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The detection of amorphous material in a nominally crystalline drug using modulated temperature DSC—a case study

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Abstract

Two batches (1 and 2) of an experimental drug (L7) which have shown marked differences in their chemical stability profiles were examined with a view to identifying the presence of small quantities of amorphous material using modulated temperature DSC (MTDSC). The external morphological characteristics of the two batches were similar although marked differences were seen in the moisture uptake profiles. MTDSC studies indicated that while no evidence for a glass transition could be seen for Batch 1, a T_g and accompanying relaxation endotherm were observed for Batch 2. Comparison with a glassy form of the drug indicated that the amorphous content was in the region of 5–6% w/w in Batch 2. Dynamic moisture sorption studies indicated that while Batch 2 showed a higher uptake profile than Batch 1, addition of 5% w/w amorphous material to Batch 1 led to the establishment of a very similar profile to that seen for Batch 2. It was concluded that Batch 2 contains amorphous material which is responsible for the greater moisture uptake (and by implication poor chemical stability) of this sample and that the glass transition of this fraction may be characterised using MTDSC.

Keywords: Amorphous; Drug; Glass transition; Temperature-modulated differential scanning calorimetry; Water sorption

1. Introduction

Inter-batch variation and difficulties associated with scale-up of drug production have been persistent problems in the development of pharmaceutical formulations. One widely held view with regard to such behaviour is that different batches may contain varying quantities of amorphous material. In a seminal review by Ahlneck and Zografi (1990), the authors discuss the interrelationship between the presence of amorphous material, moisture uptake and drug degradation. A variety of processing factors may give rise to the presence of regions of molecular disorder in otherwise crystalline solids, these regions showing greater molecular mobility and hence chemical reactivity.

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In particular, such regions are expected to exhibit greater water sorption due to the uptake process being one of miscibility rather than adsorption. The association between the presence of such energetic sites and drug degradation has been discussed (Hasegawa et al., 1975; Ng, 1975), while Ahlneck and Zografi (1990) have highlighted the influence of water in terms of plasticization of such sites. These authors emphasised that even though the amorphous content and water uptake may be small in terms of the total mass of the sample, the preferential uptake of the water into disordered sites may result in considerable lowering of the glass transition of the amorphous material with concomitant effects on physical and chemical stability.

There has been considerable interest in the development of techniques for the detection and quantification of low levels of amorphous material within both drugs and excipients. This represents a particular challenge to the formulator as, by definition, the quantity of amorphous material will be small in proportion to the crystalline mass, hence many analytical techniques are insufficiently sensitive to allow such measurements. Methods such as water vapour sorption (Duncan-Hewitt and Grant, 1986; Oksanen and Zografi, 1990) and isothermal microcalorimetry (Angberg et al., 1992; Sebhatu et al., 1994; Buckton and Darcy, 1995) have been successfully utilised, while more conventional methods such as powder XRD and DSC are generally considered to be unsuitable due to their inability to detect amorphous matter at the necessary levels.

Over and above the issue of sensitivity, there are a number of additional problems associated with the measurement of small quantities of amorphous material. Methods such as microcalorimetry rely on the measurement of the recrystallisation energy of the drug or excipient on exposure to humidity; in many cases such recrystallisation may not be easily induced. Similarly, such methods do not yield direct information on the nature of the glass present. Indeed, this latter consideration is almost entirely unexplored due to the difficulties associated with measuring the T_g of such small quantities of amorphous material.

In this investigation, we describe a case study whereby the use of modulated temperature DSC (MTDSC) has been used with a view to detecting and characterizing small quantities of amorphous material in a model drug substance. MTDSC involves the superimposition of a sinusoidal signal (in the case of the TA Instruments model) on a linear heating programme. The response may then be deconvoluted into the reversing and non-reversing components according to

$$dQ/dt = C_p dT/dt + f(t,T) \quad (1)$$

where dQ/dt is the heating rate, C_p the sample heat capacity, dT/dt the heating rate and $f(t,T)$ is a function of temperature and time and reflects kinetically-controlled events such as melting and crystallisation. More details of the technique and its applications are available from a number of sources (Reading, 1993; Reading et al., 1993; Boller et al., 1994; Coleman and Craig, 1996). One aspect of the use of this method which has not yet been fully explored for pharmaceutical systems is the ability to detect small glass transitions. This possibility is a result of the heat capacity being measured via the response to the modulation rather than the magnitude of the total heat flow, hence the baseline signal to noise ratio may be greatly improved. More specifically, the value of C_p is measured via

$$\frac{A_{mhf}}{A_{mhr}} \times K = C_p \quad (2)$$

where A_{mhf} is the amplitude of the modulated heat flow signal, A_{mhr} is the amplitude of the heating rate signal and K is the heat capacity calibration constant; this value is recorded in the reversing heat flow signal. It should be noted that the heat capacity determined is termed a complex heat capacity, comprising both in-phase and out-of-phase components. Inspection of Eq. (2) indicates that while conventional DSC measures the glass transition via a step change in the overall heat flow, MTDSC measures this event via a change in the magnitude of the response amplitude which leads to a considerably improved signal to noise ratio. This has been demonstrated in a recent study by McPhillips et al. (1999) whereby the measurement of the glass transition of HPMC

films was found to be greatly facilitated using this approach. It is therefore logical to examine the possibility of using the technique to detect small quantities of amorphous material in nominally crystalline drugs. The drug in question (L7) had been noted to exhibit considerable interbatch variation in terms of chemical stability under humid storage conditions, with one of the batches under investigation (2) showing significantly greater degradation than a different batch (1) under storage at 40% RH/75°C over 3 months; both batches showed negligible degradation over the same time period at 40°C and 20% RH (MSD internal data). Given the arguments outlined earlier it was suspected that the difference in drug stability may be associated with differences in the moisture uptake profiles of the two batches which in turn may reflect differences in the degree of amorphous material. The objective of the study was therefore to examine the possibility of using MTDSC to detect glass transitions in the supposedly crystalline materials. If this proved to be feasible, the study would raise some interesting possibilities with regard not only to the detection and quantification of amorphous material but also the characterisation of the glass transition of the material.

2. Materials and methods

L7 was supplied by Merck, Sharp and Dohme and used as received. Two batches of crystalline drug were used (1 and 2) and amorphous drug was generated by dissolving the crystalline material in a minimal amount of water before adding an excess of acetonitrile. The amorphous solid was obtained by removing the solvent on a rotary evaporator. X-Ray diffraction analysis was used to confirm the product was amorphous (data not shown). SEM studies were conducted on Batches 1 and 2 using a Camsan CS44 (samples carbon coated, accelerating voltage 20 kV). Initial water contents were determined using Karl Fischer titration and found to be 0.1% w/w for Batch 1 and 0.5% for Batch 2. The amorphous material used in this study had a water content of approximately 1.2%. X-Ray diffraction studies were conducted on the two batches using a Philips PW3710 X-ray diffractometer, with no differences being detected between the two (data not shown).

MTDSC studies were conducted using a TA Instruments MDSC 2920 with refrigerated cooling system (RCS) (TA Instruments, Leatherhead, UK). The DSC cell was purged with 30 ml/min nitrogen and the RCS was purged with 150 ml/min nitrogen. Samples were run in pinholed pans supplied by Perkin-Elmer using a heating rate of 2°C/min, a modulation amplitude of 0.212°C and a period of 40 s. Temperature calibration was performed by running cyclohexane, indium and tin standards, using the same pans and underlying temperature program as used in the sample runs. The heat flow and heat capacity signals were calibrated following the procedure outlined by Royall et al. (1998).

Water sorption profiles were determined using a Model SGA-100 moisture balance (VTI). For initial comparison of the two batches, each sample was equilibrated on the balance at 0% RH at 40°C and the humidity increased in steps of 10% RH up to 80% RH, a weight equilibrium being established at each humidity step. Dynamic experiments were performed at 40°C by holding at 0% RH until weight equilibration was achieved and then ramping immediately up to 75% RH.

3. Results and discussion

The SEM image of Batch 1 is shown in Fig. 1. In both cases, the drugs were plate-like in shape but no clear differences were seen between the two samples. Fig. 2 shows the equilibrium moisture sorption profiles for the two batches, demonstrating a greater propensity for Batch 2 to sorb water than is seen for Batch 1.

Fig. 3 shows the conventional DSC profiles of Batches 1 and 2. The two batches melt at 146.4 and 145.9°C respectively (peak temperature) with heats of fusion of 66.46 and 63.81 J/g, hence no clear difference could be detected between their melting profiles. No evidence for a glass transition was observed for Batch 1, although a small (reproducible) discontinuity in the baseline could be seen at approximately 50–60°C for Batch 2. It is possible to estimate the value of T_g if the melting

point is known as the value of the former tends to be (very) approximately 0.73 times the melting point (in K) (Hancock and Zografi, 1997; Craig et al., 1999). Consequently, one would expect a T_g at approximately 33°C in this case, hence it is possible that the discontinuity represents a glass transi-

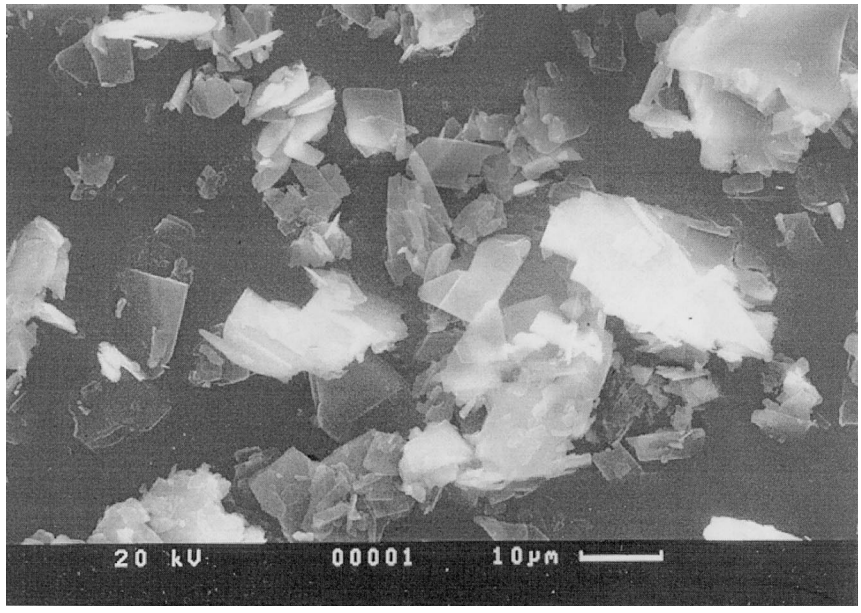

Fig. 1. SEM images of L7, Batch 1.

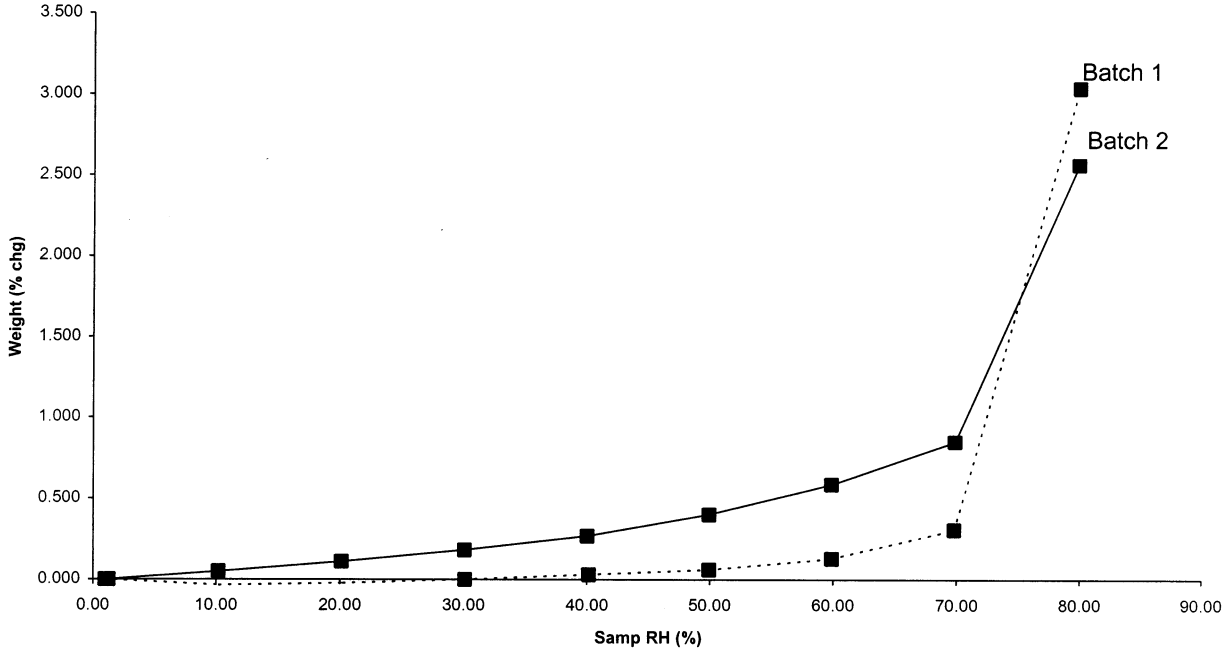

Fig. 2. Equilibrium water sorption profiles for L7, Batches 1 and 2.

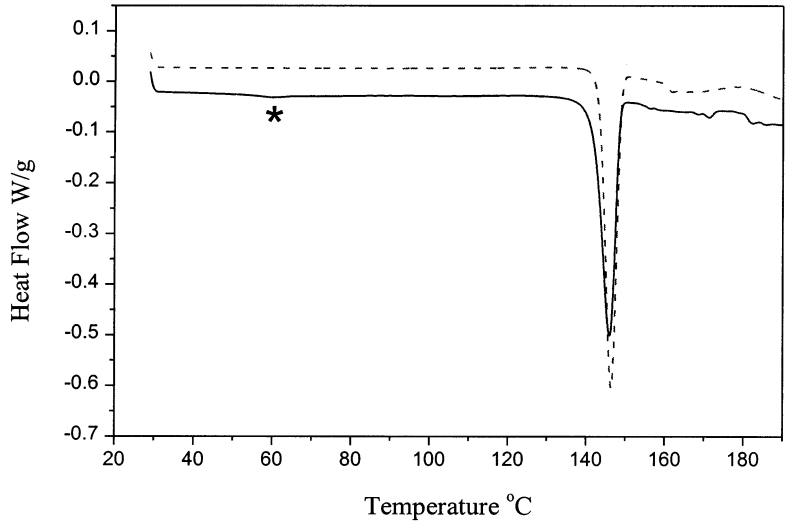

Fig. 3. Conventional DSC responses of L7 Batch 1 (dashed line) and Batch 2 (solid line). Discontinuity in baseline for Batch 2 highlighted.

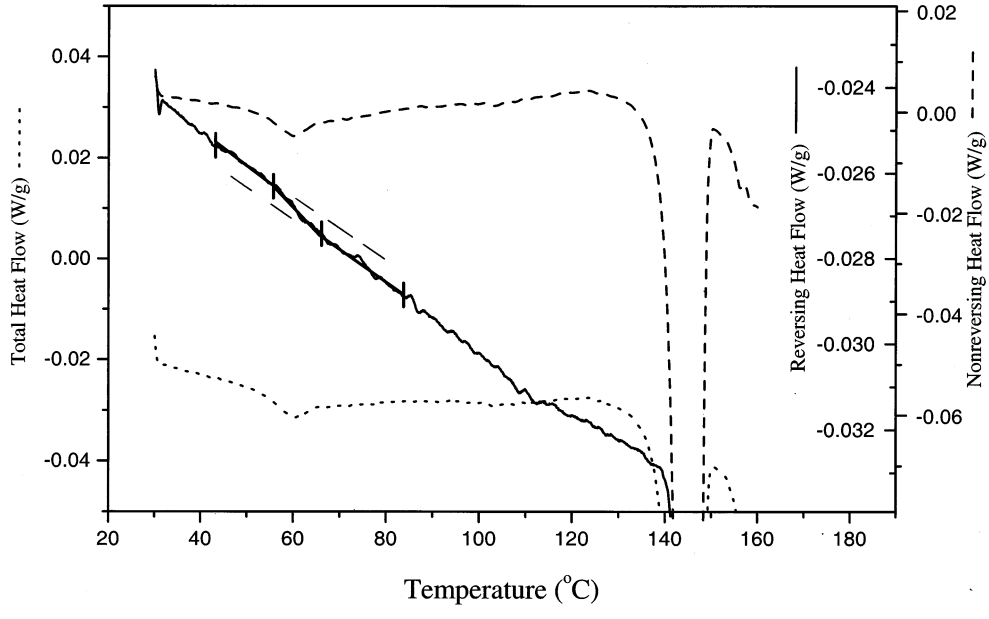

Fig. 4. MTDSC response of L7 Batch 2 showing the total, reversing and non-reversing heat flow signals.

tion. However, one would usually not rely on such a measurement as being definite evidence of the presence of amorphous material.

It was possible to see the transition in Batch 2 with considerably greater clarity using MTDSC, as shown in Fig. 4. This shows the total heat flow (effectively equivalent to the conventional response) and the reversing and non-reversing signals. Examination of these responses shows a glass transition in the reversing signal and the accompanying relaxation endotherm in the non-reversing, hence it is possible to ascribe the dis-

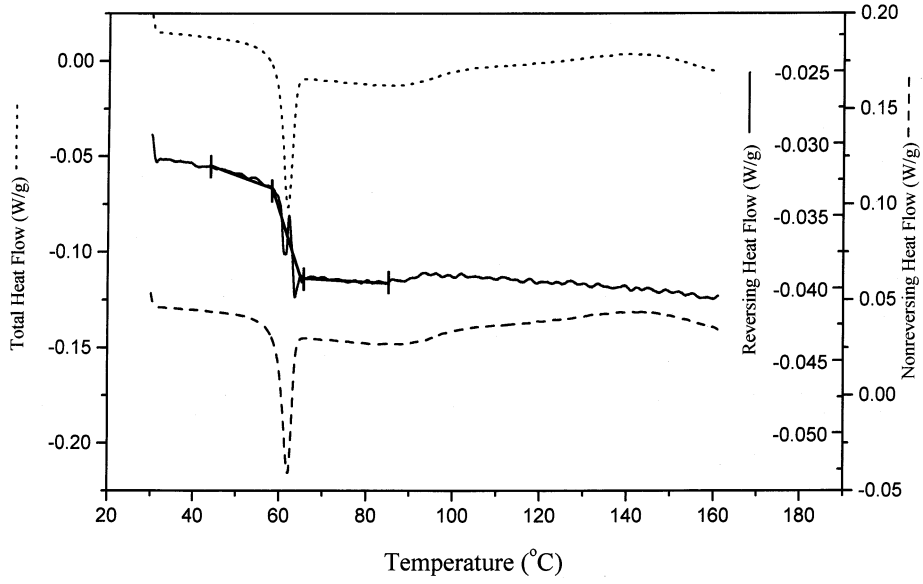

Fig. 5. MTDSC response of amorphous L7 showing the total, reversing and non-reversing heat flow signals.

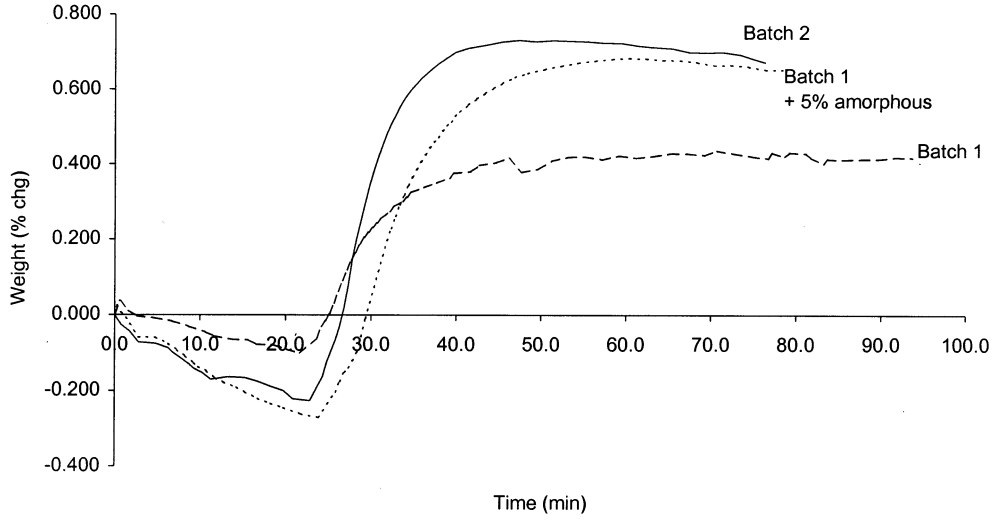

Fig. 6. Dynamic water sorption studies of Batch 1 and Batch 2 L7 and Batch 1 to which 5% amorphous drug had been added.

continuity seen in the total heat flow signal to a T_g with confidence and to ascribe a value of approximately 61°C to the transition.

In order to provide further verification, the thermal behaviour of the amorphous material was examined. This is shown in Fig. 5, whereby the T_g and relaxation endotherm are clearly separated into the reversing and non-reversing signals. The

glass transition may be easily discerned in the reversing signal and has a value of 61.5°C. While there are issues of calibration which remain to be resolved in order to quantify the amount of amorphous material present with confidence, comparison of the magnitudes of the heat capacity steps for the fully amorphous material and Batch 2 indicates that the latter has an amorphous content in the region of 5–6% w/w.

In order to study the interrelationship between amorphous content and water sorption, dynamic studies were performed on the two batches, as shown in Fig. 6. A clearly greater weight increase was seen for Batch 2 than for Batch 1, indicating that in addition to greater equilibrium moisture uptake (Fig. 2) the kinetics of the uptake process differ between the two batches (the initial decrease is due to equilibration effects). However, addition of 5% amorphous material to Batch 1 resulted in a profile which resembled that of Batch 2. Consequently, the data do support both the suggestion that the differences between the two batches are due to differences in the degree of amorphous material and the estimated level of such material.

Overall, therefore, the study indicates that MTDSC may be used to detect the presence of amorphous material in nominally crystalline materials. There is clearly potential for quantification of the amorphous content using this approach. However, preliminary studies indicated that more work is required in order to provide a reliable calibration for this approach; these studies are currently ongoing. A further interesting area of research is afforded by the possibility of being able to directly measure the glass transition of the amorphous material. One aspect of the field that has received little attention is the question of the state in which the amorphous material resides on the surface of the crystalline material. It is, for example, well recognized within the polymer science field that glassy materials may behave differently in a semi-crystalline system compared to the wholly amorphous one (Wunderlich, 1990) although to date no equivalent studies have been performed on pharmaceutical systems. The possibility of measuring T_g greatly facilitates such studies. Furthermore, the measurement of the glass transition allows prediction of the behaviour of the material, particularly in terms of plasticization effects in the presence of water. As the T_g of this material is close to room or normal storage temperatures, it is logical to suggest that this material may recrystallise on storage, particularly in a plasticized state. Given the inferior stability of Batch 2 at high humidities compared to Batch 1, the study does lend further support the arguments of Ahlneck and Zografi (1990) that regions of amorphous material are linked to moisture uptake and chemical instability.

4. Conclusions

The study has indicated that the presence of small amounts of amorphous material in a nominally crystalline drug may be identified using MTDSC via measurement of the glass transition. This opens up a range of possibilities for the prediction of the behaviour of the amorphous fraction which has not been previously explored in any depth due to the difficulties associated with measuring such small heat capacity changes. The possibility also exists of using the method to quantify the level of amorphous material present via measurement of the heat capacity change, although more work is required in order to effectively calibrate the system for such measurements.

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