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The use of MTDSC to assess the amorphous phase content of a micronised drug substance

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Abstract

Mechanical treatments such as grinding, milling or micronisation applied to crystalline drug substances may induce changes such as the occurrence of crystal defects and/or amorphous regions. These changes are likely to affect the chemical and physical properties of the material as well as the corresponding drug product performances. Various analytical techniques such as standard differential scanning calorimetry, isothermal and solution microcalorimetry as well as dynamic vapour sorption can be used to characterise and possibly quantify the amorphous phase content of these materials. These techniques have been applied for the development of analytical methods based on temperature- or solvent-induced (including water) recrystallisation of the amorphous phase in semi-crystalline drug substances and excipients and have sometimes allowed for detecting low amounts of amorphous phase. We have developed an alternative MTDSC method for the quantitation of the amorphous content in samples of a micronised drug substance co-crystal (form A), an antibiotic drug substance which does not recrystallise even when exposed to temperature or solvent vapours. This is performed through measurement of the heat capacity jump associated with the amorphous phase glass transition. The MTDSC parameters and experimental conditions were optimised for this system. The amorphous content calibration curve was established using pure crystalline and amorphous drug substance samples and their known mixtures. Limits of detection and quantification of 0.9 and 3.0% (w/w) respectively were obtained for specimen mass less than 5 mg.

Keywords: Glass transition; Heat capacity; Modulated temperature differential scanning calorimetry; Micronised drug substance; Amorphous phase content quantification

1. Introduction

The in vivo bioavailability of a drug substance (in particular in the case of a low solubility and high permeability substance) can generally be improved by enhancing its dissolution through particle size reduction. Disruption or activation of the crystalline structure often occurs during milling (Dialer and Küessner, 1973; Nakai et al., 1977; Hüttenrauch, 1978) and other pharmaceutical processes (York, 1983) such as crystallisation

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(Mullin, 1972), drying (Hüttenrauch and Keiner, 1979) and compression (Hüttenrauch, 1988), leading to various degrees of disorder in the form of crystal defects and/or amorphous regions. These changes can in turn significantly affect the powder properties, such as chemical and physical reactivity, dissolution and the corresponding dosage form performances (Pikal et al., 1978; Kim et al., 1985; Hendriksen, 1990; Hancock and Zografi, 1997).

It is therefore important to monitor and control these process-induced changes and evaluate their effect on the drug product performances using relevant and sensitive analytical methods.

Standard Differential Scanning Calorimetry (DSC) can be used to assess the degree of disorder in crystalline solids (Saleki-Gerhardt et al., 1994) and to compare the solid state disorder of materials (Grant and York, 1986). Other calorimetric methods such as solution microcalorimetry (Pikal et al., 1978) and isothermal microcalorimetry (Briggner et al., 1994; Sebhatu et al., 1994; Buckton et al., 1995; Giron et al., 1997) have been shown to probe small amounts of amorphous phase content in powders, and the corresponding limits of detection can be as low as 1 or 2% (w/w). The process of recrystallization of the specimen can also be followed using a non calorimetric approach such as dynamic vapour sorption measurements (Buckton and Darcy, 1995). In this latter case, the existence of as little as 0.05% w/w of amorphous lactose in crystalline α-lactose monohydrate could be demonstrated.

In the current study, we report the use of the recently developed Modulated Temperature Differential Scanning Calorimetry (MTDSC) technique (Gill et al., 1993; Reading, 1993; Reading et al., 1993a) to assess the amorphous phase content in micronised batches of compound X co-crystal (form A), a poorly soluble and highly permeable antibiotic, from measurements of the heat capacity jump associated with the glass transition. Detection and quantification of the amorphous phase generated upon micronisation using the previously mentioned calorimetric methods was not possible since form A of compound X undergoes decomposition during melting and since the kinetics of crystallization of amorphous compound X are very slow even under stressed experimental conditions. Details regarding the set-up and validation of this analytical method are presented including estimates of detection and quantification limits.

2. MTDSC technique overview

2.1. Theory

MTDSC is a recently developed extension of standard DSC. It was first presented by Reading at the 1992 NATAS conference (Sauerbrunn et al., 1992; Reading et al., 1993b). Since then, the technique has been extensively studied (Gill et al., 1993; Boller et al., 1994; Reading et al., 1994; Schawe, 1995a,b, 1996a; Varma-Nair and Wunderlich, 1996; Wunderlich et al., 1996) and applied to the characterisation of materials such as inorganic glasses (Schawe, 1996b; Tomasi et al., 1996), polymers (Sauerbrunn et al., 1993; Reading et al., 1994; Boller et al., 1995; Hourston et al., 1995; Sauerbrunn and Thomas, 1995; Boller et al., 1996; Van Assche et al., 1996) and more recently to pharmaceutical and food systems (Barnes et al., 1993; Alden et al., 1995; Coleman and Craig, 1996; Izzard et al., 1996; Craig and Royall, 1998; Hill et al., 1998; Bustin and Descamps, 1999). In MTDSC, a sinusoidal wave modulation is superimposed over the conventional linear (or isothermal) heating or cooling temperature programme. MTDSC refers to the same theory as standard DSC in which the heat flow signal is a combination of the specimen heat capacity (heat rate dependent component) and of any temperature dependent, often irreversible, 'kinetic' component. The resultant heat flow can be represented by:

$$\frac{dQ}{dt} = C_{p,t}\frac{dT}{dt} + f(t,T) \quad (1)$$

where Q is the heat flow absorbed by the specimen, $C_{p,t}$ the specimen heat capacity, T the absolute temperature, t the time and $f(t, T)$ the kinetically-limited heat flow rate (i.e. it represents the contribution to the total heat flow rate given by the reversible events taking place with a kinetics that is slow when compared to the experimental time-scale).

In MTDSC, the applied temperature programme can be expressed as:

$$T(t) = T_o + bt + B\sin(\omega t) \quad (2)$$

where T_o is the starting temperature, b the underlying or average heating rate, B the amplitude of the oscillation and ω the frequency of the oscillation.

Assuming that for a small temperature modulation the response of the rate of the kinetic process to temperature is linear over a modulation interval, Eq. (1) can be written as:

$$\frac{dQ}{dt} = C_{p,t}(b + B\omega\cos(\omega t)) + f'(t,T) + C\sin(\omega t) \quad (3)$$

where $f'(t, T)$ represents the contribution to the total heat flow rate given by true irreversible events, C is the amplitude of the kinetic response to sine wave modulation and the term $(b + B\omega\cos(\omega t))$ is the derivative modulated temperature.

The cyclic component of the heat flow signal depends on the value of b, ω and C. In most kinetically-controlled processes, C may be approximated to zero such that the response to the cyclic perturbation originates from the thermodynamic heat capacity contribution only, resulting for Eq. (3) in:

$$\frac{dQ}{dt} = C_{p,t}(b + B\omega\cos(\omega t)) + f'(t,T) \quad (4)$$

A Discrete Fourier Transform (DFT) algorithm is then used to separate this cyclic response of the specimen from its response to the underlying heating rate and to quantify these two signals separately. The heat capacity $C_{p,t}$ may be determined from the measurement of b, ω and B. The product of $C_{p,t}$ and the underlying heating rate may then be calculated to yield the cyclic heat flow component, also called the reversing heat flow. The non-reversing heat flow is obtained by simply subtracting the reversing heat flow component from the calculated total heat flow. It is noteworthy that, by applying this procedure, all short-term noise is removed from the deconvoluted signals and the heat capacity, which is calculated using modulation amplitudes, is not affected by instrumental baseline curvature.

Thus, thermal events such as glass transition and some melting events will be distributed in the reversing heat flow whereas the non-reversing heat flow will refer to enthalpic relaxation, evaporation, crystallisation, thermal decomposition, cure and some melting events.

MTDSC is nowadays a widely recognised technique yielding, when compared to standard DSC, particular advantages including enhancement of both sensitivity and resolution in the same experiment, analysis of complex overlapping transitions, direct measurement of the heat capacity C_p and detection of weak glass transitions.

All above listed benefits make MTDSC a powerful technique provided that the choice of the experimental parameters as well as the C_p calibration of the calorimeter are carried out properly.

2.2. Choice of MTDSC parameters

Besides the general precautions that are necessary to ensure reliable and accurate results (careful specimen preparation, appropriate specimen size, use of adequate pans and purge gas, selection of appropriate purge gas flow, calibrations carried out under conditions identical to those used for specimen measurement, etc.), the general recommendations given in Table 1 apply for all types of thermal

Table 1
General recommendations for the choice of MTDSC parameters

Parameter	Recommended ranges of experimental values
Modulation period (P)	40–100 s; a value of 60 s is generally recommended when using standard aluminium crimped pans and nitrogen purge gas
Underlying linear heating rate (R)	1–5°C/min; a value of 5°C/min should not be exceeded to allow for the specimen to follow the modulation; values below 1°C/min should be preferred whenever possible to ensure enough oscillations (at least 5–6 cycles) across the thermal event studied
Modulation amplitude (A)	± 0.1–± 3°C for a given linear heating rate, R, and period, P; larger values: enhanced sensitivity; smaller values: enhanced resolution

events to select an optimised set of MTDSC parameters, namely the underlying linear heating rate, R, the temperature modulation amplitude, A and the temperature modulation period, P. In the specific case of the glass transition which involves C_p measurement, the following additional recommendations also apply:

- the use of large modulation period values (80–100 s) allows for a maximum time for heat transfer across the specimen and is necessary to yield precise heat capacity values;
- in the case of weak glass transition signals, a larger value of the amplitude (cf. Eq. (5) below), should be preferred, typically around 1.5–2°C (working in 'heat-and-cool' instead of in 'heat only' mode is not a problem when dealing with reversible events such as a glass transition); however, this value should not be too large to prevent the modulation from over-spanning the transition width.

A general approach for selecting appropriate experimental parameters would be to first run the specimen in standard mode to evaluate the possible need for MTDSC, then choose the temperature modulation period and the underlying linear heating rate and finally select the temperature modulation amplitude.

2.3. Heat capacity (C_p) calibration and measurement

The heat capacity is obtained by continuously dividing the amplitude of the heat flow by the amplitude of the modulated heating rate, as expressed in the following equation:

$$C_p = K(C_p)\frac{Amp_{MHF}}{Amp_{MHR}} \quad (5)$$

where $K(C_p)$ is the heat capacity constant, Amp_{MHF} the amplitude of the modulated heat flow and Amp_{MHR} the amplitude of the modulated heating rate. Once the appropriate set of MTDSC parameters has been chosen, the calorimeter must be C_p calibrated by both performing a C_p baseline run and determining the heat capacity constant, $K(C_p)$, a multiplying factor which allows for the quantitative measurement of the heat capacity. These calibrations must be carried out under the same experimental conditions as those chosen for specimen analysis using closely mass matched DSC pans.

The C_p baseline run compensates the mass imbalance of the DSC measuring cell and determines its polarity (Varma-Nair and Wunderlich, 1996). It is performed using two empty DSC pans. Depending whether the thus obtained modulated temperature and modulated heat flow signals plotted versus time are in-phase or out-of-phase, the recorded C_p baseline signal will be respectively added or subtracted from the measured specimen C_p signal.

The $K(C_p)$ calibration run compensates the variation of the DSC measuring cell thermal resistivity with temperature. The heat capacity constant, $K(C_p)$, is given by the ratio of the theoretical heat capacity of a reference material to the measured heat capacity of the material studied as expressed in Eq. (6):

$$K(C_p) = \frac{C_{p,\,\text{theoretical}}}{C_{p,\,\text{measured}}} \quad (6)$$

As already mentioned, the MTDSC parameters can significantly affect the $K(C_p)$ value. Hence, it is compulsory to be in the so-called *plateau* zone of the three-dimensional ($K(C_p)$, period, amplitude) graph, a safe-operating zone that ensures reliable determination of the heat capacity constant. This zone corresponds typically to period values comprised between 60 and 100 s (a value of 100 s should be preferred for best accuracy) and to amplitude values ranging from ± 0.1 to ± 2 s. By doing so, acceptable values of $K(C_p)$ can be obtained, typically less than 1.1, by using either helium or nitrogen purge gas.

Several approaches can be applied for heat capacity measurement, including isothermal (Jin et al., 1993; Boller et al., 1994) and non isothermal methods (Varma-Nair and Wunderlich, 1996), depending upon the degree of accuracy required and the time which can be devoted to measurements. The quasi-isothermal MTDSC method (Boller et al., 1994) is a unique way of

performing C_p measurements with an average heating rate value of zero, thus keeping the specimen continuously close to equilibrium. It consists in measuring the specimen heat capacity at a given temperature for 20–30 min while applying a fixed modulation period and temperature amplitude. This procedure is repeated for several temperatures within the studied temperature range. The quasi-isothermal MTDSC method allows for obtaining highly precise C_p values and is advantageous when dealing with specimens that are sensitive to fast temperature changes. However this method is time consuming. According either to supplier's recommendations and software capabilities (TA Instruments, 1996) or to user's approach, there are several ways to obtain the $K(C_p)$ value using a dynamic MTDSC method such as by:

- calculating a single $K(C_p)$ value near the middle of the desired temperature range or around the temperature of the thermal event studied,
- averaging multiple $K(C_p)$ values obtained after performing several runs in a temperature range which brackets the transition of interest,
- using the so-called spreadsheet technique which involves performing a MTDSC scan in a temperature range spanning the transition studied, then calculating a $K(C_p)$ value each 10°C and finally applying the thus obtained $K(C_p)$ values to the measured C_p signal through the use of a spreadsheet program,
- operating as described in the latter spreadsheet procedure but averaging all obtained $K(C_p)$ values to yield a single calibration constant value.

The MTDSC dynamic method is fast and easy. However, over the temperature range of interest, there should only be a small variation in $K(C_p)$ values, on the order of less than $\pm 3\%$ of the average value (within the experimental precision limits of the technique).

3. Materials and methods

3.1. Materials

Compound X is an antibiotic which is isolated as a co-crystalline association of two molecules. To date, there is only one known crystalline form of compound X co-crystal, namely form A. Fig. 1 shows a typical standard DSC thermogram of form A. It comprises a low intensity endotherm in the temperature range 25–90°C which is attributed to evaporation of residual solvents (mainly methyl ethyl ketone) and sorbed water from the environment. This first thermal event is then followed by a main endotherm corresponding to melting of the drug substance (onset of melting of 175°C for form A as received). An exotherm corresponding to thermal decomposition of the substance is also observed during melting (the onset of thermal decomposition as assessed independently by thermogravimetric analysis (TGA) is 177°C). As a consequence, precise determination of the melting peak area is not possible by DSC.

Samples, taken to be 100% crystalline compound X co-crystal form A, corresponded to a batch isolated under mild drying agitation conditions. The X-ray powder diffraction (XRPD) pattern recorded for this batch was indexed using the lattice parameters obtained from determination of the three-dimensional crystal structure of form A (from single-crystal X-ray diffraction). All observed XRPD diffraction lines were indexed thereby indicating that this batch was crystallographically pure. Among all form A co-crystal batches manufactured, this batch exhibited the highest onset melting temperature and associated melting enthalpy as measured by standard DSC, as well as the highest onset temperature of thermal decomposition as determined by TGA. MTDSC runs performed on this batch under the conditions described below did not allow detection of any glass transition.

One batch of amorphous compound X was prepared by spray-drying. The corresponding XRPD diagram only consisted of a diffuse halo, indicating the absence of long-range order. Using standard DSC, the glass transition of dried 100% amorphous compound X appears as a broad endotherm in the temperature region 110–130°C and comprises both relaxational enthalpy and

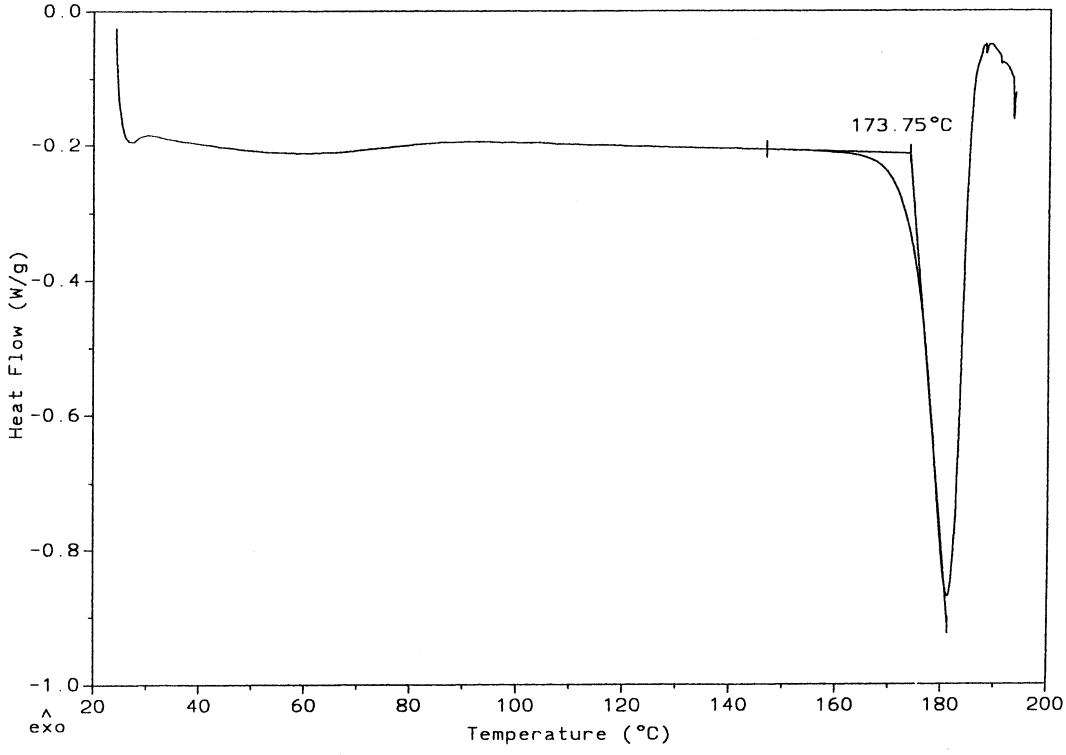

Fig. 1. Standard DSC profile for compound X co-crystal form A.

heat capacity components. No melting endotherm corresponding to form A could be detected.

The amorphous content calibration curve was established with the pure crystalline and amorphous samples and their known mixtures. Samples corresponding to pure crystalline form A and amorphous compound X were dried under vacuum to reach a maximum water content of 0.5 and 1% (w/w) respectively, as measured by TGA. They were then stored in desiccation chambers to ensure constant lowest water content as checked after 2 months storage under these conditions. Using this drying procedure the appearance of a noise signal before and after the glass transition recorded in known mixtures of pure crystalline and amorphous compound X was reduced. To analyse the mixtures, the pure crystalline and amorphous powders were directly mixed in the MTDSC pans applying the water content mass correction for each mixture composition. This in situ preparation proved to be the most adequate procedure to ensure accurate weight fractions in the pan, given the small amount of powders available.

3.2. Methods

3.2.1. Thermogravimetric analysis (TGA)

Thermogravimetric analyses were performed on a TA Instruments TGA 2950 apparatus using dry nitrogen purge gas at an average rate of 60 ml/min. Experiments were conducted using open aluminium pans contained in a platinum specimen pan. The specimens (specimen weight was 8–13 mg) were heated at a rate of 5°C/min in the temperature range 25–195°C. The instrument was mass calibrated using a 10 mg certified standard and temperature calibrated by measuring the Curie points of alumel (Perkin Elmer, reference P/N 0998-8015, 154°C) and nickel (Perkin-Elmer, reference P/N 5190-869, 354°C) at a heating rate of 5°C/min.

3.2.2. Standard DSC and MTDSC

Standard DSC and MTDSC analyses were performed using a TA Instruments DSC 2920 instrument equipped with a refrigerated cooling accessory and modulation option. Nitrogen was used as the purge gas at an average rate of 50 ml/min. Experiments (specimen weight up to 5 mg) were performed using aluminium crimped pans (suitable for autosampler) over a temperature range extending from 25 to 160°C (standard DSC mode) or from 80 to 160°C (for heat capacity measurements by MTDSC). The calorimeter was calibrated:

- for baseline on the empty cell from −20 to 350°C,
- in temperature using indium (Perkin-Elmer, reference P/N 0319-0033, onset of melting temperature of 156.6°C) and lead (Perkin-Elmer, reference P/N 0319-0035, onset of melting temperature of 327.5°C),
- in energy (cell constant determination) with indium (enthalpy of melting of 28.45 J/g), applying a heating rate of 5°C/min, and
- in heat capacity baseline,
- in heat capacity for $K(C_p)$ determination using sapphire (TA Instruments, reference P/N 915075-901) according to the procedure described in Section 2.3,

applying a heating rate of 1°C/min and using two closely mass matched DSC pans.

3.3. Experimental conditions

3.3.1. Choice of MTDSC parameters

On the basis of the recommendations listed and detailed in Section 2.2, the (R, A, P) set of MTDSC parameters which was chosen for analysing all specimens was $R = 1$°C/min, $A = 1.5$°C and $P =$ 100 s. The experimental temperature program used was the following: after a 10-min isothermal modulation step at 80°C, the specimens were heated through a modulated program up to 160°C. Fig. 2 shows the total, reversing and non-reversing

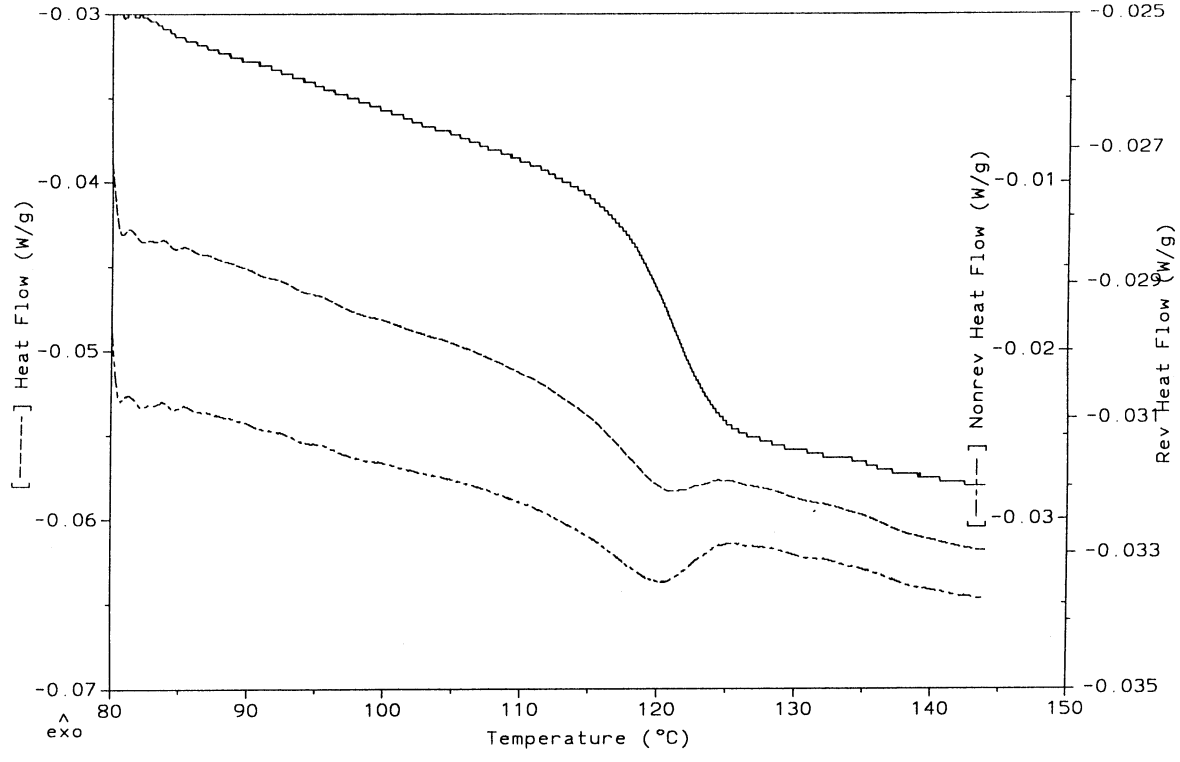

Fig. 2. MTDSC profile for dried 50/50 (w/w) mixture of pure crystalline and amorphous compound X: total heat flow, reversing and non-reversing heat flow signals.

MTDSC heat flow signals recorded on a 50/50 (w/w) mixture of pure crystalline and amorphous compound X. Deconvolution of the total heat flow into reversing and non-reversing heat flows allows the transition to be easily identified at 120°C and the heat capacity jump to be quantified with a high sensitivity. As can be seen in Fig. 3, the applied experimental conditions allowed the specimens to follow the modulation, since no distortion of the modulated heat flow could be observed and a sufficient number of temperature oscillations (at least six) spanned the glass transition event. The glass transition temperature was about 120°C, as determined by MTDSC using the six-point method.

3.3.2. Heat capacity calibration

Heat capacity baseline runs have been carried out using closely mass matched empty pans for both reference and specimen. Determination of the heat capacity constant, $K(C_p)$, was performed in dynamic mode with a sapphire disk (see Section 2.3) using for the MTDSC R, A and P parameters the values described in the previous paragraph. Each of the thus obtained seven C_p experimental values in the temperature range 80–160°C (one value every 10°C) has been compared to the theoretical sapphire value for a given temperature and the resulting seven $K(C_p)$ values have been averaged to finally yield a mean $K(C_p)$ value. This method was found to be reliable since the deviation in $K(C_p)$ values was much less than 3%. Note that all MTDSC experiments were carried out using closely mass matched pans (typically less than 0.01 mg mass difference between reference and specimen pans).

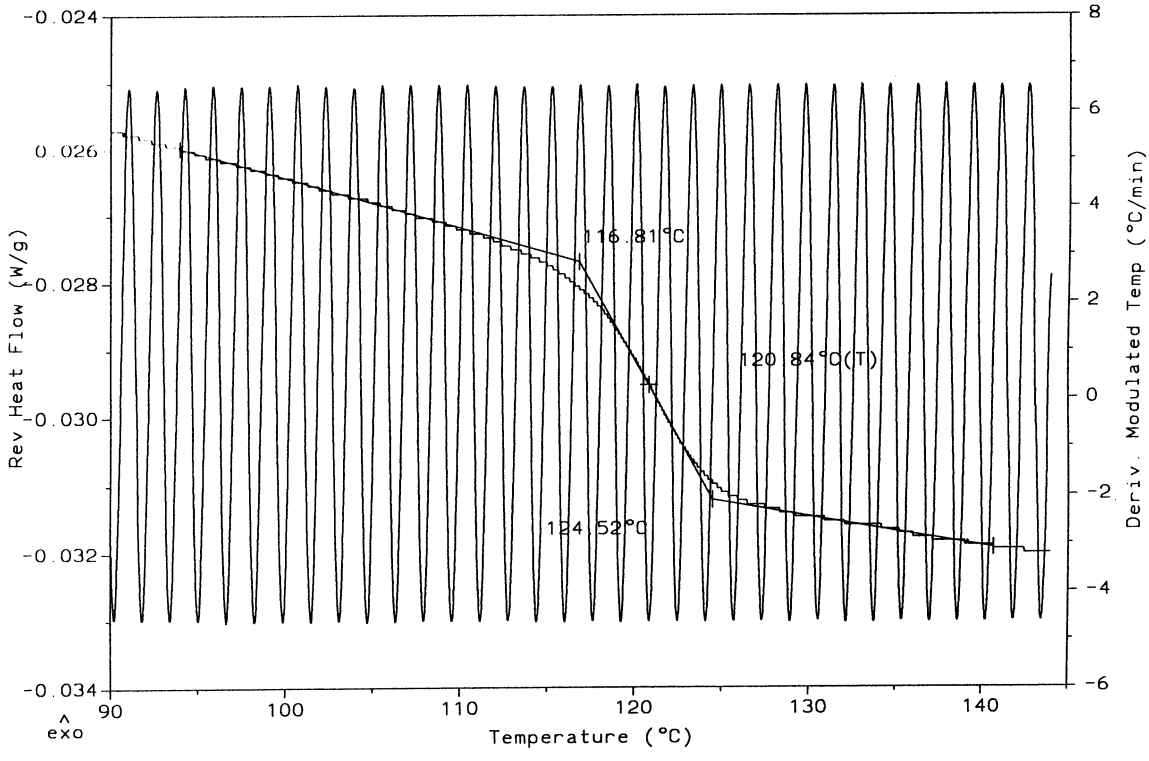

Fig. 3. MTDSC profile for dried 50/50 (w/w) mixture of pure crystalline and amorphous compound X: applied modulated heating rate and resulting reversing heat flow signals.

4. Results and discussion

In Fig. 4 the heat capacity jump values, ΔC_p, recorded for mixtures of amorphous and crystalline compound X show a linear relationship as a function of weight fraction of amorphous content in mixtures. The evolution of the recorded MTDSC C_p signal as a function of several percent weight fractions of amorphous compound X in the mixtures is shown in Fig. 5. Consecutive measurements of sample mixtures suggest a reproducibility in ΔC_p measurement of about $\pm 12.2\%$. The line of best fit is plotted in Fig. 4 and is defined by Eq. (7):

$$\Delta C_p \text{ (J/g per °C)} = 0.0057 + 0.0038(\%\text{ wt fraction}) \quad (7)$$

where '% wt fraction' is the percent weight fraction of amorphous compound X in the mixtures. This line, when extrapolated towards low amorphous % weight fraction values, crosses the x-axis in the close proximity of the zero point. This slight deviation from the origin is therefore considered as a result of simple experimental scatter. The amorphous phase % weight fraction in any sample can be extrapolated using Eq. (7) from the experimentally obtained heat capacity jump, ΔC_p.

The limit of detection, as expressed in analyte weight fraction, can for instance be determined (Skoog and Leary, 1992; The United States Pharmacopoeia, 1994; Phadnis and Suryanarayanan, 1997) from measurement of the signal-to-noise ratio obtained by comparing results from specimens with known analyte weight fractions with those of blank specimens. The minimum level at which the analyte can be reliably detected under the stated experimental conditions would correspond to a signal-to-noise ratio of 2:1 or 3:1. The limit of detection can also be determined by measuring the magnitude of analytical background response obtained by analysing a number of blank samples and calculating the S.D. of this response. The thus obtained S.D. multiplied by a factor $k = 2$ or 3 provides an estimate of the limit of detection as explained in the following:

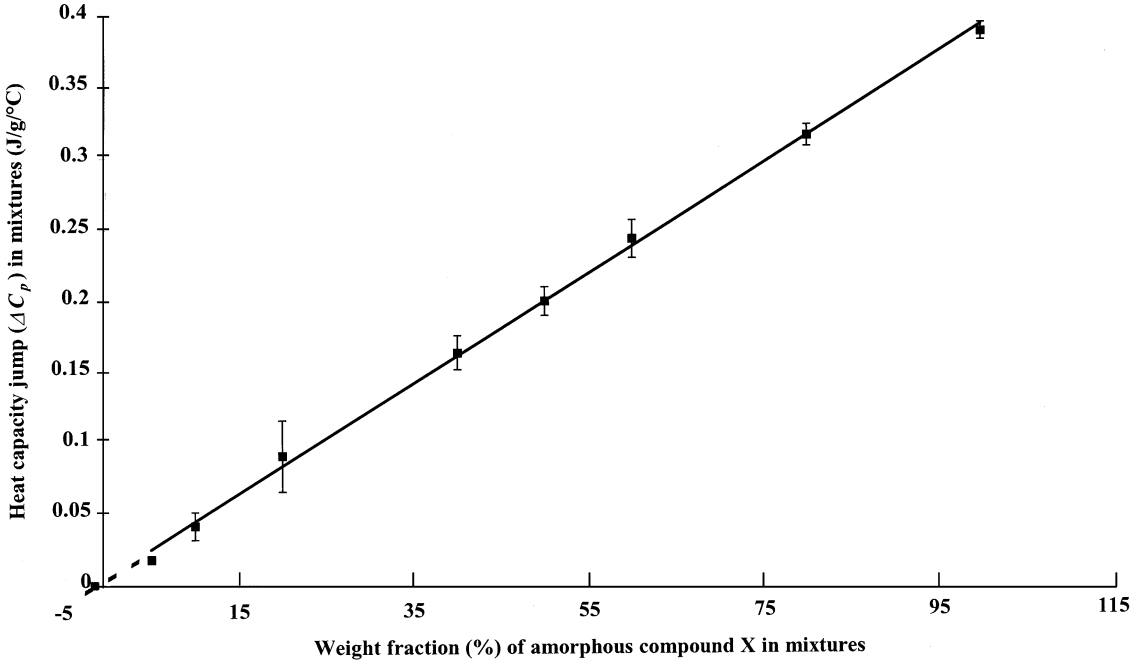

Fig. 4. Compound X amorphous phase content calibration curve obtained from analysis of known mixtures of pure crystalline (form A) and amorphous compound X.

The minimum detectable analytical signal, S_{min}, is expressed as:

$$S_{min} = \overline{S}_{blank} + ks_{blank} \quad (8)$$

where $\overline{S}_{blank}$ is the mean blank signal and s_{blank} the S.D. of the blank signal.

The measured signal, S, and the analyte weight fraction, w, are related by the equation:

$$S = mw + S_{blank} \quad (9)$$

where m is the slope and S_{blank} the instrumental blank signal.

The minimum weight fraction, w_{min}, at which a measurable signal can be expressed using Eq. (9) is:

$$S_{min} = mw_{min} + \overline{S}_{blank} \quad (10)$$

The minimum detectable weight fraction of analyte can then be calculated by substituting into Eq. (10), the values of S_{min}, $\overline{S}_{blank}$ and m.

In the case of compound X, this latter approach was used. The measured signal, S, is expressed as a heat capacity jump, ΔC_p, and the relationship between ΔC_p and the amorphous compound X% weight fraction is described by Eq. (7). The S.D. of the analytical background response (0.0011 J/g per °C) was estimated before and after the heat capacity jump for all mixture compositions specimens analysed. This S.D. value multiplied by $k = 3$ yields a value of 0.9% for the minimum detectable % weight fraction of amorphous compound X. The quantification limit (The United States Pharmacopoeia, 1994) can be estimated by the same procedure but multiplying this time the S.D. of the analytical background response by a factor $k = 10$ to yield a value of 3.0% for the minimum quantifiable % weight fraction of amorphous compound X.

Specimens of compound X form A micronised under different conditions have been analyzed by

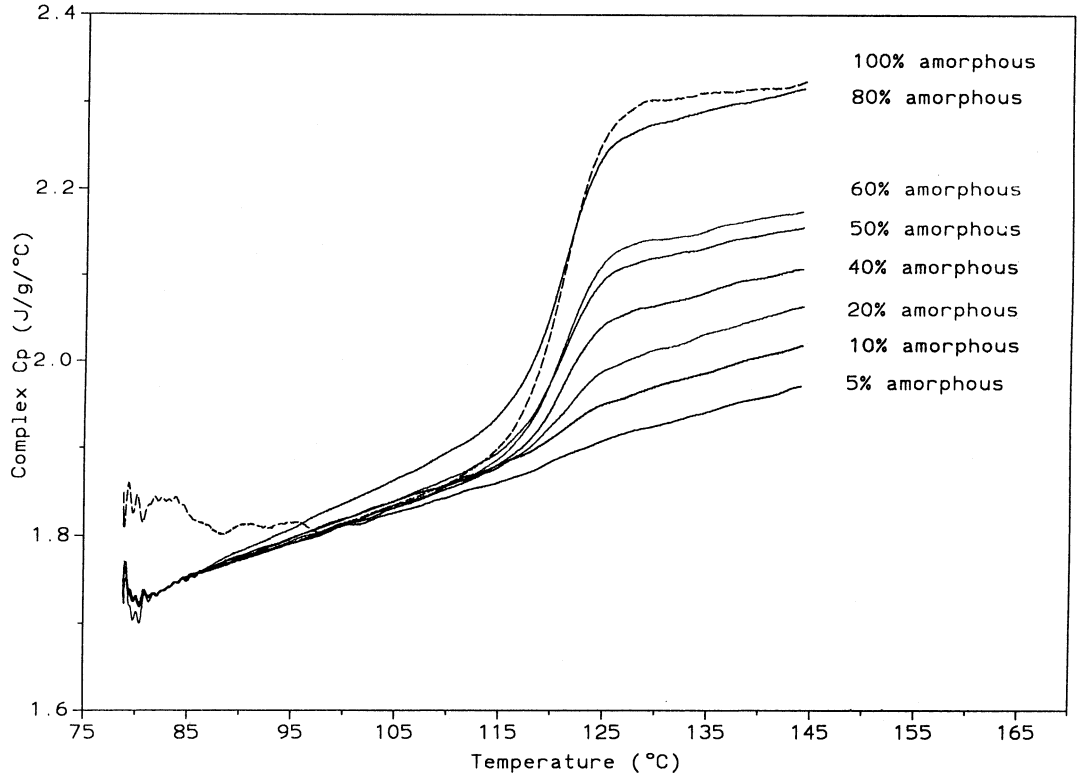

Fig. 5. Heat capacity jumps, ΔC_p, recorded on various known mixtures of amorphous and crystalline (form A) compound X.

MTDSC under the experimental conditions described in Section 3. They yielded MTDSC profiles similar to those recorded with the pure amorphous and crystalline mixtures used for determining the ΔC_p–(% wt fraction) calibration curve. In particular, the values of the glass transition temperatures, as determined by the six-point method, were around 120°C as for pure amorphous compound X. The higher the applied jet-milling intensity, the higher the corresponding recorded ΔC_p values. These specimens being semi-crystalline, the onset of melting of form A was observed around 175°C as in the case of pure crystalline compound X form A specimens. During MTDSC analysis, no recrystallization exotherm could be detected, although a 'heat-and-cool' mode was used. The C_p changes measured on these specimen corresponded to extrapolated amorphous contents ranging from 10 to 20% (by weight).

5. Conclusions

We have shown that detection and quantification of low levels of amorphous phase in crystalline drugs can be achieved using MTDSC through measurements of the heat capacity jump associated with the amorphous phase glass transition. For micronised compound X and under our experimental conditions, the limits of detection and quantification are respectively 0.9 and 3.0% (w/w). To ensure that the specimen follows the imposed modulated temperature program and given the small quantities of 100% amorphous drug substance available, we have used in this study low specimen weight values (less than 5 mg). The limits of detection and quantification obtained proved to be adequate, within the framework of our study, for investigating amorphous phase content variability in micronised drug substance batches. However, if need be, these values could be lowered by using larger specimen weights. This method can in particular be considered as valuable especially in the case of crystalline drug substances which, when exposed to solvent vapour, do not recrystallise at experimental timescales or which exhibit thermal degradation during melting.

As is always the case when setting up a calibration curve, the procurement of a 100% amorphous sample is very important to properly determine the associated heat capacity jump since calculation of the amorphous phase content is based on this value. It is important that the specimen be dried prior to analysis to reduce the C_p noise signal. Also, the choice of optimised MTDSC parameters as well as proper calibration of the calorimeter are crucial steps to ensure precise and accurate heat capacity measurements. In that respect, given our experimental conditions and the characteristics of our measuring cell, heat capacity measurements performed with or without C_p baseline correction yielded similar C_p values. Provided that all above conditions are met, MTDSC can be used as a sensitive and fast method to assess the amorphous phase content of drug substances, even within the framework of a quality control environment.

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