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Invited review

Modulated temperature differential scanning calorimetry: a novel approach to pharmaceutical thermal analysis

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Abstract

Modulated temperature differential scanning calorimetry (MTDSC) is a novel thermoanalytical technique which involves the application of a sinusoidal heating programme to a sample and the resolution of the response into reversing and non-reversing signals, thereby enabling the deconvolution of complex and overlapping thermal processes. This represents an important advance on conventional differential scanning calorimetry (DSC), which involves the use of a linear heating programme, and does not allow the separation of the signal into component responses. In this review, the principles and current uses of conventional DSC will be discussed and compared to those of MTDSC, particularly with a view to emphasising the comparative advantages of the new technique with respect to existing methods. A discussion will be given of how this technique may be applicable to a range of pharmaceutical systems.

Keywords: Modulated temperature differential scanning calorimetry; Polymers; Thermal analysis

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1. Introduction

Differential scanning calorimetry (DSC) is a well established method of thermal analysis within the pharmaceutical sciences. The technique may be used to characterise physical and chemical events via changes in either enthalpy or heat capacity of a sample. As virtually all processes of pharmaceutical interest are accompanied by such changes, the technique has found wide application within the field. In particular, applications include the detection of polymorphism, measurement of reaction and decomposition kinetics, assessment of the compatibility of dosage from constituents, purity determination and glass transition temperature studies. Numerous texts are available in which the theory, principles, instrumentation and applications of DSC are discussed (Wendlandt, 1974; Ford and Timmins, 1989; Wunderlich, 1990; Haines, 1995).

Modulated temperature differential scanning calorimetry, MTDSC, is a recently developed extension of DSC in which a sine wave modulation

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is applied to the standard, linear temperature programme, as shown in Fig. 1. A discrete Fourier Transform algorithm is applied to the resultant data to deconvolute the sample response to the underlying (linear) and modulated temperature programmes (Reading et al., 1994). The response to the underlying signal is essentially indistinguishable from the signal yielded by conventional DSC. However, in addition, the method offers a number of advantages which will be described in detail later and include the separation of overlapping phenomena and deconvolution of complex transitions, greater resolution without loss of sensitivity, the detection of metastable melting phenomena, and greater ease of collection of heat capacity data.

In this review, an overview will be given of the principles and some of the general pharmaceutical uses of conventional DSC. A number of texts, particularly that of Ford and Timmins (1989), have already discussed pharmaceutical applications of DSC in detail, hence the purpose of the summary given here is to provide a suitable context for discussion of the MTDSC technique. The principles underlying the types of measurement that may be made using DSC will be outlined rather than a detailed discussion of actual thermal studies that have been conducted in the pharmaceutical field. A discussion of the principles of MTDSC will then be given, along with an outline of some of the considerations pertinent to making MTDSC measurements and the advantages and disadvantages of MTDSC compared to those of conventional DSC. The systems to which the MTDSC technique has been applied to date will be reviewed and the potential uses of the technique within the pharmaceutical sciences will be discussed.

It should be noted that references involving a number of DSC methods in which a periodic perturbation (usually a sine wave) is applied to the standard linear or isothermal temperature programme have recently appeared in the literature (e.g. Sauerbrunn et al., 1993; Sauerbrunn and Gill, 1993; Alden et al., 1995; Song et al., 1995; Wulff and Alden, 1995a; Wulff and Alden, 1995b). Various terms such as oscillating, alternating, cyclic, and modulated DSC have been used to distinguish these approaches from those of conventional DSC, although the basic principles of these approaches are similar. It has recently been suggested by Dr. Mike Reading, who has pioneered this approach, that the generic term modulated temperature DSC (MTDSC) should be used to describe these techniques as a group, while the individual terms cited above should be used to identify the different models available. At this early stage in the development of the technique within the pharmaceutical sciences, we would strongly suggest that this nomenclature is adopted, as otherwise considerable confusion will rapidly develop within the literature. While there are differences between the various MTDSC techniques, the principles outlined here will be very largely applicable to all the methods. It should, however, be stated that the review is based on our experience with the TA Instruments model, which was developed by Dr. Reading and consequently uses the data deconvolution techniques outlined in his published work; the data analysis used by other models may not exactly be the same hence care should be taken in extrapolating *verbatim* the information given here to other models.

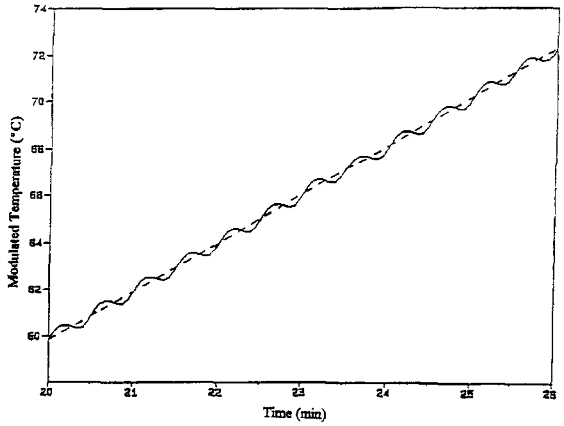

Fig. 1. The comparison of an MTDSC temperature profile (depicted by the unbroken line) and constant heating rate ramp (depicted by the dotted line). Heating rate 2°C min^{-1}, modulation amplitude 0.3°C and period 30s. (After Seferis et al., 1992).

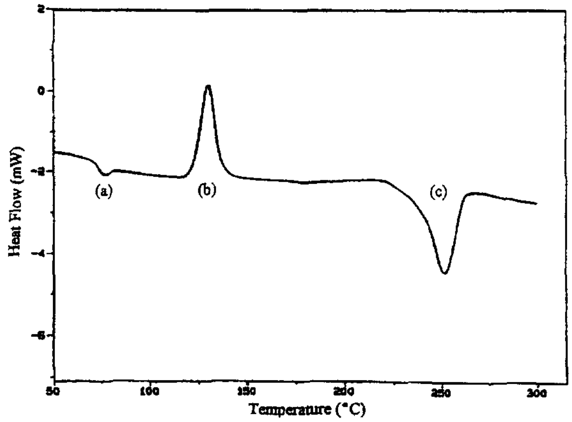

Fig. 2. Conventional DSC thermoanalytical curve of PET showing: (a) a glass transition (with associated enthalpic relaxation), (b) a cold crystallisation exotherm, and (c) a melting endotherm.

2. Basic principles of conventional DSC

Thermal methods of analysis involve the manipulation of temperature to produce a measured parameter, from which information concerning the structure and behaviour of a material may be derived. In particular, DSC has been widely used in a number of fields and involves the indirect measurement of differential power (i.e. heat flow, usually expressed in mW) during a thermal event. To date, DSC has almost invariably involved the application of a linear or isothermal temperature programme to a sample system and the continuous measurement of heat flow as a function of temperature or time, respectively.

Thermal events which are detectible by DSC may be endothermic (e.g. melting, dehydration), exothermic (e.g. crystallisation) or may involve a change in the heat capacity of a sample (e.g. glass transition phenomena). These events are depicted in Fig. 2, which shows the DSC trace for polyethylene terephthalate (PET), for which all three major types of thermal event may be observed. The remainder of this section describes the two recognised forms of DSC and their modes of indirect heat flow measurement.

Heat flux DSC is the most common form of the technique and consists of a sample and reference positioned symmetrically in a furnace. The sample and reference pans are heated from the same source and the differential temperature is measured. The resultant signal is converted to heat flow using the following relationship (which is derived from Newton's law of cooling and may be considered as a thermal analogue of Ohm's law):

$$\Delta Q = (T_s - T_r)/R_T \qquad (1)$$

where Q (J) is heat, R_{T} (KJ^{-1}), the thermal resistance of the cell, T_{s} (K), the temperature of the sample and T_{r} (K), the reference temperature. An assumption is made that the thermal gradients within the components of the cell (e.g. between the sample, reference and their holders) are negligible.

Power compensation DSC, comprises a system in which the sample and reference pans are placed in isolated furnaces, as opposed to both pans being heated from the same source. The differential temperature between the sample and reference is (nominally) maintained at zero whilst the power (supplied by the differential heaters), required to maintain the same temperature in the two pans, is measured. At the onset of an enthalpic event (e.g. fusion, recrystallisation, decomposition) the sample temperature begins to deviate from that of the reference, hence energy is supplied to one or other pan in order to maintain isothermal conditions between the two. In the advent of an enthalpic process power compensation DSC supplies a measured quantity of heat per unit time to the sample (in the case of endothermic events) or to the reference (during exothermic events) to maintain a differential temperature of zero. The power delivered by the differential heaters is given by the following expression:

$$P = \mathrm{d}Q/\mathrm{d}t = I^2R \qquad (2)$$

where P (W) is power, I (A) is current supplied to the heater and R (Ω) is the resistance of the heater.

DSC data are presented in Cartesian form (a thermoanalytical curve, formerly known as a thermogram). Irrespective of the type of instrumentation used, differential power is plotted against temperature (or time for isothermal heating programmes). Thus for an ideal system in which the sample and reference are identical (i.e. are of the same mass and possess identical heat capacities and thermal conductivities) the differential heat flow signal recorded on the ordinate axis would be zero as the heat flow to and from the sample would perfectly match that of the reference. For systems in which the heat capacities of the sample and reference differ a horizontal displacement of the baseline is noted. The baseline reading of the thermoanalytical curve is perturbed when an enthalpic event occurs; exo- and endothermic events are registered as peaks and troughs. According to convention, endotherms usually appear as peaks although either method of plotting is acceptable (and may be determined by the particular instrumentation used). The nature and interpretation of the signals arising from changes in heat capacity and enthalpy are treated in subsequent sections.

2.1. Sample preparation and operating conditions

The data collected from a DSC scan are a result of the source, pre-treatment and intrinsic nature of the sample and the instrumental conditions (e.g. scan rate, atmosphere, reference system, pan configuration) under which the investigation is conducted. This section discusses some of the effects of sample preparation and operating conditions, as such considerations become even more important when using MTDSC.

To ensure accurate heat flow measurements it is necessary to minimise thermal gradients within the sample; this requires the use of small quantities (generally a few milligrams) of sample. Previous studies (e.g. Craig and Newton, 1991) have suggested that the particle size of the sample may have a profound effect on the thermoanalytical curves obtained. It is preferable to fully encapsulate the sample in a closed pan to achieve optimum thermal conductivity. In the event of highly enthalpic reactions, an 'inert' diluent may be intimately mixed with the sample although its presence may greatly influence the thermal, and hence heat transfer, characteristics of the system. The reference system usually comprises an empty pan of the same type and configuration as that of the sample (and should include a quantity of diluent if it has been included in the sample system).

Aluminium pans are used for most DSC investigations with the exception of systems which are likely to react with aluminium and those which require a temperature programme exceeding 600°C. Copper, platinum and gold pans can be heated to at least 700°C and may be used for samples which react with aluminium. Non-hermetic pans are suitable for use with most solid samples. Lids may be placed or crimped onto the top of the pans to minimise thermal gradients throughout the sample and to ensure good thermal contact between the sample and detection system. Open pans are employed if contact between the purge gas and sample is required or if phenomena such as hydrate desolvation are being studied (e.g. Miller and York, 1985; Sawh et al., 1993) in order to observe water losses more clearly. Some workers advocate the use of pinholes in the lids of pans to allow controlled evaporation of volatile materials. Hermetically-sealed pans are required for use with aqueous solutions, volatile liquids, and sample matter which sublimes, since they possess an airtight seal. The resistance to internal pressures which may build up during heating of hermetic pans depends on their design and should be considered when planning DSC experiments.

The heating rate used in conventional DSC experiments is typically between 10 and 20°C min^{-1}. Heating rate influences the nature of the thermoanalytical curve. In general, low heating rates result in high resolution (between thermal events which occur over similar temperature ranges) and low sensitivity, hence smaller events may not be detected. In addition, if the sample is not heat-stable the longer scanning times may result in degradation of the material. The converse is true of high heating rates whereby an increase in sensitivity is obtained at the expense of resolution. Fig. 3 demonstrates the effect of heating rate on the nature of a typical endothermic melting signal. The following explanation is based on heat flux DSC although the principle is easily applied to power compensation DSC.

A sample substance will absorb heat energy through the melting range. The temperature of the sample will essentially remain constant throughout the melting process whereas the reference will continue to increase in temperature according to the programmed heating rate. When the melting process is complete reequilibration of the sample temperature with that of the reference and temperature programme will occur. At low heating rates the temperature lag of the sample with respect to that of the reference is relatively small. The area (represented by A′ in Fig. 3) mapped out by this deviation of sample temperature with respect to that of the reference is proportional to the heat flow during the melting process. At higher heating rates the same principle applies although the lag between the temperature of the sample and that of the temperature programme and reference is greater as a consequence of the higher heating rate. Hence, at the point of reequilibration of the sample and reference temperatures a greater area (represented by A″) has been mapped out, as shown in Fig. 3.

An explanation of the loss of resolution at higher heating rates may be provided if two thermal processes of similar temperature are considered. Consider that, at some low heating rate, the first thermal process will be complete before the second commences. In this instance the two processes will be resolved. At some higher heating rate, due to the increased temperature progression of the reference with respect to that of the sample, it is possible that the temperature reequilibration following the first process will not have occurred before the onset of the second event. The two processes will not be resolved in this instance. It should also be noted that poor heat transfer is associated with large sample sizes which consequently prolongs the temperature lag of the sample with respect to that of the reference. Hence, large sample sizes are associated with poor resolution and good sensitivity.

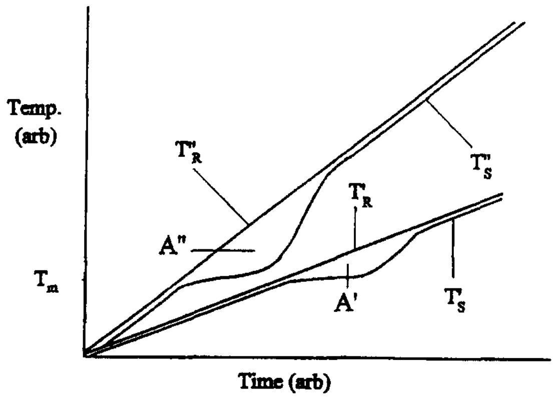

Fig. 3. The effect of heating rate on signal sensitivity.

An important consideration is the classification of thermal events as reversible or irreversible processes. Reversible processes are those which may be reversed by an infinitesimal modification of a variable. A system undergoing a reversible process is considered to be in equilibrium with its surroundings at each stage during that process. In other words, an ideal, reversible, process (taking place in an ideal DSC instrument) will absorb or radiate heat to perfectly match the temperature programme. The heat flow associated with such processes is thus dependent on the rate at which heat is applied to the sample. In contrast, irreversible processes are not in equilibrium with the temperature programme and tend to be kinetically controlled processes which are dependent on absolute temperature. Hence, if a sample is subjected to a thermal cycle (beginning and ending at the same temperature) the integral of the heat flow associated with reversible phenomena will be zero, that associated with irreversible events will be finite (Seferis et al., 1992).

The terms used to describe the thermodynamic reversibility of processes should not be confused with those terms used to describe chemical reversibility, e.g. a weak electrolyte dissociating reversibly into constituent ions. This is an important distinction, as the concepts of thermodynamic reversibility are fundamental to an understanding of MTDSC and will be discussed in more detail later. A useful text on the subject of thermodynamic reversibility is Atkins (1978).

2.2. Heat capacity measurements

Heat capacity measurements are not currently widely used pharmaceutically. However, as MTDSC provides a simple and rapid means of assessing heat capacities, the principle of how these measurements are made using conventional DSC will be outlined here for comparative purposes.

The energy required to raise the temperature of a substance by 1 K is a measure of its heat capacity (or specific heat capacity when unit mass of sample is considered). Heat capacity may be represented as the following:

$$C_p = (\delta Q/\delta T)_p \tag{3}$$

where C_p (JK^{-1}) is the heat capacity, Q (J) the (heat) energy and T (K) the temperature. This may also be expressed in an alternative form as in Eq. (4), where $\delta Q/\delta t$ is the heat flow and $\delta t/\delta T$ is the reciprocal heating rate:

$$C_p = (\delta Q/\delta t)_p \times (\delta t/\delta T)_p \tag{4}$$

Since the baseline value is a measure of differential heat flow (i.e. $\delta Q/\delta t$) then, for a given heating rate, the difference in baseline values obtained in the presence and absence of sample material is proportional to the heat capacity according to:

$$C_p = K\Delta Y/b \tag{5}$$

where the constant of proportionality, K, is the calorimetric sensitivity, ΔY is the difference in baseline values obtained in the presence and absence of sample material, and b is the heating rate, $\delta T/\delta t$. The calorimetric sensitivity may be found by calibration with a substance of well established heat capacity (usually pure, industrially manufactured sapphire, Al_2O_3). It should be noted that heat capacity is a function of temperature and that tables of C_p against T for sapphire are available.

The procedure for heat capacity determination involves three DSC scans; baseline measurements in the presence and absence of a sample of known mass and then a similar scan for a known mass of calibrant. An ‘empty pan’ baseline measurement is made by loading the cell with empty sample and reference pans and scanning over the required temperature range (at the desired heating rate). Isothermal portions should be included at the beginning and end of each scan. At the beginning of a run a baseline deflection from the initial equilibrium point may be seen. This deflection depends upon and is proportional to the difference in heat capacity of the sample and reference pan systems.

This procedure is then repeated under identical conditions with an accurately weighed calibrant material (e.g. pure, crystalline sapphire). The calorimetric sensitivity, K, may then be estimated by substitution into Eq. (5). The ΔY value is the difference in baseline measurements between the ‘empty pan’ baseline and the ‘sapphire’ baseline at the temperature of interest. The procedure is then repeated for an accurately weighed sample material to obtain a ‘sample’ baseline. The difference between the ‘empty pan’ baseline and the ‘sample’ baseline (i.e. ΔY) may then be substituted into Eq. (5) to obtain a value for the heat capacity of the sample. The specific heat capacity may then be calculated by dividing the heat capacity by the mass of the sample.

2.3. Quantitative concentration and enthalpy determinations

The area under a signal peak is directly proportional to the heat evolved or absorbed during the event from which it arose and also to the mass of sample substance present. Similarly, the height of the curve (for any given system) is directly proportional to the rate of reaction. The peak area (A) is related to enthalpy change by the following relationship:

$$A = k'm(-\Delta H) \tag{6}$$

where k' is a calorimetric sensitivity (an electrical conversion factor rather than one based upon sample characteristics as in differential thermal analysis, DTA), m is the mass of the sample and $-\Delta H$ is the enthalpy change. Strictly speaking, enthalpy changes are heat exchanges with the surroundings at constant pressure (e.g. those occurring in open pans). Heat exchanges which take place at constant volume (e.g. those in hermetically sealed pans) are referred to as internal energy changes. However, for simplicity, this review refers to all heat exchanges as changes in enthalpy. The relationship described by Eq. (6) is applicable to systems of a given sample type and heating rate. The end of an enthalpic event is denoted by the reestablishment of the baseline (unlike DTA where the reaction may terminate some time before). Quantitative analysis requires

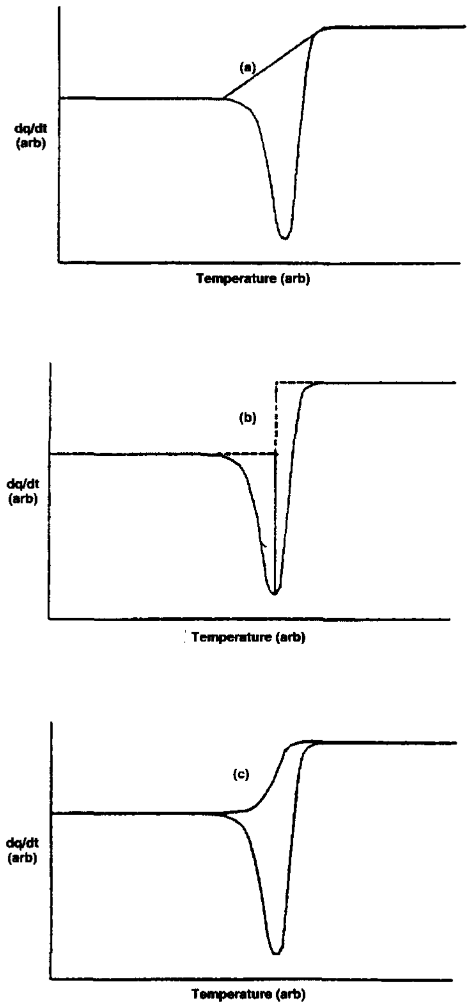

Fig. 4. Methods of determining peak area by the construction of: (a) tangential baseline, (b) stepped baseline, and (c) sigmoidal baseline.

calibration of the temperature scale and calorimetric sensitivity. A variety of substances are available for this purpose, the most widely used being 99.999% pure indium whose melting temperature and enthalpy of fusion are 156.61°C and 28.71 J g^{-1}.

The baseline values preceding and following enthalpic events are almost invariably different owing to the change in heat capacity which accompanies processes in which the properties of the sample are altered (as indicated in Fig. 4). The lack of definition of a true baseline across the peak region presents a problem in the estimation of peak area and a number of methods are available in order to overcome this difficulty, all of which involve certain assumptions. A peak area calculation based upon the enclosure of the signal by a tangent drawn from the onset to a point at which the baseline in reestablished (as shown in Fig. 4a) generally results in an overestimation of peak area. The construction of a stepped (Fig. 4b) or sigmoidal (Fig. 4c) baseline across the peak are also employed to compensate for the baseline deviation although no standard procedure exists. However, providing that suitable calibration has been executed, melting points, heats of fusion, enthalpies of crystallisation, reaction temperatures and enthalpies for numerous other processes may be determined fairly accurately by DSC. Quantitative concentration measurements may also be made on the basis that the mass of a sample (as appears in Eq. (6)) is related to concentration.

2.4. Glass transition temperatures

The glass transition is not actually a true phase transition but is a process in which 'frozen' segments (e.g. polymer chain segments, side chain pendant groups etc.) are unfrozen. Many solids (particularly thermoplastic polymers) form supercooled liquids when rapidly cooled from above the 'melt'. Electronic repulsive forces, such as those between segments of a polymer, may be 'frozen' into the structure. On heating, energy is supplied to the sample and partial segmental rotation begins such that the repulsive forces are relieved. As the segmental mobility increases the polymer changes from a glassy to a rubbery state. The polymer may be considered as a number of sub-systems all of differing segment lengths. The onset temperatures of segmental mobility for each of the sub-systems are different. The overall glass transition, T_g, is a consequence of all of the different segmental motions and is accompanied by an increase in heat capacity (and possibly a small relaxation endotherm). Glass transitions are associated with the amorphous regions of the polymer and the temperature at which they occur is influenced by the polymer preparation temperature, cooling rate, molecular weight (and distribution), degree of cure and the presence of additives. Many drugs, despite their low molecular weights, exhibit glass transition phenomena. There has been considerable pharmaceutical interest in drugs in the glassy state because their high energy states are thought to contribute to fast dissolution rates.

Glass transition temperatures and the accompanying changes in heat capacity may be determined by DSC on account of the associated baseline displacement (as depicted in Fig. 2). It is not always possible to detect the glass transition of polymers which possess a very small amorphous content as the associated change in heat capacity will also be very small. For example, the glass transitions of carbon fibre reinforced polyimides are difficult to determine by conventional DSC since the signal intensity is very low and the technique is insufficiently sensitive to enable the separation of the signal from the baseline (Seferis et al., 1992). As will be discussed later improved detection of glass transition phenomena is one of the advantages of MTDSC over the conventional technique.

3. The basic principles of MTDSC

Modulated temperature differential scanning calorimetry, MTDSC, is an extension of DSC in which a sine wave modulation is applied to the standard, linear, temperature programme, as indicated earlier in Fig. 1. A discrete Fourier Transform algorithm is applied to the resultant heat flow signal to deconvolute the calorimetric responses to the modulated and underlying (i.e. standard, linear) temperature programmes. MTDSC is therefore, at present, a software development rather than a change in the basic DSC equipment. As will be discussed in more detail later, the use of the modulated signal improves both the quality and quantity of information which may be obtained from the hardware, although certain disadvantages and areas requiring caution have been identified which will also be outlined.

In order to understand the principles of MTDSC, it is necessary to consider the basic theory of conventional DSC. The heat flow signal of the latter is a combination of 'kinetic' and 'heat capacity' responses, i.e. the heat flow from the sample (or reference) is a function of both the heat capacity of the sample and of any kinetic heat flow component. Broadly speaking, the occurrence and rate of an irreversible 'kinetically' controlled event is dependent on the absolute temperature, whereas reversible 'heat capacity' phenomena tend to be proportional to the rate of change of temperature. The resultant heat flow signal may be expressed in the following way:

$$dQ/dt = C_p dT/dt + f(t,T) \tag{7}$$

where Q is the (heat) energy, C_p is the 'thermodynamic' heat capacity (i.e. that due to the energy stored in vibrations, rotations and translations of molecular constituents of the sample), T is the absolute temperature and $f(t,T)$ is some function of the time and temperature which expresses the calorimetric response of any kinetically controlled chemical or physical phenomena.

During a typical linear heating programme, in the absence of any physical or chemical reaction, the heat flow signal is dictated by the heat capacity. When the temperature attains a certain value such that a kinetically controlled 'chemical' event occurs (e.g. polymer cure, melt or crystal reorganisation) the resultant heat flow signal is a combination of the heat flow associated with the heat capacity and that associated with the chemical event. There is a fundamental difference in the nature of the energy arising from the two phenomena in that the former is reversible and the latter is irreversible. MTDSC is capable of separating these two processes, while conventional DSC heat flow signal represents the sum of the two types of process. The basis of the separation of the two types of heat flow signals is their difference in response to the underlying and modulated temperature programmes.

The modulated temperature programme may be expressed in the following way:

$$T = T_o + bt + B\sin(\omega t) \tag{8}$$

where T_o is the initial temperature, ω is the angular frequency (i.e. $2\pi f$), b is the linear heating rate and B is the amplitude of the temperature modulation. Differentiation of Eq. (8) and substitution into Eq. (7) yields the following expression:

$$\mathrm{d}Q/\mathrm{d}t = C_p(b + B\omega\cos(\omega t)) + f'(t,T) + C\sin(\omega t) \quad (9)$$

where $f'(t,T)$ is the average underlying kinetic calorimetric response (after subtraction of the response to the sine wave modulation), C is the amplitude of the kinetic response to the sine wave modulation and $(b + B\omega\cos(\omega t))$ is equivalent to $\mathrm{d}T/\mathrm{d}t$. Hence the heat flow signal will contain a cyclic component which is dependent on the values of B, ω and C. The kinetic contribution $f'(t,T) + C\sin(\omega t)$ only occurs during irreversible enthalpic processes although the heat capacity contribution, $C_p(b + B\omega\cos(\omega t))$, is always present. For many kinetically controlled processes C may be approximated to zero such that the response to the cyclic perturbation originates from the thermodynamic heat capacity contribution alone (Eq. (10)):

$$\mathrm{d}Q/\mathrm{d}t = C_p(b + B\omega\cos(\omega t)) + f'(t,T) \quad (10)$$

Discrete Fourier Transform is used to separate the cyclic (modulating) heat flow component from the underlying heat flow signal. The heat capacity, C_p, may be determined since b, B and ω are measured. The cyclic heat flow component, the product of C_p and the underlying heating rate, may then be calculated and is termed the reversing heat flow component. The non-reversing heat flow component is obtained by subtraction of the reversing component from the calculated total heat flow. All noise appears in the non-reversing signal.

The theory of MTDSC and the interpretation of data obtained from this technique are based on the following assumptions and requirements:

- The use of small, thin, completely encapsulated samples minimises temperature gradients and maximises conductivity during the heating and cooling cycles. Good thermal contact must also be ensured between the pans and conducting plates.
- Heat flow is measured by an ideal device which responds instantaneously (with no lag).
- The heat capacity heat flow contribution during the heating and cooling cycles is completely reversible (with no hysteresis).

It should be noted that actual calorimeters do not conform to the ideal specifications cited above and that the distinction between heat flows arising from thermodynamic heat capacity and kinetically controlled processes, for real samples, is less well defined than is suggested by the theory outlined here. Nonetheless, this model has proven suitable as a first approximation for the explanation of data generated from preliminary MTDSC investigations.

Fig. 5 shows the total, reversing, and non-reversing heat flow signals for a sample of quench cooled polyethylene terephthalate (PET), the most widely cited MTDSC 'pilot' substance. The data was obtained at an underlying heating rate of 3°C min^{-1}, a modulation period of 50 s and a modulation amplitude of ±2°C. The glass transition is seen in the reversing heat flow signal, whereas the recrystallisation appears in the non-reversing heat flow signal. Under the operating conditions selected the melting endotherm appears in both.

3.1. MTDSC operating conditions

One of the features of MTDSC compared to that of conventional DSC is that the number of

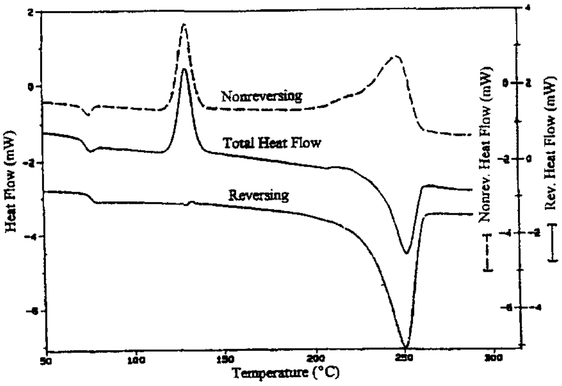

Fig. 5. MTDSC thermoanalytical curve of PET showing the total, reversing, and non-reversing heat flow signals.

operational variables is considerably greater for the former. In addition to the sample size, choice of pans and (underlying) heating rate, the frequency and amplitude of modulation must also be considered; the choice of these parameters is highly important, and, if not properly considered, will result in the generation of artefacts.

The underlying heating rate of an MTDSC experiment is equivalent to the heating rate employed in standard DSC. MTDSC typically involves heating rates of 1–5°C min^{-1} compared with the 10–20°C min^{-1} heating rates employed in conventional DSC. This heating rate gives rise to the (underlying) total heat flow signal which represents the sum of all thermal events. The accuracy and precision of the total heat flow measurement are equivalent for both techniques (for a given heating rate).

DSC sensitivity for most reversible transitions is a function of the maximum instantaneous heating rate. Large modulation amplitudes produce large instantaneous heating rates and hence give rise to increased heat flow sensitivity. Since the underlying heating rate of an MTDSC experiment is synonymous with the heating rate of a conventional DSC experiment, low underlying heating rates are associated with increased resolution. It is the combination of a large modulation amplitude and low underlying heating rate which enables an increase in sensitivity without the need to sacrifice resolution.

The amplitude of the temperature modulation is typically selected from a range ± 0.1 to ± 1.0°C. The period time (that time taken for one complete oscillation, i.e. reciprocal frequency) of the temperature modulation is currently selected from the range 30–80 s to allow sufficient time for heat flow to and from the sample during the temperature cycles. However, one of the limitations imposed on the conditions of operation is that at least six modulations are required throughout the duration of each thermal event (to enable the complete separation of cyclic and underlying responses). The comparatively slow underlying heating rates used for MTDSC experiments are chosen to allow this condition to be satisfied.

The cooling capacity of the cell imposes a restriction on the modulation amplitude for a given period time (especially small period times). Distortion of the heat flow sine wave (which is likely to result in misinterpretation of the deconvoluted results) will occur if the cell is unable to cool sufficiently during the cooling portion of the modulation cycle. Maximum modulation amplitudes are achieved with small period times when using a cell purge gas of high thermal conductivity (e.g. helium as opposed to nitrogen) at a high flow rate. Empty pan runs may be conducted to ensure that no distortion of the heat flow sine wave occurs when large modulation amplitudes are used in conjunction with small period times.

It is possible to select modulation amplitudes and period times such that the net heating rate is always positive i.e. the temperature is continuously rising, even though the signal is oscillating. Similarly, for experiments requiring ‘continuous cooling’ certain values of modulation amplitude and period times will ensure that the net heating rate is always negative. These values may also be selected to produce heating and cooling within a cycle. Some thermal events may produce different separations between the reversing and non-reversing heat flow signals depending on whether the sample is exposed to heating and cooling within a cycle or continuous heating (or cooling) only. For example, during the analysis of melting processes it is necessary to select operating parameters such that the net heating rate is always positive if exothermic melt reorganisation of metastable crystal forms is to be prevented.

The MTDSC cell calibration procedure (i.e. that for baseline correction, temperature scale and calorimetric sensitivity) does not differ from that of conventional DSC although an additional calibration for heat capacity is required. The heat capacity calibration constant enables the accurate measurement of sample heat capacities and allows the correct separation and calculation of the total, reversing and non-reversing heat flow data. The heat capacity calibration is carried out by scanning a calibrant of know heat capacity (i.e. sapphire) under the same conditions as those of the sample run (i.e. the same modulation amplitude, period time, and underlying heating rate). The measured heat capacity of the calibrant is then compared with the literature value at the temperature of interest. The ratio of the literature to measured value is the required heat capacity constant. The measurement of sample heat capacities will be discussed later.

3.2. Advantages and disadvantages of MTDSC

As discussed above, the use of MTDSC allows the deconvolution of the total heat flow signal into two components. This provides a number of advantages, some of which will be discussed below, although a number of concomitant difficulties have been identified, which will also be discussed. As most of the initial work performed using MTDSC has been concerned with polymeric samples, this class of materials will be used to furnish examples of the features of the technique.

3.2.1. Advantages of MTDSC

3.2.1.1. The combination of high resolution and high sensitivity. As outlined in the previous section, the combination of a high modulation amplitude and low underlying heating rate satisfies the conditions for both high resolution and sensitivity. This alone means that small and overlapping transitions may be seen with greater clarity, over and above the separation of the total heat flow signal into reversing and non-reversing components.

3.2.1.2. The measurement of heat capacity by MTDSC. The measurement of heat capacity by conventional DSC requires three scans and a certain amount of operator expertise in the production of precise, accurate results. However, the determination of heat capacity by MTDSC requires a single sample run providing that suitable heat capacity calibration has been carried out. This opens up the possibility of exploring the measurement of heat capacity (by MTDSC) as a pharmaceutical tool, as changes in physical structure or chemical composition may be reflected by changes in this property. Knowledge of heat capacities may also be of use in the design of pharmaceutical manufacturing processes which involve a heating stage.

Direct heat capacity measurements may be made by simply running the sample under identical conditions (i.e. same modulation amplitude, period time and underlying heating programme) to those used to obtain the heat capacity calibration constant. A plot of heat capacity against temperature (or time) may then be obtained directly (using the standard software which accompanies MTDSC instrumentation) and the heat capacity at the temperature of interest observed and reported. Long period times (those of around 80 s) and large modulation amplitudes (± 0.5 to ± 1.0) are recommended for optimum measurements. The use of long period times results in maximum accuracy whilst large modulation amplitudes (which are readily available at long period times) increase the signal-to-noise ratio of the heat flow modulation. Underlying heating rate has been found to have a less influential effect on the accuracy and precision of the heat capacity measurement; an underlying heating rate of 5°C min^{-1} is recommended. Along with a threefold reduction in the number of scans required in the determination of heat capacity data the noise and precision of MTDSC heat capacity measurements are approximately twice as favourable as those of conventional DSC (Gill et al., 1993).

3.2.1.3. The detection of glass transitions by MTDSC. The procedure for the detection and measurement of glass transition phenomena by MTDSC is the same as that for conventional DSC. However, the high instantaneous heating rate supplied by the sine wave modulation results in superior sensitivity. This increased sensitivity permits the detection of weak transitions (e.g. those of systems containing 'diluents' or possessing low amorphous contents) which are not detectible by conventional DSC. Furthermore, the detection and measurement of glass transitions by conventional DSC often requires preconditioning of the sample to reduce (and preferentially remove) the accompanying volume relaxation endotherm. This procedure involves heating and cooling through the glass transition. MTDSC allows the separation of the glass transition which appears in the reversing heat flow signal and the relaxation endotherm which appears in the non-

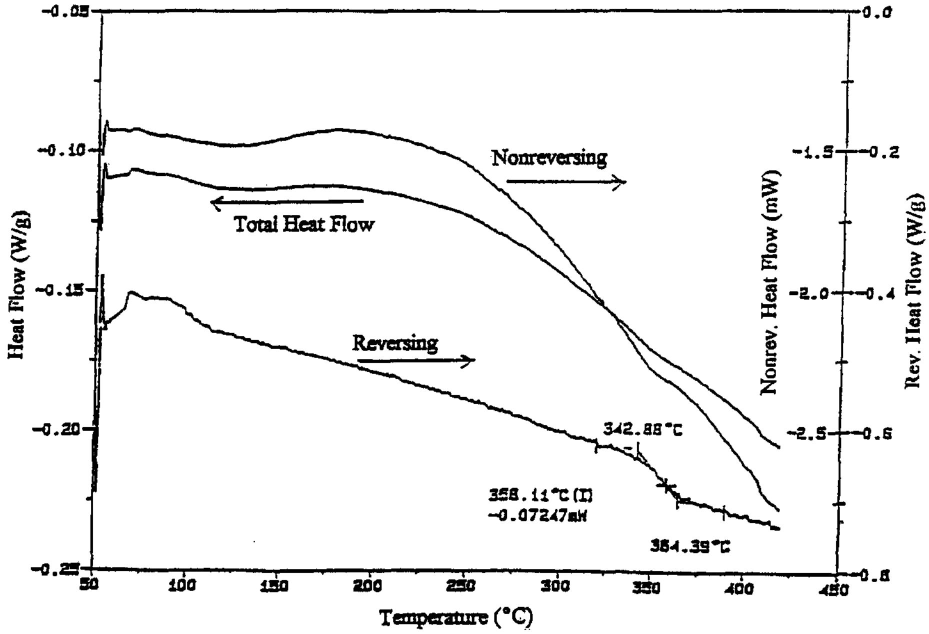

Fig. 6. The total, reversing, and non-reversing heat flow signals for the high temperature thermosetting polyimide, NR-150, showing the measurement of the glass transition in the reversing heat flow signal. (After Seferis et al., 1992).

reversing signal. This separation eliminates the requirement for sample preconditioning. This capability is especially important in the investigation of thermoset polymer systems as heating above the glass transition may advance the cure and affect results (as noted in the following section).

Seferis et al. (1992) observed the glass transition of carbon fibre reinforced PET and established that the T_g values determined from the total heat flow signals of both conventional DSC and MTDSC increased as the (underlying) heating rate was increased. However, the glass transition determined from the MTDSC reversing component exhibited no apparent heating rate dependence (over the observed heating rate range of 1 to 10°C min^{-1}). The onset temperature of the enthalpic relaxation associated with the glass transition, as observed in the non-reversing signal, was found to increase as the heating rate increased. This implies that the heating rate dependence of T_g (as observed by with conventional DSC) can be attributed to the enthalpic relaxation. This observation also indicates that the relaxation of the molecules associated with the glass transition is fast compared with that of the enthalpic relaxation. Obviously, conventional DSC is not capable of providing such information.

The detection of the glass transition of the high temperature thermosetting polyimide, NR-150, is not possible by conventional DSC as the transition is weak and the technique insufficiently sensitive. In the same publication, Seferis et al. (1992) report that it was possible to determine the glass transition of this substance by analysis of the reversing heat flow signal of the MTDSC thermoanalytical curve (as shown in Fig. 6). The results were found to be in excellent agreement with those of dynamic mechanical analysis (DMA).

A polymer blend may be considered to be miscible when only one glass transition is observed. If the polymer constituents of a binary blend are immiscible then two T_gs will be recorded. If the difference between the glass transition temperatures of the two polymers is within 15°C it is almost impossible to assess the extent of mixing by conventional DSC. The enhanced resolution and sensitivity of MTDSC has enabled the analysis of physical mixtures of the two polymers, poly(methyl methacrylate) and poly(styrene-co-

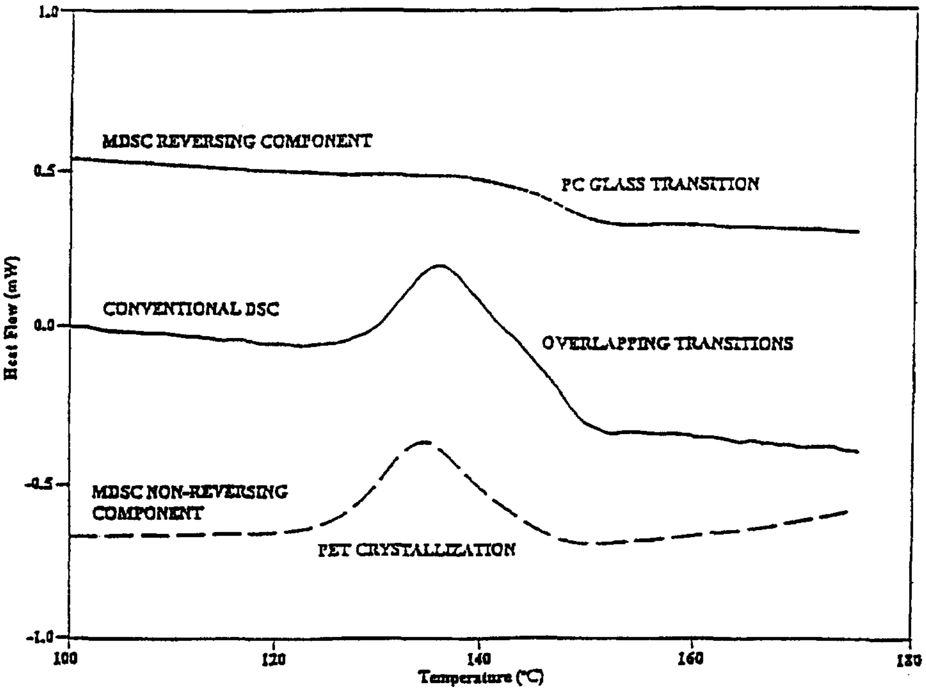

Fig. 7. A comparison of the reversing and non-reversing heat flow signals, and the total heat flow signal for a mixture of polycarbonate and polyethylene terephthalate.

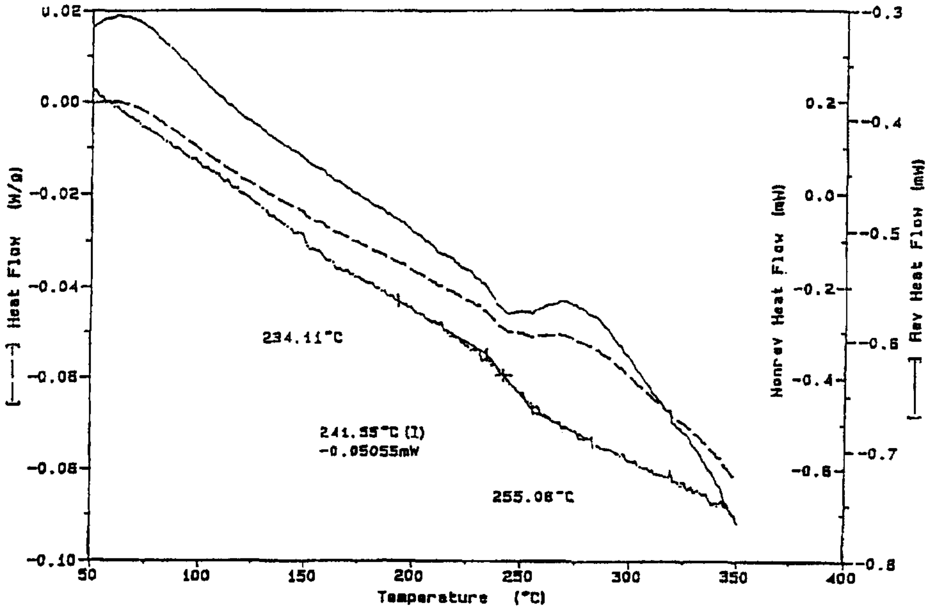

Fig. 8. Total, reversing, and non-reversing heat flow signals for a sample of carbon-fibre reinforced bismaleimide. (After Seferis et al., 1992).

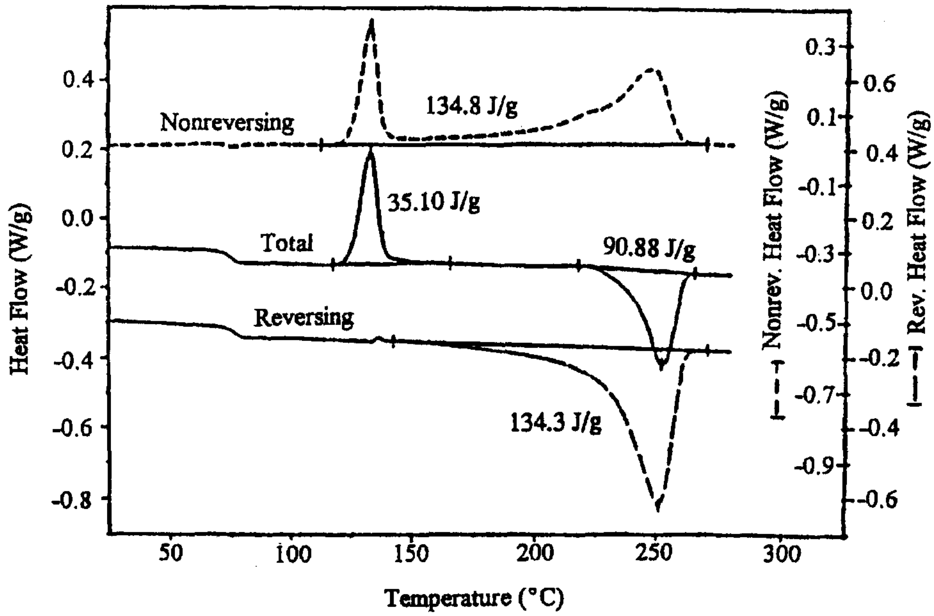

Fig. 9. The measurement of initial crystallinity of a sample of quench cooled PET by MTDSC. (After Sauerbrunn and Thomas, 1995).

acrylonitrile) whose glass transition temperatures are within 10°C (Song et al., 1995).

3.2.1.4. The detection of hidden phenomena by MTDSC. Seferis et al. (1992) investigated a bilayer film of polycarbonate (PC) and PET. Conventional DSC is not an appropriate technique for the investigation of this system as the PC glass transition and the PET cold crystallization occur in the same temperature range. However, MTDSC allowed the separation of these overlapping transitions; the T_g of PC and the cold crystallization exotherm of PET were found to appear in the reversing and non-reversing signals respectively (as shown in Fig. 7). In the same publication the authors also reported the results of an investigation into the properties of a carbon-fibre reinforced bismaleimide laminate by MTDSC. The glass transition temperature could not be accurately determined from the heat flow signal of conventional DSC as a cure exotherm was observed which immediately followed the glass transition. Upon separation of the total heat flow signal into its components, the cure was observed exclusively in the non-reversing signal and the glass transition was determined for the reversing signal (as shown in Fig. 8).

3.2.1.5. The investigation of initial crystallinity by MTDSC. The term 'initial crystallinity' refers to the 'amount' of crystallinity a sample possesses as received. Sauerbrunn and Thomas (1995), have reported the results of an initial crystallinity study of a number of thermoplastic polymers by MTDSC. Conventional DSC measures the sum of all thermal events and cannot independently measure the crystal structure formation which may be occurring during heating. Comparison of the enthalpies of cold crystallisation (ΔH_{cc}) and melting (ΔH_f) of rapidly quench cooled PET indicated that some initial crystallinity is present in the sample (since $|\Delta H_{cc}| \neq |\Delta H_f|$). However, X-ray diffraction studies indicated that no initial crystallinity was present. The non-reversing MTDSC signal (Fig. 9) showed that exothermic ordering/crystallisation begins at the onset of the cold crystallisation signal and continues to occur up to and through the melting process. The reversing signal indicated that endothermic melting was occurring simultaneously. The sum of the integrals of these two signals was found to be zero which represented the actual initial crystallinity of the sample. The measurement of initial crystallinity of other thermoplastic polymer substances by the of MTDSC where the use of conventional DSC has failed to indicate substantial differences in this property is also demonstrated in this publication.

3.2.2. Disadvantages of MTDSC

There are a number of associated disadvantages of the MTDSC technique which have been identified thus far. Firstly, to satisfy the requirement for at least six modulations throughout the duration of each thermal event, low underlying heating rates are required. These may not always be desirable. This restriction is particularly significant when analysing sharp transitions. Secondly, it is arguable that DSC is often regarded a routine screening technique within the pharmaceutical sciences (certainly within industry) and many of the experimental variables and theoretical considerations associated with the technique are not explored. While this is due to DSC being used as a tool for detecting specific phenomena, it would be unwise to extend this approach to MTDSC, as the technique is more complex, involves the use of a greater number of experimental variables and requires a more sophisticated understanding of the theory of differential calorimetry. Finally, the technique suffers the drawback of all novel approaches, namely that all operators are still in the process of establishing the capabilities of the technique. The interpretation of MTDSC data is also rarely simple. While the technique is clearly of great importance and interest (and is being hailed as the most exciting innovation in thermal analysis for several decades), such enthusiasm reinforces the need for rigorous examination of experimental parameters and careful interpretation of results.

4. Current and future applications of MTDSC to pharmaceutical systems

Sebhatu et al. (1994) compared the results from microcalorimetry, X-ray diffraction and MTDSC experiments in an assessment of the degree of disorder of various lactose samples. A measure of the degree of disorder of a sample system may be derived from a value of the heat evolution during crystallisation. The separation of the total heat flow signal of lactose into its components revealed that the crystallisation exotherm, as observed by conventional DSC comprised both an endothermic reversing peak and an exothermic non-reversing peak (under the selected conditions). The heat of crystallisation was measured from the non-reversing exothermic signal and the reversing endotherm was attributed to a conversion between two crystalline forms. The degree of disorder calculated from this measurement was found to be in close agreement with the data obtained from X-ray and microcalorimetric analyses.

Alden et al. (1995) have investigated the effect of variations in modulation frequency, amplitude and underlying heating rate on the reversing and non-reversing heat flow signals for the melting of griseofulvin and PEG 6000. They have divided the product of the modulation frequency and amplitude by the underlying heating rate and have expressed this combination as the 'degree of oscillation'. It is suggested that, if an appropriate degree of oscillation is used, the ratio $\Delta H_c/\Delta H$ is a measure of the degree of crystallinity of the system, where ΔH_c is the energy associated with the reversing component of the melting process and ΔH is the heat of fusion. However, care is required in the use of the degree of oscillation as an experimental parameter as different combinations of modulation frequency, amplitude and underlying heating rate which give the same value of the degree of oscillation yield different values for ΔH_c.

Wulff and Alden (1995b) used MTDSC to examine the thermal behaviour of dispersions of griseofulvin, PEG 3000 and various alkali (sodium, potassium and lithium) dodecyl sulphates (NaDS, KDS and LiDS, respectively). Exothermic reversing and non-reversing components were observed for each of the melting signals of the dispersions (under the selected conditions). The melting temperature and enthalpy of fusion, as measured from the total heat flow signal, of the PEG 3000/griseofulvin solid dispersion were similar to those of the PEG 3000/griseofulvin/LiDS solid solution. The solid solutions containing NaDS and KDS also exhibited similar melting temperatures and enthalpies of fusion (which were both slightly lower than those of the PEG 3000/griseofulvin and PEG 3000/griseofulvin/LiDS systems). However, differences in the enthalpy changes of the reversing and non-reversing components of the melting peaks of these systems were reported.

Given the advantages of the technique, it is possible to postulate the ways in which MTDSC could be of future benefit within the pharmaceutical sciences. One possibility is the detection of polymorphism, which often proves difficult using conventional DSC as the melting points may be very similar and transformation for one form to another may occur during the melting process. The independent optimisation of sensitivity and resolution, along with the separation of the signal into reversing and non-reversing heat flow components may allow the resolution of such complex and overlapping phenomena. In addition, the ability of the technique to detect hidden glass transition phenomena has resulted in interest being generated for the study of freeze dried products (Pikal et al., 1995). It is also of interest to speculate on the implications of direct heat capacity measurements in terms of manufacturing processes and as a quality control tool.

5. Conclusions

MTDSC represents a new and potentially highly useful approach to pharmaceutical thermal analysis as it allows the independent optimisation of sensitivity and resolution, the separation of the heat flow signal into reversing and non-reversing components and the detection of 'hidden' phenomena. These capabilities allow a more sophisticated understanding of various thermal events. The use of the technique requires a greater understanding of thermal analysis than is currently necessary for conventional DSC although the potential rewards are considerable.

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