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Characterisation of the glass transition of HPMC using modulated temperature differential scanning calorimetry

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Abstract

The glass transitional behaviour of HPMC powder and film samples has been studied using modulated temperature differential scanning calorimetry (MTDSC) in order to explore the ability of the technique to detect transitions which involve small changes in heat capacity. HPMC E4M Prem samples were studied in both powder and film form using a TA Instruments MDSC 2920 using a range of pans, modulation amplitudes and underlying heating rates. Moisture contents were measured using a TA Instruments TGA 2950. Studies on HPMC powder demonstrated the greater clarity with which the glass transition, seen at approximately 162°C, may be seen using MTDSC compared to conventional DSC. The practical difficulties associated with casting suitable HPMC films are discussed, with similar results for T_g being found for hermetically sealed pans and pin-holed pans. Increasing the modulation amplitude from 0.212 to 0.5°C improved the signal to noise ratio and increased the magnitude of the measured T_g. Increasing the underlying heating rate from 2 to 5°C/min also improved the signal. The study has outlined several features which need to be considered in association with the measurement of HPMC glass transitions using MTDSC; these include the method of sample preparation, the choice of pans, the modulation amplitude and the underlying heating rate.

Keywords: Differential scanning calorimetry; Film; Glass; Hydroxypropyl methylcellulose; Modulated differential scanning calorimetry

1. Introduction

Modulated temperature differential scanning calorimetry (MTDSC) is a thermoanalytical technique which involves the application of a sinusoidal heating or cooling signal to a sample (in the case of the TA Instruments model) and the subsequent measurement of the reversing and non-reversing components of the heat flow response (Reading, 1983; Reading et al., 1993; Coleman and Craig, 1996; Hill et al., 1998). The technique

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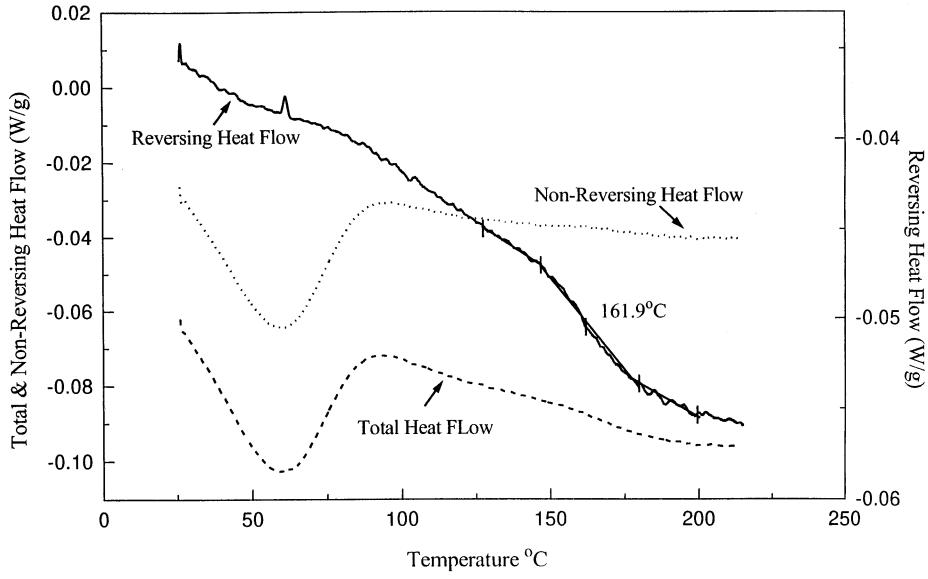

Fig. 1. MTDSC response of HPMC powder, showing separation of the response into reversing and non-reversing signals. Underlying scan rate 2°C/min, modulation amplitude 0.212°C, modulation period 40 s, pin-holed pans.

has received considerable attention in the polymer science field, particularly due to the possibility of seeing glass transitions in the reversing signal in isolation from overlapping thermal events such as endothermic relaxation peaks which are seen in the non-reversing response. On this basis, there is a growing body of literature suggesting the applicability of the technique to the study of glassy pharmaceuticals such as spray dried excipients (Hill et al., 1998) and amorphous drugs (Royall et al., 1998). However, a perceived advantage which has received comparitively little attention (and none to date within the pharmaceutical sciences) is the possibility of measuring transitions with a low value of ΔCp, thus producing a small inflexion in heat flow response which may be difficult to distinguish from baseline noise. When using MTDSC, the T_g is measured via analysis of the amplitude of the heat flow oscillation rather than simply the shift in the baseline, hence the technique should demonstrate greater sensitivity than conventional DSC to such events.

In this study, we investigate the use of the technique for the measurement of the glass transition of hydroxypropyl methylcellulose (HPMC). Despite the widespread applicability of this polymer, surprisingly little information is available regarding the glassy behaviour (examples of published work including that of Rowe, 1980; Hogan, 1989; Kararli et al., 1990; Doelker, 1993; Hancock and Zografi, 1994; Joshi and Wilson, 1993; Picker and Mielck, 1998). Given the well established association between the T_g and properties such as mechanical strength and stability, it is clearly desirable to develop means by which this value may be quantified. Due to the novelty of the use of the technique in this respect, particular emphasis will be placed on the sample preparation and experimental considerations associated with the measurements.

2. Methodology

2.1. Hydroxypropyl methylcellulose

HPMC (E4M Prem) was supplied by the Dow

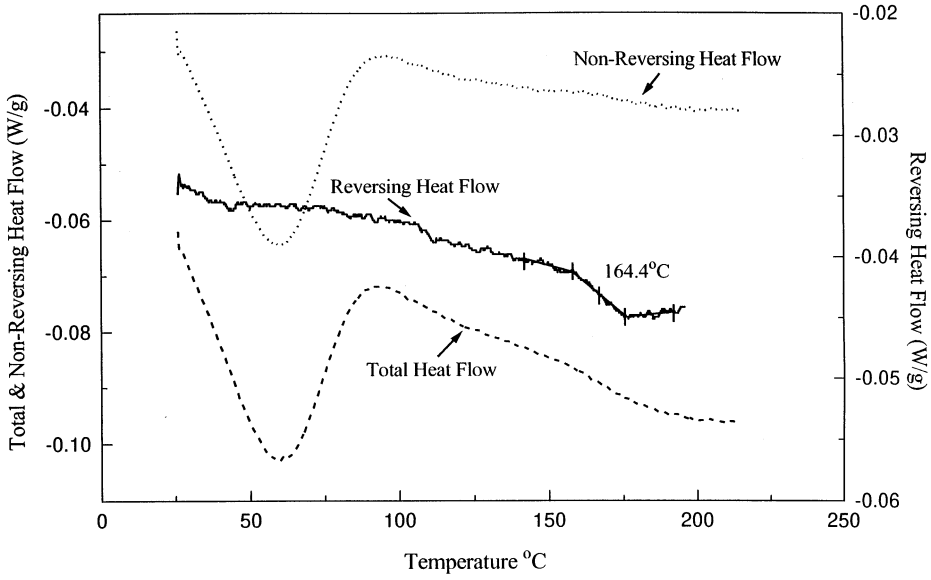

Fig. 2. MTDSC response of HPMC films in hermetic pans. Underlying scan rate 2°C/min, modulation amplitude 0.212°C, modulation period 40 s, hermetic pans.

Chemical Company. For the HPMC films, solutions were prepared by addition of weighed powder in small aliquots to boiling distilled water, stirring vigorously using a Heidolph mixer and making up to 2% w/w with water and remixing until homogeneous.

2.2. MTDSC studies

Modulated temperature differential scanning calorimetry studies were performed over a temperature range of 30–225°C using a DSC 2920 (TA Instruments, New Castle, DE, USA) with a refrigerated cooling accessory (RCS) and modulated capability. The DSC cell was purged with 30 cm^3/min dry nitrogen and the RCS was purged with 150 cm^3/min nitrogen or helium as required. The DSC cell was calibrated for baseline using empty pans of matched weight and for temperature using *n*-octadecane (28.24°C) and indium (156.61°C). Enthalpy and heat capacity calibration were performed using alumina (Al_2O_3) post analysis using a spread sheet. Experimental conditions were as stated in the Section 3. The pan types used were aluminium 20 μl hermetic or 50 μl pin-holed hermetic as stated (Perkin Elmer). All experiments were repeated at least twice. For HPMC powder studies, the sample size used was approximately 5 mg, while for the film studies the size was approximately 1–2 mg unless otherwise stated.

2.3. Thermogravimetric analysis

Thermogravimetric analyses were made using a TGA 2950 (TA instruments, New Castle, DE, USA) using a dry nitrogen purge. Indium was used to calibrate the temperature reading and the instrument was weight calibrated according to the manufacturer's instructions.

3. Results and discussion

3.1. HPMC powder

The response of the HPMC powder, run using a scanning speed of 2°C/min, an amplitude of

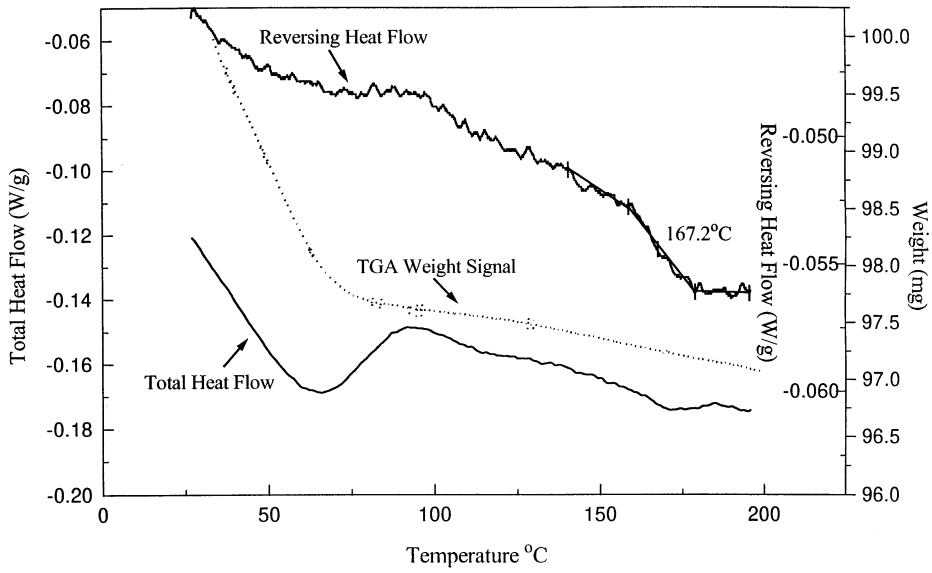

Fig. 3. MTDSC response for HPMC run in pin-hole pans with the corresponding TGA profile overlaid. Underlying scan rate 2°C/min, modulation amplitude 0.212°C, modulation period 40 s. TGA heating rate 2°C/min.

± 0.212°C, a period of 40 s and a mass of approximately 6 mg, in pin-holed pans is shown in Fig. 1. These parameters were chosen in order to maintain 'heat only' conditions during a run (i.e. the temperature would be continually increasing irrespective of the fluctuations in heating rate). The total heat flow shows a broad low temperature endotherm and a small discontinuity in the baseline at approximately 160°C. It was not possible to discern a glass transition from the baseline with confidence, even using magnified scales, due to the signal to noise ratio of the heat flow data. As the glass transition is essentially a change in sample heat capacity, one sees this response in the reversing signal but not the non-reversing component. This may be understood with reference to the basic heat flow equation associated with MTDSC

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

where dQ/dT is the total heat flow (J/s or W), C_p is the heat capacity (J/K) and dT/dt is the heating rate. The $C_p\, dT/dt$ term is always present, termed the 'reversing' heat flow component and is dependent on the rate of change of temperature and the heat capacity. The 'non-reversing' heat flow component, $f(t,T)$, contains the heat flow contribution from kinetically controlled events that are dependent on both temperature and time. The $C_p\, dT/dt$ component is calculated from the response to the oscillation via

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

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. The non-reversing signal is calculated as the difference between the total heat flow response and the reversing signal which is obtained from Eq. (2). It is important to note that ΔC_p is calculated from the amplitude of the oscillation rather than an inflexion in the baseline. Consequently, one may reasonably expect the technique to demonstrate an en-

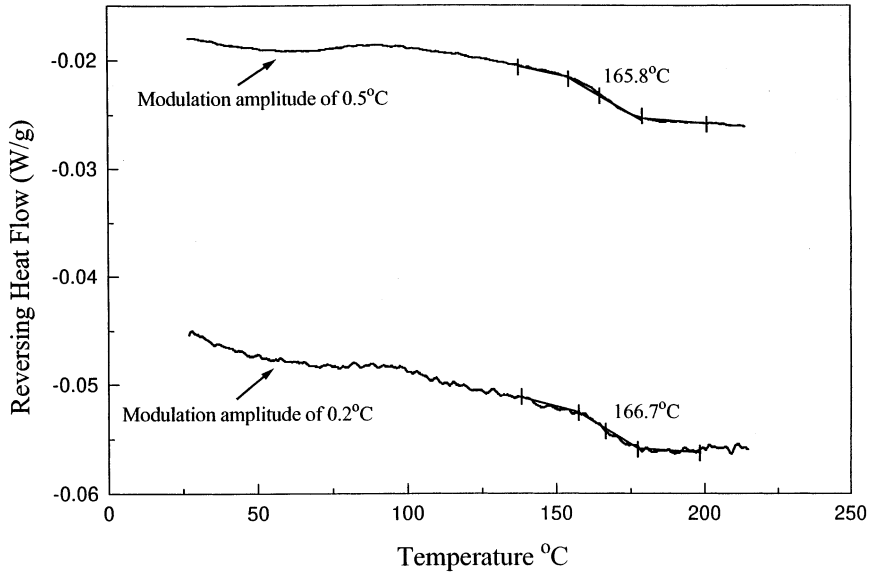

Fig. 4. The effect of changing the modulation amplitude on the reversing MTDSC response of HPMC films. Underlying scan rate 2°C/min, modulation amplitude 0.212 and 0.5°C as stated, modulation period 40 s, pin-holed pans.

hancement in sensitivity due to the limits of T_g measurement being less dependent on the baseline quality. It should be noted that in this and subsequent deconvolutions we have used the assumption discussed by Reading et al. (1992), Lacey et al. (1997) that the response of the rate of the kinetic response to the temperature is linear over the modulation interval, hence the phase lag between the modulated heat flow and the derivative modulated temperature is negligible.

Inspection of Fig. 1 shows that the glass transition can be clearly seen in the reversing heat flow signal. The midpoint was measured as 161.9°C which is in reasonable agreement with previously reported values. TGA studies indicated that the endotherm seen at lower temperatures corresponded to a weight loss process which it is reasonable to assume represented loss of sorbed water ($0.98 \pm 0.1\%$).

3.2. HPMC films-choice of pans and film preparation

Other than the difficulty in seeing the small transition associated with HPMC, the measurement of this material in the powdered form does not present any marked difficulties in terms of sample preparation. However, the measurement of the T_g of HPMC films using DSC is a non-trivial task. Extensive preliminary studies identified the following difficulties; (a) it is necessary to have a relatively large sample size in order to measure the small T_g (b) the sample must be in intimate contact with the pan in order to optimise the signal to noise ratio (c) the choice of pan must be such that the water is either driven off altogether or maintained at a controlled level within the sample.

Hermetic pans were initially used with the intention of retaining the moisture associated with the films, thereby allowing the relationship between the moisture content of the sample and the T_g value to be ascertained in a similar manner to that described in studies by Hancock and Zografi (1994) and Picker and Mielck (1998). Theoretically, one could simply cast films, cut them and place them in the pans. However, there are two difficulties associated with this.

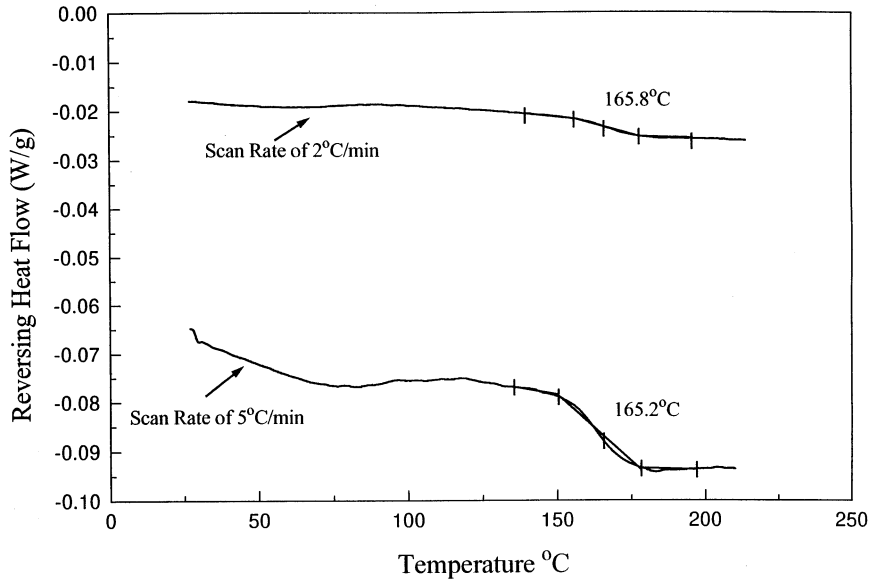

Fig. 5. The effect of changing the underlying scanning rate on the reversing MTDSC response of HPMC films. Underlying scan rate 2 and 5°C/min as stated, modulation amplitude 0.5°C, modulation period 40 s, pin-holed pans.

Firstly, the shape of the hermetic pans is such that the flat base area is comparatively small, hence limiting the sample mass that could be placed in the pan. Given the previous observation that the glass transition of HPMC is small, it is clearly desirable to use a reasonably large sample. A related disadvantage of using cast films is that it is essential to have good contact between the film and the bottom of the pan in order to optimise the signal to noise ratio of the response. It was therefore decided to cast the films within the pan itself. However, this again carries associated problems. In order to cast a film of suitable thickness, it was necessary to add a reasonable volume of the 2% solution; this quantity was limited by the volume of the pans. This difficulty was overcome by preparing multilayer films, whereby three consecutive films were prepared, each using approximately 20 mg of solution. The film would be dried by placing over silica gel and holding at 30°C overnight (these drying conditions were found to result in avoidance of wrinkling and other film distortion effects), giving a final mass of approximately 1–2 mg.

Fig. 2 shows the response of the films prepared in hermetic pans, using the conditions outlined above. The profiles again show the T_g in the reversing signal, although the signal was much noisier than for the powder, almost certainly due to the smaller sample mass for the film sample. However, it is interesting to note that the broad low temperature endotherm was also observed. TGA studies using open pans again indicated that this may correspond to water evaporation. However, this was in itself surprising, as one would not expect to see such effects in hermetic pans. Reweighing the pans after measurement indicated that the effect was not due to evaporation out of the capsule. We ascribe this effect to water evaporation into the headspace of the pan, given the small size of the dried film in relation to the total capsule volume. It was decided, however, that the use of hermetic pans was suboptimal for three reasons. Firstly, if water was indeed leaving the films during heating, then the main advantage of using hermetic pans was being lost, as one would no longer know what the water content at the T_g would be. Secondly, it was difficult to build up a film of suitable thickness due to the small flat area

of the DSC pans. Finally, there was some concern regarding the integrity of the seal at the temperatures associated with the T_g; depending on the water content, the pans should remain intact up to approximately 200°C. However, it was found that in many cases the seal appeared to leak below this temperature, leading to artefacts.

The films were then run in hermetic pin-hole pans; these pans allow moisture loss under controlled and reproducible conditions due to the presence of a small pin-hole drilled in the lid. The pans had the added advantage of having a large volume and flat surface area, hence it was possible to increase the sample weight up to 2–3 mg. The corresponding MTDSC responses are shown in Fig. 3, with the TGA response overlaid. The value of T_g was similar to that seen using hermetic pans, which suggests that the films had lost water in the hermetic pans before reaching T_g. The pin-hole pans were used for all subsequent experiments.

3.3. HPMC films-choice of experimental parameters

One means by which glass transitions may be seen with greater clarity is to increase the amplitude of the modulation, as inspection of Eq. (2) indicates that while the amplitude ratios will remain constant within the region of response linearity, the increased size of the signal may be expected to enhance differentiation from the noise of the baseline. Inspection of Fig. 4 shows this to be the case; inspection of the raw modulated heat flow data indicated that the sample was following the sinusoidal signal at both amplitudes (data not shown). The effect of the underlying scanning speed was also investigated, with higher scanning speeds generally tending to lead to greater sensitivity but lower resolution. The improvement in sensitivity may be predicted by inspection of Eq. (1), as the reversing term $C_p\,dT/dt$ will be larger at higher scan rate values. The approach of using higher scan rates is clearly of use for identifying small glass transitions, although it should be noted that such an improvement in sensitivity does not necessarily imply an improvement in the signal to noise ratio of the complex heat capacity. Moreover, when performing MTDSC experiments the maximum usable underlying scanning speeds tend to be limited by the necessity of having at least four modulations through the thermal event under examination. Fig. 5 shows the effects of changing the underlying heating rate from 2 to 5°C/min. The glass transition is seen with greater clarity at the higher scan rate due to the reversing heat flow component being the product of the complex heat capacity and the underlying heating rate. However, given the restrictions outlined above it was not considered prudent to increase the underlying heating rate any further.

4. Conclusions

This investigation has sought to meet the dual objectives of developing MTDSC within the pharmaceutical sciences, particularly in terms of measuring small transitions, and also to contribute to the knowledge base regarding the characterisation of HPMC. It is arguable that one of the principal restrictions regarding the use of the technique lies in the extended choice of experimental parameters. The use of approaches such as increasing the amplitude or altering the underlying scanning speed may be beneficial, although these approaches may also lead to artefact generation if used inappropriately. At present, there is a paucity of information in this respect, particularly for pharmaceutical systems. The study has demonstrated that MTDSC may be highly useful as a means of visualising small transitions, providing that suitable measuring conditions are chosen.

The study has also explored the practicalities of measuring the T_g of HPMC, particularly in film form. Factors such as film preparation method and the choice of sample pans have been investigated, indicating that, for example, the use of hermetic pans does not guarantee that the effective water content of the sample at T_g may not be the same as the total water content within the pan. An understanding of such factors underpins the use of glass transition measurements for further applications such as the study of the effects of different plasticisers on the mechanical properties of film coats and the effects of chain substitution on the molecular mobility of this polymer.

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References

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

Doelker, E., 1993. Cellulose derivatives. Adv. Polym. Sci. 107, 199–265.

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

Hill, V.L., Craig, D.Q.M., Feely, L.C., 1998. Characterisation of spray dried lactose using modulated differential scanning calorimetry. Int. J. Pharm. 161, 95–107.

Hogan, J.E., 1989. Hydroxypropyl methylcellulose sustained release technology. Drug Dev. Ind. Pharm. 15, 975–999.

Joshi, H.N., Wilson, T.D., 1993. Calorimetric studies of dissolution of hydroxypropyl methylcellulose E5 (HPMC E5) in water. J. Pharm. Sci. 82, 1033–1038.

Kararli, T.T., Hurlbut, J.B., Needham, T.E., 1990. Glass–rubber transitions of cellulose polymers by dynamic mechanical analysis. J. Pharm. Sci. 79, 845–847.

Lacey, A.A., Nikolopoulos, C., Reading, M., 1997. A mathematical model for modulated differential scanning calorimetry. J. Therm. Anal. 50, 279–333.

Picker, K.M., Mielck, J.B., 1998. Effect of relative humidity during tabletting on matrix formation of hydrocolloids: densification behaviour of cellulose ethers. Pharm. Dev. Tech. 3, 1–11.

Reading, M., Elliott, D., Hill, V.L., 1992. Some aspects of the theory and practice of modulated differential scanning calorimetry. In: Proceedings of the 21st NATAS Conference, pp. 145–150.

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

Reading, M., 1983. Modulated differential scanning calorimetry—a new way forward in materials characterisation. Trends Polym. Sci. 1, 248–253.

Rowe, R.C., 1980. The molecular weight and molecular weight distribution of hydroxymethyl cellulose used in the film, coating of tablets. J. Pharm. Pharmacol. 32, 116–119.

Royall, P.G., Craig, D.Q.M., Doherty, C., 1998. Characterisation of the glass transition of an amorphous drug using modulated DSC. Pharm. Res. 15, 1117–1121.