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Commentary

The Use of Modulated Temperature DSC for the Study of Pharmaceutical Systems: Potential Uses and Limitations

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Modulated temperature differential scanning calorimetry (MTDSC) is a recently introduced thermoanalytical method which is now an established tool within the polymer sciences and is beginning to generate considerable interest within the pharmaceutical sciences. The method was invented by Reading (1) and, in the instrument developed by TA Instruments (modulated DSC), involves the superimposition of a sinusoidal heating signal on a linear scan (or isothermal) programme. The total heat flow response dQ/dT (which is equivalent to that obtained from a conventional DSC) may be considered to be composed of two components, the first corresponding to the product of the underlying heat capacity C_p and the scanning rate dT/dt and the second to kinetic events, i.e. those that are a function of the sample temperature and the rate of heat loss or gain during the process, designated $f(t, T)$. The total heat flow is therefore given by

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

The $C_p dT/dt$ and $f(t, T)$ components are termed reversing and non-reversing respectively by TA Instruments; in brief, the reversing signal allows apparent changes in heat capacity to be observed and is measured from the response to the modulation, while the non-reversing component is obtained simply by subtracting the reversing signal from the total heat flow response. It is therefore possible to see changes in heat capacity such as glass transitions in isolation from kinetic events such as relaxation endotherms. It should be noted that it is also possible to measure the in- and out-of-phase components of the response; this issue will not be discussed here for reasons of brevity but further information is available on this topic (2,3).

The principal benefits of the technique are the ability to separate overlapping thermal events, greater resolution between events with no loss of sensitivity and the possibility of measuring heat capacities in a single run. More details regarding the technique are available from a number of texts (1,4,5,6). The recent interest in using this technique within the pharmaceutical sciences necessitates consideration of both the principal applications and limitations of the technique. In this commentary we outline some of the current thinking regarding the type of problem into which MTDSC may (or may not) provide new insights but also the difficulties associated with the use of the technique and recommendations for their resolution.

The issue of the type of sample and problem for which MTDSC is suitable is not a trivial one. The most common pharmaceutical use of conventional DSC is in the study of melting phenomena; however, we have to recommend that, at the present stage, pharmaceutical scientists should generally avoid using the instrument for this purpose. This is because many systems show signals in both the reversing and non-reversing components during the melt; the interpretation of this signal splitting is not yet fully understood, although some of the mechanisms involved are known (7). For example, during a melt the sample will tend to maintain isothermal conditions due to absorption of the applied thermal energy for bond breakage, hence it becomes difficult to reliably modulate the material. It is not correct to assign such splitting to specific events such as recrystallization, dehydration etc.. It is widely believed that the problems associated with the interpretation of signal splitting during melting will be solved in the foreseeable future and a great deal of useful information will then become available. At present, however, it is simply not possible to interpret the mechanism by which this is occurring for pharmaceutical samples with any confidence.

Our own view is that MTDSC is, for the moment, best applied to glass transitional phenomena. Many systems of pharmaceutical relevance are amorphous, including drugs, freeze and spray dried materials, excipients and polymeric drug delivery systems. A highly useful means of characterising such materials is to measure the glass transition temperature, Tg, which may in turn be related to parameters such as mechanical properties and both physical and chemical stability. However, measurement of Tg using conventional DSC is often difficult due to the transition being observed as a shift in the baseline rather than a peak, leading to problems in terms of differentiation from baseline noise. Furthermore, a relaxation endotherm is often superimposed on the transition, thereby impeding identification and quantification of the glass transition. MTDSC offers improved signal to noise and reduced baseline curvature compared to conventional DSC, hence small transitions may be seen

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in the reversing signal with greater clarity than was previously possible. Furthermore, the relaxation endotherm and glass transition are separated into non-reversing and reversing signals respectively, hence it is possible to visualize Tg in isolation. The availability of the technique therefore opens up a sufficiently broad range of problems to maintain interest in the approach while the theoretical aspects of the melting response interpretation are worked out.

With regard to the limitations of the technique, we would like to outline our own experience of the most commonly encountered problems and our recommendations for their resolution:

a) Sample Not Following the Heating Signal

Over and above the underlying heating signal, samples must be able to follow the oscillation as otherwise one is simply modulating the sample pan rather than the material itself. This will occur if the chosen frequency is too fast or the amplitude is too large. Clearly, the problem can be partially alleviated by using small samples, but we recommend the following general guidelines for most pharmaceutical samples; a maximum underling scanning rate of 5°C/min (we usually use 1°C/min or 2°C/min), a maximum amplitude of 1°C (we usually use 0.1–0.5°C for ramping studies and 0.5–1°C for quasi-isothermal work; smaller transitions require larger amplitudes but we would not recommend going above 3°C under almost any circumstances), a minimum period of 20 s (we usually use 30–60 s). The use of helium as a purge gas may also be advantageous for periods shorter than approximately 40 seconds provided that the flow rate is carefully controlled, preferably using a mass flow controller. It is possible to gain some idea of whether the sample is following the signal by looking at the raw heat flow data; if the sample is not following the program, distortion of the sinusoidal signal may be seen. It is also possible to use more sophisticated methods of analysis such as Lissajous figures (8,9) which will be discussed in more detail in a forthcoming publication.

b) Insufficient Number of Cycles During a Thermal Event

It is necessary to have a sufficient number of modulations during a thermal event in order for the deconvolution program to function reliably. This will be a function of period and underlying scanning rate and is probably the most important experimental limitation associated with the technique. The general opinion appears to be that four modulations are sufficient, although six yields a safer margin if practically feasible. This problem may be avoided by choosing an underlying heating rate and period which allow a sufficient number of modulations to appear during the transition and is the primary reason for the use of slow scan speeds using the technique. It is possible to check for this problem either by examining the raw data (simply counting the number of oscillations during the event) or by the use of Lissajous figures.

c) Sample Undergoing Heating and Cooling Within the Program

As the sample is experiencing both an underlying and sinusoidal heating signal, it is possible to obtain programes in which the sample is actually undergoing a decrease in temperature even if the underlying heating rate is positive. This may be desirable in some cases but for most purposes is not helpful and may be problematic if the operator is not aware of it taking place. The problem may be easily prevented by appropriate choice of underlying heating rate, amplitude and period. The amplitude (*amp*, °C) required for any underlying heating rate (H_R, °C/min) and period (P, sec) which will ensure a zero or positive overall heating rate is given by (4)

$$amp \leq H_R \cdot \frac{P}{2\pi.60} \tag{2}$$

d) Inadequate Calibration

While it is standard practice to calibrate the baseline and to perform temperature and heat flow calibration using, for example, indium during conventional DSC experiments, it is also necessary to calibrate for heat capacity when performing MTDSC runs, as otherwise quantitative interpretation of the enthalpy data is not possible. This is usually performed using a materials such as sapphire disks or powdered alumina which have a well defined heat capacity. It is also highly advisable to run a baseline using empty pans so as to check that the heat capacity is near to zero and correct as necessary.

We would stress that, like all novel techniques, new developments are continually forthcoming. However, the recommendations described above are in line with current thinking within the MTDSC field. Clearly, each sample should be considered individually as far as experimental conditions are concerned and the above is for guidance only; we do nevertheless feel that it is necessary to be aware of some of the pitfalls associated with the technique as well as the benefits.

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