; Thermogravimetric analysis

1. Introduction

Modulated differential scanning calorimetry (MDSC) is a relatively recent development from the established technique of differential scanning calorimetry (DSC). In an MDSC experiment a sinusoidally varying temperature programme is used instead of the conventionally linear heating or cooling ramp (Reading et al., 1992). Benefits of MDSC have been shown to include the more accurate measurement of heat capacity, the separation of overlapping thermal transitions and the improved identification of thermal processes (Reading, 1993; Reading et al., 1993; Boller et al., 1994). Although MDSC has been available for several years (the first MDSC instrument was commercialised by TA Instruments in 1992), its use has mainly been restricted to the study of polymers (Sauerbrunn et al., 1993a,b; Sauerbrunn and Thomas, 1995; Boller et al., 1995, 1996; Wun-

* Corresponding author

PII S0378-5173(97)00334-7

derlich et al., 1996) and thermoplastics (Van Assche et al., 1996; Maistros et al., 1997). Very little non-polymeric work has been carried out with the exception of studies on the melting and solidification of metals (O'Reilly and Cantor, 1996) and a limited number of studies in the food and pharmaceutical literature (e.g. Barnes et al., 1993; Aldén et al., 1995; Wulff and Aldén, 1995; Bell and Touma, 1996; Coleman and Craig, 1996; Izzard et al., 1996). Further development of the capabilities and limitations of this technique is therefore required, particularly for pharmaceutical applications.

The aim of this study was to investigate the use of MDSC to characterise spray-dried lactose in order to determine the extent to which the technique can provide extra information compared to conventional DSC. An emphasis has been placed on evaluating the effects of experimental parameters on the results obtained and on the calibration of the data, as very little information is available on this aspect of MDSC usage as applied to pharmaceutical systems. Spray-dried lactose was chosen for investigation, firstly because lactose is a material with considerable pharmaceutical relevance, and secondly because conventional DSC studies show that amorphous lactose demonstrates a range of thermal transitions on heating. Lactose can be converted to an amorphous form by various processes such as spray drying, freeze drying or milling. In the amorphous state the sample will show a characteristic glass transition on heating as the structure changes from a glassy to a more mobile phase. It is important to characterise this transition thoroughly since it may influence many properties of the material, such as the dissolution rate, mechanical properties and physical stability. One of the perceived advantages of MDSC, at least in the study of polymeric systems, is improved measurement of glass transitions, hence it is logical to explore the use of the technique for the characterisation of low molecular weight amorphous materials of pharmaceutical interest. The moisture content of the sample has also been assessed as water is known to plasticise amorphous lactose, thereby lowering the glass transition temperature with concomitant effects on storage stability (Hancock and Zografi, 1994).

1.1. MDSC theory

In MDSC experiments a sinusoidally oscillating temperature ramp (or isotherm) is used instead of the conventionally linear temperature programme. The temperature profile can be characterised by three parameters; the period of oscillation (p), the amplitude of oscillation (A) and the underlying or average heating rate (q). The modulated temperature programme can then be expressed as;

$$T = T_0 + qt + A\ \sin(\omega t) \tag{1}$$

where T = temperature; T_0 = starting temperature; t = time; ω = frequency of the oscillation = $2\pi/p$.

The heat flow in the calorimeter during a conventional DSC experiment is given by;

$$\mathrm{d}Q/\mathrm{d}t = C_\mathrm{p}\mathrm{d}T/\mathrm{d}t + f(t,T) \tag{2}$$

where $\mathrm{d}Q/\mathrm{d}t$ = heat flow; C_p = heat capacity; $\mathrm{d}T/\mathrm{d}t$ = heating rate, q; $f(t,T)$ = a function of time and temperature representing any kinetic response.

When the expression for the modulated temperature is inserted in the equation for the heat flow the following equation is produced, representing the modulated heat flow produced during an MDSC experiment;

$$\mathrm{d}Q/\mathrm{d}t = C_\mathrm{p}(q + A\omega\ \cos(\omega t)) + f'(t,T) + C\ \sin(\omega t) \tag{3}$$

where $(q + A\omega\ \cos(\omega t))$ = derivative modulated temperature; $f'(t,T)$ = the kinetic response excluding the effect of the modulation; C = the amplitude of the kinetic response to the modulation.

In the analysis of the modulated heat flow it is assumed that the temperature oscillation is small enough that the kinetic response over this interval is approximately linear. The contribution due to the sine component can be assessed by measurement of the phase lag between the modulated heat flow and modulated heating rate. When a significant kinetic response to the modulation is observed, the phase lag can also be used to separate this response from the heat capacity component. In the case where the phase lag is negligible, the modulated heat flow can be deconvoluted, using a discrete Fourier transform algorithm, into revers-

ing and non-reversing heat flow. As the data is collected the instrument software measures the amplitude of the sine wave modulation in the modulated temperature and modulated heat flow signals. This is done by comparing the modulated signals to a reference sine wave of the same frequency that is generated by the software. These amplitudes are then used to calculate the sample heat capacity using the equation;

$$C_p = -K_{C_p}(Q_{amp}/T_{amp})(p/2\pi) \quad (4)$$

where K_{C_p} = a heat capacity calibration constant; Q_{amp} = the measured heat flow amplitude; T_{amp} = the measured temperature amplitude.

The heat capacity component is then converted to reversing heat flow by multiplying by the underlying heating rate. The deconvoluted (total) heat flow and temperature are calculated by taking a moving average over one cycle of modulated data. The deconvoluted heat flow is the heat flow response at the underlying heating rate and can be compared to a conventional DSC experiment at the same heating rate. Subtraction of the reversing heat flow from the total heat flow yields the non-reversing heat flow. Thus, the reversing signal will contain the heat flow from processes that are heating rate dependent, and the non-reversing signal will contain the heat flow from processes that are kinetically hindered in some way (i.e. are slow compared to the frequency of the modulation). The deconvolution algorithm looks only for modulation of the chosen frequency when calculating the heat capacity (and hence the reversing signal), so all short-term noise is removed from these signals. Also, since the heat capacity is calculated using modulation amplitudes it is not influenced by instrumental baseline curvature. This helps makes the MDSC technique excellent for the study of glass transitions.

1.2. Experimental variables

The choice of experimental parameters must be carefully made in MDSC experiments, as a poor choice could result in inaccurate or misleading data. In this paper the rationale for choosing experimental parameters has been detailed so as to help develop an understanding of the practical aspects of MDSC experiments. Some examples of poor results are also presented to illustrate these choices. It should be noted that most of the factors discussed are also applicable to obtaining good conventional DSC results, but become more important in MDSC experiments due to the more complex temperature and heat flow profiles. Factors that affect the measured data include the choice of modulation parameters (heating rate, period and amplitude), the quality of the sine wave, the calibration of the data and the pan type.

2. Materials and methods

2.1. Materials

α-Lactose monohydrate was purchased from Sigma Chemicals (Poole, Dorset, UK). A 10% w/v aqueous solution of lactose was spray dried using a Büchi 190 mini spray drier set with an inlet temperature of 130°C, an outlet temperature of 80°C, a pump speed of approximately 5 ml/min, a spray flow of 3 bar and an aspirator setting of 90%. The spray-dried material was stored in a vacuum oven at 50°C and 200 mbar for 24 h and then transferred to a desiccator containing silica gel. Cyclohexane (99.9%, Riedel–de Haën), indium (99.999%, Aldrich), tin (99.999%, Aldrich) and aluminium oxide (99.9%, −100 mesh, Aldrich Gillingham, Dorset, UK) were used for instrument calibration.

2.2. Methods

2.2.1. Thermogravimetric analysis (TGA)

Thermogravimetric analyses were made using a TGA 2950 (TA Instruments, New Castle, DE, USA) using a dry nitrogen purge. Indium was used to calibrate the temperature reading and the instrument was weight calibrated according to the manufacturer's instructions. A heating rate of 10°C/min and open pans were used to determine the moisture content of the lactose sample. A heating rate of 2°C/min was used for runs when the weight loss profile obtained was to be compared with the equivalent MDSC result. In this

case the same sample pan type was used in both the TGA and MDSC.

2.2.2. Modulated differential scanning calorimetry (MDSC)

Modulated differential scanning calorimetry and conventional differential scanning calorimetry analyses were made over a temperature range from -30 to 225°C using a DSC 2920 (TA Instruments) with a refrigerated cooling accessory (RCS) and modulated capability. The DSC cell was purged with 30 cm^3/min dry nitrogen and the RCS was purged with 150 cm^3/min nitrogen or helium as required. The DSC cell was calibrated for baseline using empty pans of matched weight and for temperature using three temperature standards (cyclohexane, $T_m = 6.54$°C; indium, $T_m = 156.61$°C; tin, $T_m = 231.93$°C). Enthalpy and heat capacity calibration were performed post analysis in a spread sheet and are discussed in further detail in a later section. All MDSC experiments were made using pairs of aluminium pans of matched weight, i.e. the empty sample and reference pans were of equal weight to within ± 0.1 mg. Analyses were made using several pan types; open pans, non-hermetically sealed pans and hermetically sealed pans. Hermetically sealed pans were purchased from both TA Instruments and Perkin-Elmer and are referred to in the text as 'hermetic (TA)' and 'hermetic (PE)', respectively.

2.3. Choice of modulation parameters

In MDSC experiments the sensitivity is determined by the instantaneous heating rate, while the resolution is determined by the underlying heating rate. Therefore, when large amplitudes are combined with slow underlying heating rates, it is possible to optimise both sensitivity and resolution. In most cases, MDSC experiments require much slower heating rates than usually used in DSC (typically 1–5°C/min). In this study an underlying heat rate of 2°C/min was chosen. The same rate was used for both the standard DSC and MDSC analyses so that the heat flow signals could be compared.

An important consideration is that there are enough cycles through any exothermic or endothermic peaks to enable the deconvolution process to work properly (TA Instruments DSC 2920 Operators Manual, 1993). It is recommended by the manufacturer that there be at least four cycles through any transition (although the results presented in the next section would suggest that more cycles would be preferable). The period must therefore be chosen in conjunction with the heating rate to ensure that at least this number of cycles appear through the peak; this will require a preliminary analysis of the sample to determine the peak width. It is generally better to slow the heating rate rather than reduce the period as, at very small periods (20 s or less), it may not be possible to achieve the required temperature amplitude, resulting in a distorted sine wave. Large periods are recommended for measuring glass transitions, since they give more accurate heat capacity measurements. If the sample shows both glass transition and melting behaviour, and both are to be measured in the same scan, it will be the width of the peak that dictates the choice of period. For the analysis of this lactose sample a relatively short period of 30 s was required due to the narrowness of the crystallisation exotherm.

Large temperature amplitudes will increase the signal-to-noise ratio and so improve the data. However, for samples that show crystallisation and melting it may be useful to choose a temperature amplitude that does not allow any cooling as part of each cycle. This should prevent any processes from taking place that would not have been seen in a comparable, heat-only conventional DSC experiment. The largest amplitude that can be used without cooling the sample can be calculated from the expression,

$$\text{amplitude} = (\text{heating rate} \cdot \text{period})/(2\pi 60) \quad (5)$$

For the selected modulation parameters of 2°C/min and 30 s, this gives an amplitude of 0.16°C. These parameters were used for the analysis of the lactose sample in each pan type. The same parameters were also used to measure the heat capacity of the aluminium oxide calibration material at 100°C for a range of sample masses in both hermetic pan types and non-hermetic pans. In order to determine how the chosen period would affect the data obtained during the exotherm, the

lactose sample was run in hermetic (TA) pans using a heating rate of 2°C/min, a range of periods between 10 and 80 s, and an amplitude calculated to the keep the derivative temperature amplitude constant for each period. A quasi-isothermal analysis of the lactose sample was made at 20°C using a range of periods between 10 and 90 s, an amplitude of 0.5°C and hermetic (PE) pans, to assess the use of Lissajous figures in assessing the quality of the sine wave modulation.

3. Results and discussions

3.1. Determination of sine wave quality

A Lissajous figure of the modulated heat flow minus the average heat flow plotted against the modulated temperature minus the average temperature can be used to show when a poor choice of parameters has been made (TA Instruments application note TA-210, 1996; Varma-Nair and Wunderlich, 1996). Lissajous figures are composed of two sinusoidally oscillating signals plotted against each other, and the shape of the figure produced depends on the frequency and phase of the two signals. They are commonly used to investigate the harmonic response of a system to an applied harmonic stimulus. In the analysis of MDSC data, the figure will show when the instrument is in steady state; such a plot should be a smooth ellipse. Any distortion of the ellipse would indicate a corresponding distortion of the sine wave due to loss of steady state; any parameters that cause this should then be avoided. In order to determine if such a plot would allow easy assessment of the sine wave, the lactose sample was isothermed at 20°C for 20 min at each period and approximately five cycles are shown for each period setting (Fig. 1). At large periods the figure is a smooth oval indicating that both modulated signals are sine waves of the same frequency. At the shortest periods the trace has become distorted as the heat can no longer be transferred in and out of the sample at the required rate and steady state has been lost. Thus, this method of presenting the data is a good check on the quality of the modulation. Fig. 2 shows the Lissajous figures for the lactose sample run in each pan type; each experiment shows a good ellipse. The slope of the major axis through each ellipse could be used to calculate the heat capacity of the sample, and the width of the ellipse across this axis is a measure of the phase lag. Both measurements are affected by the thermal contact between the sample, pan and DSC cell.

3.2. Calibration and phase correction of data

MDSC experiments require calibration to correct the measured heat capacity signal in the same way that the heat flow is corrected in conventional DSC. This calibration will depend on many factors, including the period, amplitude, pan type, and purge gas. The current software used with the MDSC instrument only allows for one enthalpy and heat capacity calibration point to be entered. Both these values change with changing temperature, so either a value which is correct for the

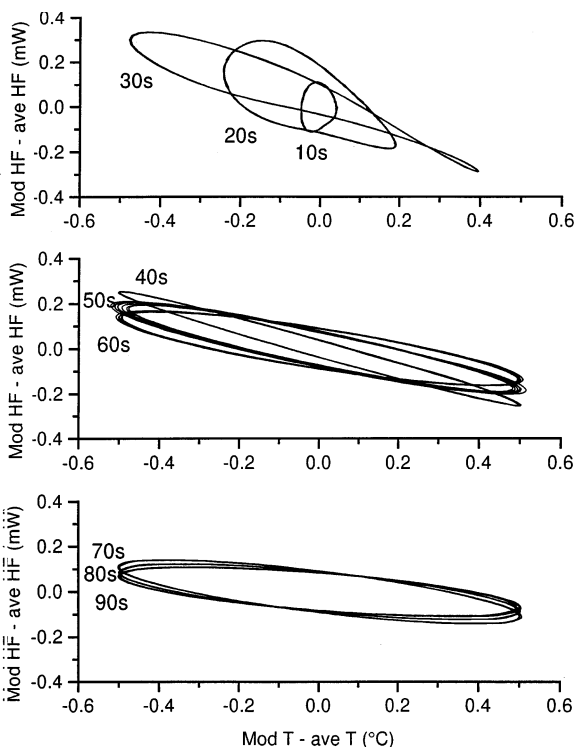

Fig. 1. Lissajous figures for spray-dried lactose analysed quasi-isothermally at 20°C using a range of periods from 10 to 90 s.

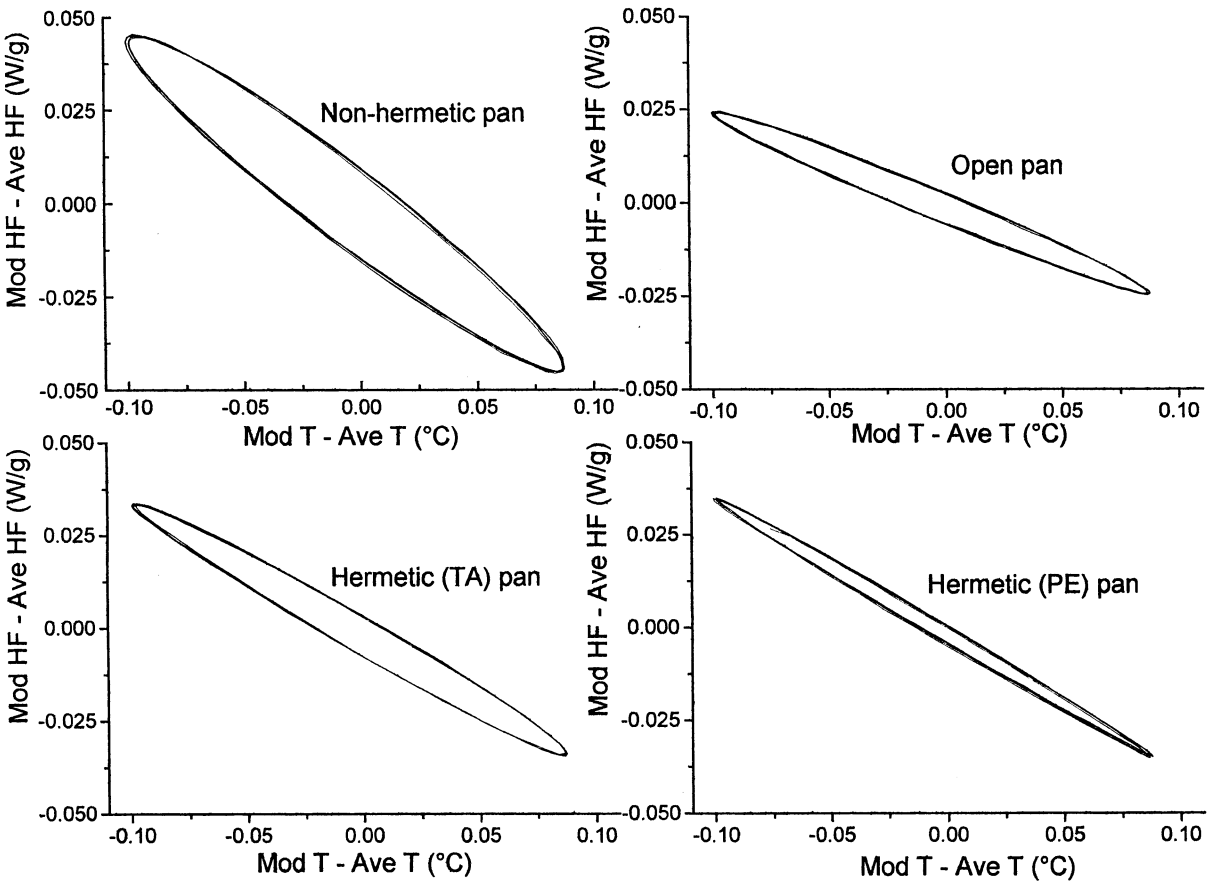

Fig. 2. Lissajous figures for spray-dried lactose run in each DSC pan type. Approximately five cycles are shown for each pan type.

middle of the temperature range or a value representing an average of values for the whole range can be used. It was found that over a temperature range of 25–250°C the measured calibration constants changed by 4% for the non-hermetic pans, 11% for the hermetic (PE) pans and 19% for the open pans. The larger change in calibration constant for the open pans is probably due to poor heat transfer when the sample is not compressed on to the pan base. If the MDSC analysis is being made to aid in the identification of the types of thermal transitions present, this simple one-point calibration will be sufficient. However, if accurate heat capacity data is required over a large range of temperature, a temperature-dependent calibration constant should be calculated. In this study such a calibration was made by comparing the measured heat flow and heat capacity for an aluminium oxide heat capacity standard with the literature values at each temperature. The heat flow and heat capacity measured for empty pans, which is due to the thermal imbalance of the cell, was also measured and subtracted form the data during this method.

For modulation parameters of a heating rate of 2°C/min, a period of 30 s and an amplitude of 0.16°C, the method resulted in a calibration constant of between 1.3 and 1.7 for each pan type, except for the hermetic (TA) pans which gave a much higher value. When various masses of the calibration material (aluminium oxide) were run in this pan type using the same modulation parameters, it was found that the measured heat capacity could not be distinguished from the

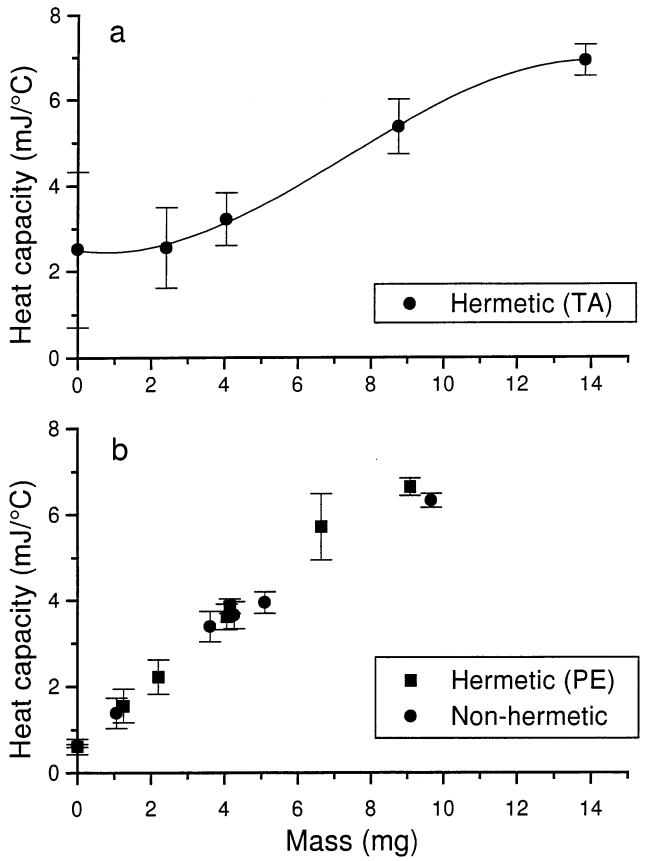

Fig. 3. Measured heat capacity (uncalibrated) for aluminium oxide at 100°C showing the effect of sample mass for both hermetic pan types and non-hermetic pans. Each point is an average of three measurements.

empty pan result at the small masses typically used in MDSC experiments (Fig. 3a). Studies by Varma-Nair and Wunderlich (1996) have also shown difficulties in making accurate heat capacity measurements with this pan type. Other pan types could be used to measure small masses accurately, as the heat capacity showed the expected linear dependence on mass so that the slope would give a specific heat capacity measurement in J/g/°C (Fig. 3b). It is useful, for all pan types, to test a range of sample masses in this way to determine the range over which linearity is seen. When the sample mass is too large, a low heat capacity value can be measured, as seen for the two highest points in Fig. 3b. This happens when temperature gradients build up in the sample. The maximum mass that can be accurately used will depend on the modulation parameters chosen, with longer periods giving more accurate data for large masses.

As discussed earlier, the measured heat capacity, the complex C_p, can be separated into in-phase (rapidly reversing heat capacity) and out-of-phase components using the phase lag signal. There does not yet seem to be a clear understanding of the meaning of the out-of-phase or loss component. This correction of the data was found to make only a 0.2% difference to the measured heat capacity in the region of the glass transition of lactose, and so the method has not been used in this study.

It should also be noted that the difference in pan weights will also cause an error on the measured heat capacity, as any weight difference will

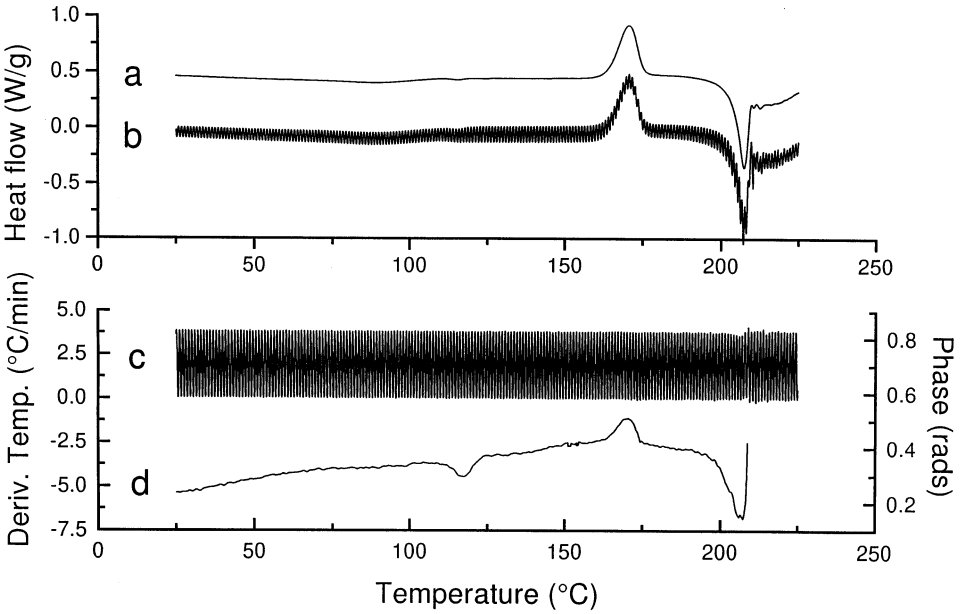

Fig. 4. MDSC raw data (before calibration) for spray-dried lactose: (a) total heat flow; (b) modulated heat flow; (c) modulated derivative temperature; (d) phase lag.

be measured as an excess heat capacity on either the sample or reference side. For small sample masses this is likely to be the major contribution to any inaccuracy in the measured heat capacity, and should be minimised by matching the sample and reference pan weights as closely as possible when accurate heat capacity data are required.

3.3. Identification of thermal transitions by MDSC

Fig. 4 shows the modulated heat flow, modulated derivative temperature, phase lag and deconvoluted heat flow signals produced during an MDSC experiment on spray-dried lactose analysed using the following modulation parameters: 2°C/min heating rate, 30 s period, 0.16°C amplitude and non-hermetic pans. The deconvoluted heat flow has been shifted vertically relative to the modulated signal so that it can be seen easily. The derivative modulated temperature signal shows that the chosen modulation parameters produce a heating profile with an instantaneous minium heating rate of 0°C/min and a maximum of 4°C/min. Thus, the aim of avoiding any cooling as part of each cycle has been achieved. The phase signal shows three small peaks with maxima at 117, 171 and 206°C. As discussed earlier this phase signal was not found to be large enough to influence the accuracy of the measured heat capacity in the glass transition region. Fig. 5 shows the deconvoluted heat flow compared to the heat flow from a standard DSC experiment and the weight profile from a TGA analysis. The sample was heated in a non-hermetic pan using a heating rate of 2°C/min in each case. The heat flow measured by the conventional and modulated techniques was found to be in good agreement with both signals, showing a broad endotherm between 10 and 110°C as residual water is lost from the sample. This is confirmed by the TGA trace which shows a weight loss over the same temperature region. TGA analysis of the lactose sample showed a residual moisture content of $2.6 \pm 0.4\%$ ($n = 10$).

A second small endotherm is seen in both DSC traces with a peak temperature of 116°C. It would be difficult to assign this to a glass transition unless the transition temperature was previously known. Fig. 6 shows the total heat flow, reversing

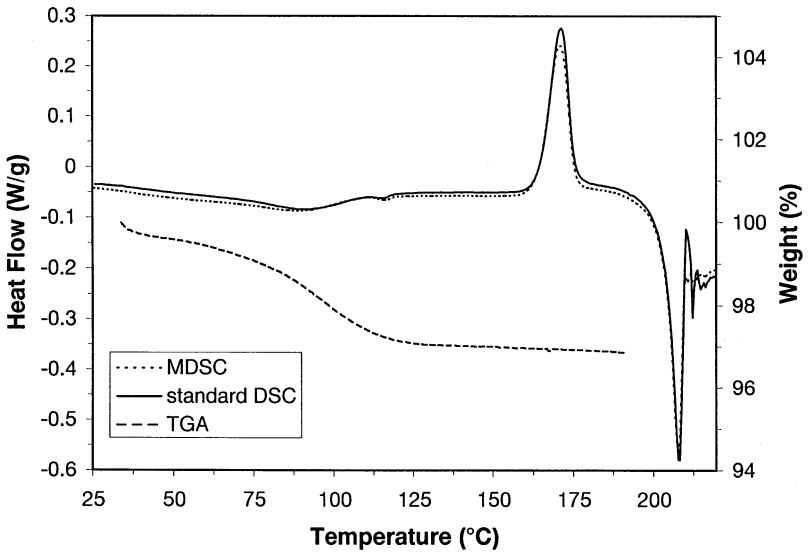

Fig. 5. Comparison of the heat flow from a standard DSC analysis, total heat flow from an MDSC analysis and weight profile from a TGA analysis of the spray-dried lactose sample run in non-hermetic pans.

heat flow and non-reversing heat flow deconvoluted from the MDSC experiment. The separation of the total heat flow into the reversing and non-reversing components by the MDSC method allows the transition to be easily identified. The reversing heat flow clearly shows the endothermic step due to the increase in heat capacity, while the non-reversing signal shows the associated endotherm which masked the heat capacity change in the total and standard DSC heat flows. Thus, MDSC has identified a glass transition that was difficult to determine by conventional DSC. The reversing heat flow signal also revealed a second change in heat capacity as the sample crystallises at 170°C. The exotherm due to the recrystallisation is seen in the non-reversing signal since it is an irreversible process at the time and temperature of measurement. This is followed by melting above 200°C which is seen in both the reversing and non-reversing signals. This suggests that the kinetics of this melting process are such that it can at least in part follow the modulation. However, interpretation of such results are difficult as the use of MDSC for the measurement of melting phenomena is still under investigation.

3.4. Effect of pan type on the transition temperature

The sample can be prepared in various pan configurations for DSC analysis. This can have a marked effect on the results obtained, especially if the sample contains a small amount of residual moisture. Fig. 7a shows the TGA weight profile for spray-dried lactose run in three pan types; open pans, non-hermetic pans and hermetic (PE) pans. In open pans the water can escape easily and the weight loss is seen at the lowest temperature. The non-hermetic pans still allow the water to escape but at higher temperatures. The hermetic pans prevent loss of water up to 200°C. The total heat flow for the spray-dried lactose run in each pan type is shown in Fig. 7b. The curves have been separated on the y-axis so that they do not overlap. The runs made using open pans and non-hermetic pans show similar results with a broad endotherm below 110°C, followed by the small endotherm at the glass transition. The temperatures of the water loss endotherms are in good agreement with the weight loss regions seen in Fig. 7a.

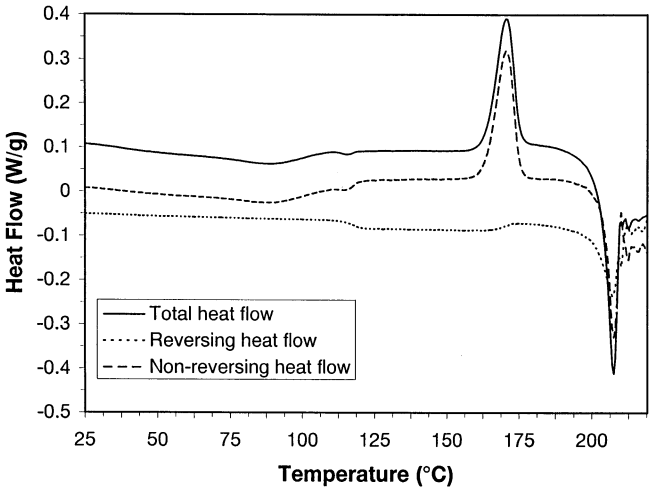

Fig. 6. Deconvoluted heat flow signals for the modulated heat flow shown in Fig. 4. The curves have been separated vertically to aid presentation.

The hermetic pans show a very different result. No broad endotherm is seen below 110°C and the glass transition is seen with an onset at 75°C. This decrease of the glass transition is due to the strong plasticising effect of the residual water on the sample. Similarly, the recrystallisation temperature has been depressed to 129°C. The depression of the glass transition temperature can be easily identified by using MDSC to measured the heat capacity (Fig. 7c). The glass transition onset is seen at 114 and 113°C for the open and non-hermetic pans, and at 83°C for the hermetic pans. The difference in the onset temperature measured from the total heat flow and from the heat capacity is due to the presence of the endotherm in the total (equivalent to the standard DSC) signal. When the glass transition onset is measured from the total heat flow, the value produced is closer to the onset of the endotherm than the onset of the step change in the heat capacity. It was noted that the step change at the glass transition was less defined in the open and hermetic pans, which is probably due to poor thermal contact between the sample and pan. The non-hermetic pans are crimped in such a way that the sample is compressed into the base of the pan.

3.5. Effect of modulation period on calculated total heat flow

Ideally, the total heat flow should be identical to the heat flow obtained from a conventional DSC experiment. However, it is sometimes found that this is not the case (Jin et al., 1996). One cause of such a discrepancy could be the choice of modulation period, as it is thought that when there are insufficient cycles through the peak this can be detrimental to the deconvolution process. In order to test this theory the amorphous lactose sample was analysed using a range a periods from 10 to 80 s. The amplitude was adjusted in each case so that it was the maximum value without introducing cooling as part of the cycle. Fig. 8a shows the total heat flow measured during the recrystallisation exotherm using hermetic (TA) pans; this pan type was chosen as the hermetic pans gave the narrowest peak and so presented the greatest problem. The exothermic peak is seen to become shorter and broader as the period is increased. The deconvolution process has a smoothing effect on the data when there are only a few cycles through the peak (Fig. 8b). This result would imply that the shortest period would be preferred since it gives a results closest to the standard DSC trace. However, care must be taken

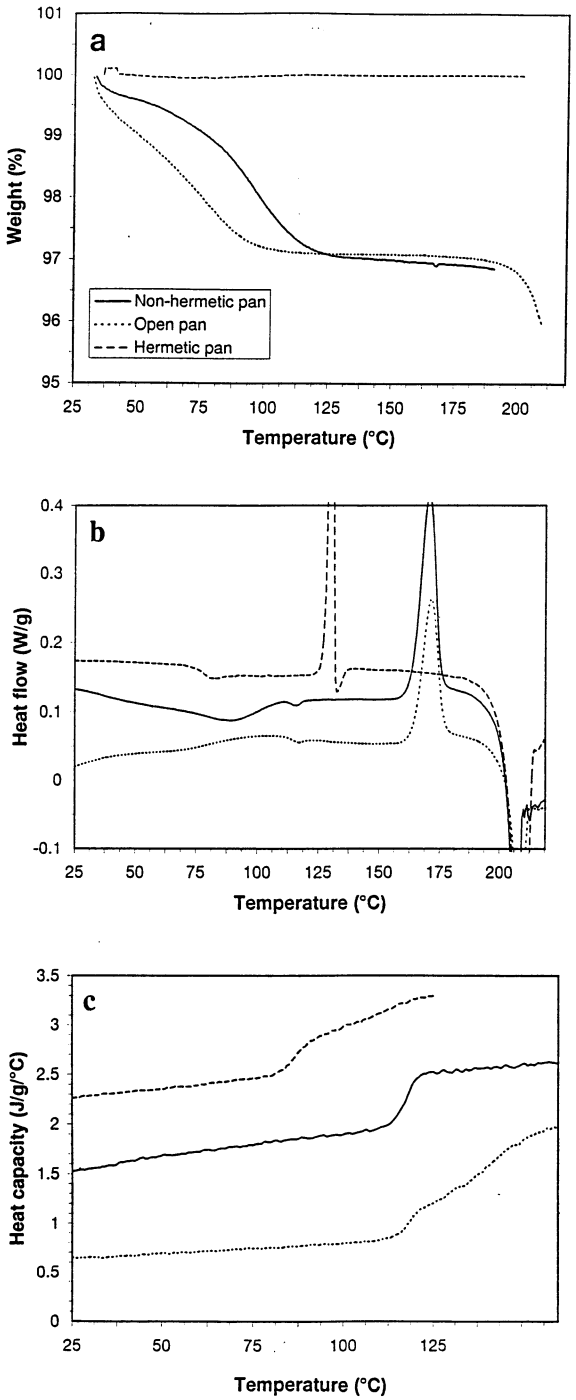

Fig. 7. Analysis of spray-dried lactose in three pan types: (a) TGA weight profiles; (b) MDSC total heat flow; (c) MDSC heat capacity. The curves in plots (b) and (c) have been separated in the y-axis to aid presentation.

with short periods as it may not be possible to reach steady state or achieve the required amplitude. For the combinations of period and amplitude chosen here, all achieved the required amplitude except for the 10-s modulation. The very small amplitude used at this period is not recommended by TA Instruments since such small amplitudes are difficult to detect and control. It should be noted that the maximum and minimum amplitude that can be used at each period will depend on the cooling accessory used.

It was noted that there was some irreproducibility in the crystallisation temperature when these pans were used. This was not found to correlate to the age of the sample, initial water content or sample mass, and was thought to be due to variations in the temperature at which the water escaped from the sample. When these pans were tested in the TGA it was found that the temperature at which the seal ruptured and the water escaped was not reproducible and, in some cases, the water loss was in the region of the crystallisation temperature. This irreproducibility does not detract from the smoothing effect seen at long periods.

4. Conclusions

This investigation into the characterisation of an amorphous sample has shown that there are benefits to using the modulated technique over conventional DSC. The ability to separate reversing and non-reversing heat greatly improves the analysis of the glass transition and allows changes in heat capacity to be revealed where, by conventional DSC, they would be difficult to detect. However, care must be taken with the choice of experimental parameters. The user may need to make several choices of modulation parameters in order to find a combination that best fulfils the requirements of the sample under analysis. The final choice should also be assessed by plotting the Lissajous figure to ensure that steady state can be maintained. For narrow transitions, such as the melting of pure pharmaceutical materials, it may difficult to fulfil the requirement of having enough cycles through the transitions. In such cases quasi-isothermal methods could be considered. Overall,

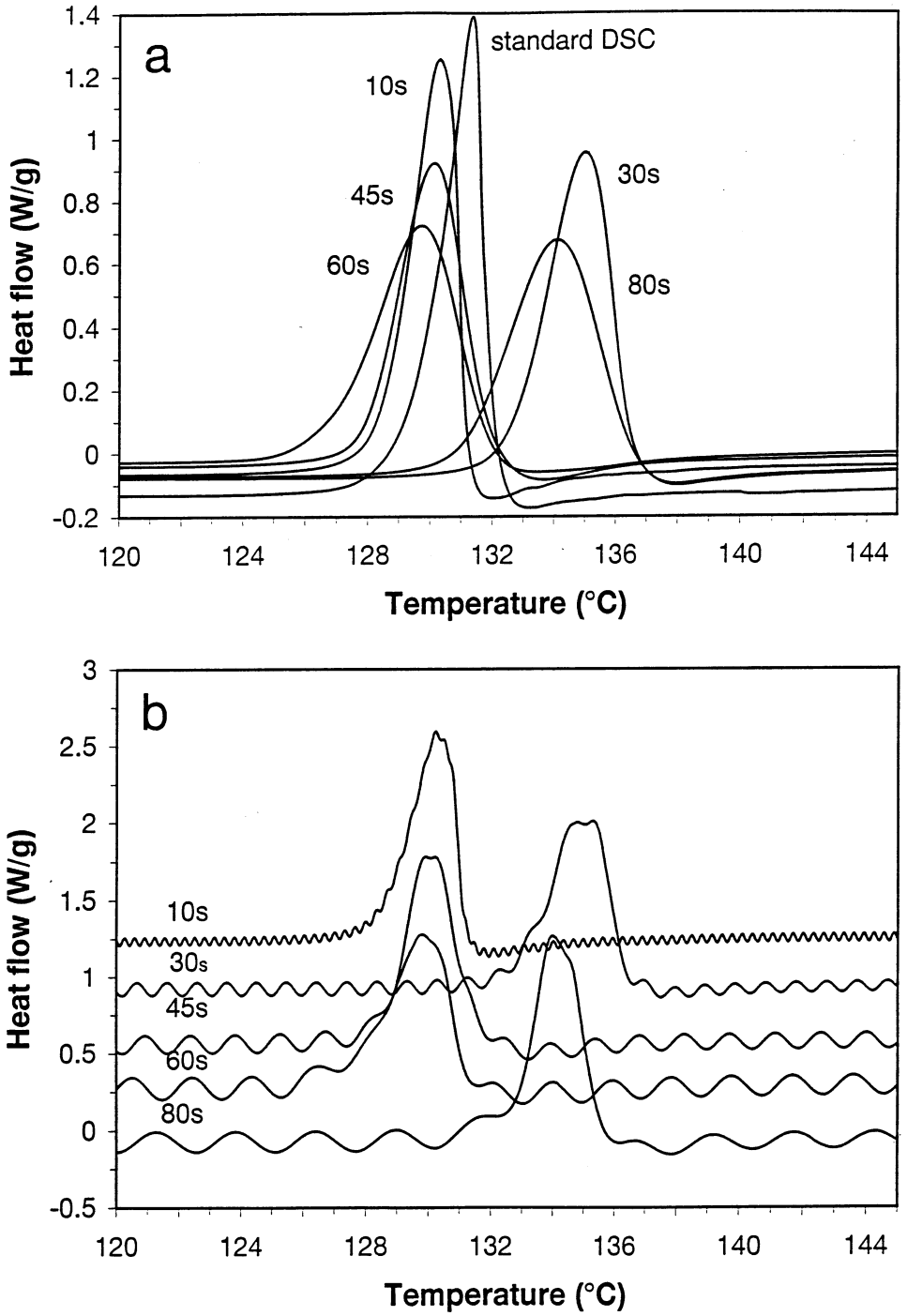

Fig. 8. MDSC analysis of spray-dried lactose in hermetic (TA) pans using a range of modulation periods: (a) total heat flow; (b) modulated heat flow (separated on the *y*-axis to aid presentation).

although extra time will need to be spent initially investigating such experimental details as discussed here, this time investment should be well compensated by the extra information that can be obtained by this technique.

Acknowledgements

Financial support was provided for this project by Abbott Laboratories Ltd. and the BBSRC.

References

Aldén, M., Wulff, M., Herdinius, S., 1995. Influence of selected variables on heat of fusion deteriminations by oscillating DSC. Therm. Acta 265, 89–102.

Barnes, A.F., Hardy, M.J., Lever, T.J., 1993. A review of the applications of thermal methods within the pharmaceutical industry. J. Therm. Anal. 40, 499–509.

Bell, L.N., Touma, D.E., 1996. Glass transition temperatures determined using a temperature-cycling differential scanning calorimeter. J. Food Sci. 61 (4), 807–810.

Boller, A., Jin, Y., Wunderlich, B., 1994. Heat capacity measurement by modulated DSC at constant temperature. J. Therm. Anal. 42 (2-3), 307–330.

Boller, A., Schick, C., Wunderlich, B., 1995. Modulated differential scanning calorimetry in the glass transition region. Therm. Acta 266, 97–111.

Boller, A., Okazaki, I., Wunderlich, B., 1996. Modulated differential scanning calorimetry in the glass transition region. Part III Evaluation of polystyrene and poly(ethylene terephthalate). Therm. Acta 284, 1–19.

Coleman, N.J., Craig, D.Q.M., 1996. Modulated temperature differential scanning calorimetry: a novel approach to pharmaceutical thermal analysis. Int. J. Pharm. 135, 13–29.

Hancock, B.C., Zografi, G., 1994. The relationship between the glass transition temperature and the water content of amorphous pharmaceutical solids. Pharm. Res. 11 (4), 471–477.

Izzard, M.J., Ablett, S., Lillford, P.J., Hill, V.L., Groves, I.F., 1996. A modulated differential scanning calorimetric study. Glass transitions occurring in sucrose solutions. J. Therm. Anal. 47, 1407–1418.

Jin, Y., Bonilla, J., Lin, Y.-G., Morgan, J., McCracken, L., Carnahan, J., 1996. A study of PBT/PC blends by modulated DSC and conventional DSC. J. Therm. Anal. 46, 1047–1049.

Maistros, G., Fontana, Q.P.V., Attwood, D., Hudd, J.S., 1997. Use of modulated differential scanning calorimetry to observe vitrification during epoxy resin cure. J. Mater. Sci. Lett. 16, 273–275.

O'Reilly, K.A.Q., Cantor, B., 1996. Cyclic differential scanning calorimetry and the melting and solidification of pure metals. Proc. R. Soc. London A 452 (1952), 2141–2160.

Reading, M., 1993. Modulated differential scanning calorimetry—a new way forward in materials characterisation. Trends Polym. Sci. 1 (8), 248–253.

Reading, M., Elliott, D., Hill, V., 1992. Some aspects of the theory and practise of modulated differential scanning calorimetry. In: Proc. 21st NATAS Conf., Atlanta GA, Sept. 13–16, 1992, pp. 145–150.

Reading, M., Elliott, D., Hill, V.L., 1993. MDSC, a new approach to the calorimetric investigation of physical and chemical transitions. J. Therm. Anal. 40 (3), 949–955.

Sauerbrunn, S., Thomas, L., 1995. Determination of initial crystallinity in polymers by modulated differential scanning calorimetry. Am. Lab. 27 (1), 19–22.

Sauerbrunn, S.R., Blaine, R.L., Foreman, J.A., 1993a. Affect of ageing on the enthalpic relaxation of amorphous PET. In: Proc. 22nd NATAS Conf., Denver, Sept. 19–22, 1993, pp. 514–519.

Sauerbrunn, S.R., Gill, P.S., Marcozzi, C.L., 1993b. Quantifying PET/PC blends with modulated DSC. In: Proc. 22nd NATAS Conf., Denver, Sept. 19–22, 1993, pp. 313–318.

TA Instruments DSC 2920 Operators Manual, TA Instruments, 1993, New Castle, DE, USA.

TA Instruments application note TA-210. Modulated DSC compendium. Basic theory and experimental considerations. TA Instruments, 1996, New Castle, DE, USA.

Van Assche, G., Van Hemelrijck, A., Rahier, H., Van Mele, B., 1996. Modulated differential scanning calorimetry: Non-isothermal cure, vitrification, and devitrification of thermosetting systems. Therm. Acta 286, 209–224.

Varma-Nair, M., Wunderlich, B., 1996. Non isothermal heat capacities and chemical reactions using a modulated DSC. J. Therm. Anal. 46, 879–892.

Wulff, M., Aldén, M., 1995. Phase equilibria in drug-polymer-surfactant systems. Therm. Acta 256, 151–165.

Wunderlich, B., Boller, A., Okazaki, I., Kreitmeier, S., 1996. Modulated differential scanning calorimetry in the glass transition region. Part II The mathematical treatment of the kinetics of the glass transition. J. Therm. Anal. 47 (4), 1013–1026.

.