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THE DEVELOPMENT OF GAS-FLOW MODULATION FOR HIGH-FREQUENCY MTDSC MEASUREMENTS

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Abstract

The purpose of this study was to investigate the feasibility of modulating the temperature programme of a conventional DSC by use of an alternating gas-flow system. Modulated temperature differential scanning calorimetry (MTDSC) is an important thermal analysis technique but suffers from a limited applicable frequency range due to the mass of the sample and DSC cell leading to the impingement of thermal conductivity effects. We suggest that the frequency limit can be increased by replacing the cell as the source of temperature modulation with an external gaseous source, directed towards the sample and reference pans. In this evaluation, an alternating gas-flow was passed through a line to a forced gas-flow accessory (FGFA). The FGFA consisted of two matched cylinders containing chambers that allowed pre-temperature-equilibration of the stream of gas before it was passed over the sample and reference pans. The development of this device revealed the essential practical requirements of gas-flow modulation for high-frequency temperature modulation. These include the following: an appropriately sealed tunable gas supply to both sample and reference pans, an effective method for high-frequency cycling of the gas-flow rate, a small aperture to deliver the flowing gas directly over the pan and a temperature equilibration chamber. The results from samples of quenched PET and amorphous Saquinavir indicate that gas-flow modulation is indeed feasible, with the FGFA able to raise the attainable temperature modulation frequency by an order of magnitude compared to conventional MTDSC.

Keywords: forced gas-flow accessory, gas-flow modulation, high-frequency temperature modulation, MTDSC, PET and Saquinavir

Introduction

The development of modulated temperature differential scanning calorimetry (MTDSC) [1–3] has generated considerable interest not only in the area of thermal analysis [4] but also in a range of applied fields such as polymer [5, 6] and pharmaceutical sciences [7–9]. MTDSC is a modification of differential scanning calorimetry whereby a temperature oscillation is superimposed on the conventional linear heating programme. This perturbation allows both the response to the underlying signal and the response to the modulation to be obtained. Separation of the total heat

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flow into two signals may facilitate the identification and quantification of hidden transitions and the clearer visualization of non-overlapping events. In addition, the modulation of the temperature programme improves the sensitivity of the DSC with no loss of resolution, hence very small transitions may be seen with minimal baseline noise [10]. A number of texts are available which describe the principles of the technique [1–3] and the method is now well established as a thermoanalytical tool.

In conjunction with the identified advantages of the approach, there are also a number of inherent difficulties associated with its use. In particular, in order to calculate the total heat flow signal accurately and, therefore, the non-reversing heat flow signal, at least four modulation cycles are required through any given transition [11]. The total heat flow is determined simply by an averaging procedure that effectively removes the modulation, thus providing the heat flow signal that would have been obtained had the modulation not been applied. If there are a low number of cycles through a particular transition, then the calculated average will not be representative of the underlying process and the total heat flow signal is likely to contain artifacts. The number of modulations sufficient to allow a reliable de-convolution will depend on the modulation period, the underlying scan rate, and the nature of the particular transition. The manufacturers suggest that a minimum of four modulation cycles through a transition is required for the successful operation of the deconvolution procedure [11], but, in our view, six modulation cycles yields a safer margin, if practically feasible [12]. Consequently, one would wish to use a high-frequency modulation in order to fulfill this requirement. However, the large thermal mass of conventional DSC furnaces imposes a limit to the frequency and amplitude of the temperature modulation. This limitation usually necessitates the use of slower heating rates for MTDSC experiments compared to conventional DSC runs. If it were possible to increase the range of measurable frequencies, then the scientific and commercial implications would be considerable. These include faster underlying scan rates and the measurement of narrow transitions by MTDSC. Not only would this increase throughput time considerably, but it would also facilitate analysis of narrow transitions and increase the range of experimental conditions under which the sample may be measured in steady-state, meaning in this context that the sample is able to follow the temperature modulation. In addition, a greater measurable frequency range would permit frequency sweep experiments, thus introducing the possibility of a new form of frequency domain analysis. When one considers the wide applicability of oscillatory rheology and dielectric analysis, the possibility of being able to perform parallel frequency sweep experiments with an oscillating thermal signal becomes extremely interesting. Indeed, this was the concept behind the development of A.C. calorimetry to which MTDSC bears some resemblance.

This communication describes the development of a gas modulation system for the purpose of performing high-frequency MTDSC measurements. The approach described in this paper involves the use of an external attachment to the conventional DSC equipment which passes an intermittent gas-flow onto the sample and reference pans. The fundamental difference between this approach and standard MTDSC is that

the underlying heating programme is supplied by a conventional DSC cell, while the temperature modulation is brought about by modulating the gas-flow.

Methods and materials

Basic design of the gas-flow system

The basic instrumentation used is described in Fig. 1, which shows how the gas-flow accessory fits into a standard TA Instruments 2920 MDSC. The gas was supplied via a cylinder of oxygen-free nitrogen using a constant 0.3 bar pressure for all experiments. Tygon® tubing (O.D. 9 mm and I.D. 6 mm) formed the gas lines that connected the system. From the cylinder, nitrogen was fed into a Brooks 'Sho-Rate 150' Rotameter, a flowmeter (FM) that uses a ball float to indicate the flow rate, combined with an adjustable inlet valve to control the rate of gas-flow. The flow rate used throughout the experiment was between 0 and 150 cm^3 min^{-1}, as stated in the text. The nitrogen flow was passed through a TA Instruments Gas Switching Accessory (GSA) supplied by TA Instruments. The unit essentially consists of a solenoid-operated valve that connects an output alternately between two input gas supplies. In the present case, only one of the gas-inlets is attached to the nitrogen line, so the output switches between on and off flow. Automatic regulation of the switching time period was operated through a TA Instruments Hi-Res TGA 2950. After passing through the GSA, the nitrogen flow is passed into another Rotameter flowmeter with the inlet valve fully open, which therefore measures the flow rate of the emitted gas. For most experiments the flow rates were between 100 and 150 cm^3 min^{-1}.

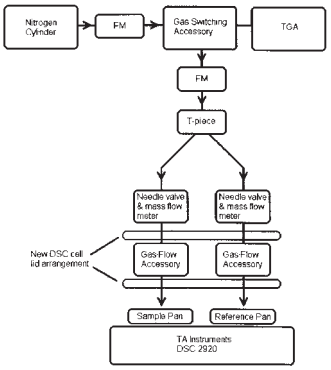

Fig. 1 Flow diagram of the nitrogen flow line

The nitrogen line from the output of the second Rotameter was split in two with a 'T' piece. From the 'T' piece onwards, the nitrogen line consisted of narrow-bore, gas-tight tubing (O.D. 3.2 mm and I.D. 1.6 mm). The two outlets from the 'T' piece were connected to needle valves and then mass-flow meters, both being supplied by Krohne LTD as one unit (a Hitec Thermal Mass Flowmeter and Needle Valve, Model F111C-HA-11V). All the connections from the 'T' piece onwards were made with

gas-tight nut and ferrule adapters, thus producing an air-tight gas line. This meant that the flow rates measured by the meters corresponded to the actual flow entering the 'cylinders' over the sample and reference pans in the sample holder, termed the forced gas-flow accessory (FGFA), which is described in more detail below. The final connection to the FGFA was made via two 105 mm lengths of the HPLC tubing (O.D. 3.2 mm and I.D. 2.0 mm) which were connected to the inlets of the gas-flow accessory via an aluminium block. The block was machined in such a way that the HPLC and inlet tubes met at right angles, with the ends of the tubes cut at 45°. The tubes were cemented in to prevent any escape of nitrogen gas-flow. When screwed in place on the new lid, the 12 mm high aluminium block covered one-third of the lid's area, with its curved side following the lid's circumference, almost touching the inner wall of the DSC cell.

The forced gas-flow accessory

Figure 2a shows a schematic illustration for the final design of the forced gas-flow accessory. The FGFA was designed so as to allow a stream of gas to pass directly onto the sample and reference pans. This modification consisted of a new aluminium lid attachment, which replaced the inner silver lid of the conventional TA cell design. The new lid design consisted of a base plate with two 7 mm holes positioned directly over the sample and reference pans. Two machined cylinders were fitted exactly into these holes, each having a lip to prevent them falling through and constructed so that when in place the ends would be 0.5 mm above the surface of the pans. Two holes in the cylinders allowed gas to pass over the DSC pan and then to escape from the cell. Early versions of the design simply passed the gas down a fine-bore tube in the cylinders. The more refined final design, shown in Fig. 2a, allows the gas to enter a chamber within the cell before it leaves through an aperture at the bottom. As can be seen by the technical drawing of the cylinder (Fig. 2b), the cavity is created by placing a specifically machined insert into a hollow cup. Running through the center of this

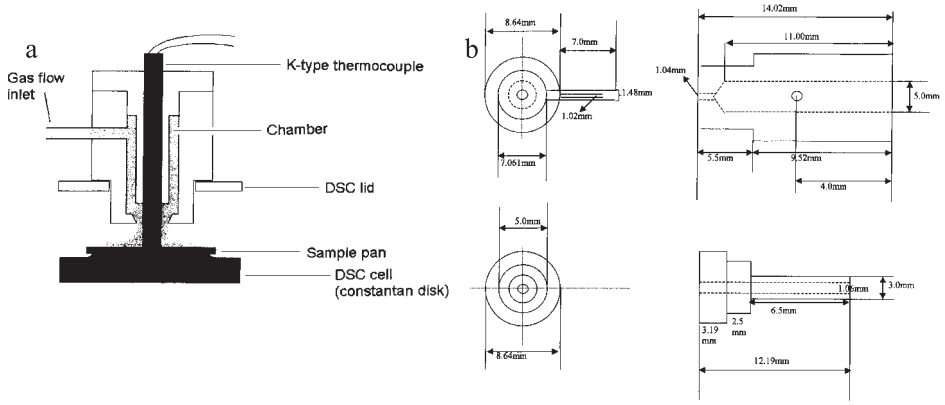

Fig. 2 a – Sketch of the mark III design for the gas-flow accessory; b – Technical drawing of the mark III design

set-up is a narrow hole which will hold a thermocouple in a snug fit. The hole in the bottom of the cup has a larger diameter than the thermocouple to allow gas to escape directly onto the DSC pan. The K-type thermocouples were 1 mm in diameter and 45 mm long, and were held in the design so that the tip just rested on the top of the DSC pan. Gas-flow was delivered via a side inlet tube, shown in both Figs 2a and 2b.

A specialized amplifier system for the thermocouples was built. This amplifier could either increase the output from the sample and reference thermocouples, displaying them as a temperature reading, on a digital readout, or amplify and display the differential signal between the two thermocouples. For most experiments, the differential signal was recorded with respect to time on a paper-chart recorder. In addition to the new forced gas-flow accessory, the final design set-up had a specially constructed outer lid. This was identical to the conventional lid supplied with the instrument, but had the appropriate holes to allow the nitrogen flow lines and thermocouples access to the accessory. The TA Instruments 2920 was operated with a TA Instruments refrigeration cooling system (RSC) unit.

Materials

Samples of fully quenched PET were used as the test material, because this is a standard in the fields of DSC and MTDSC, thus allowing the results to be readily comparable to the literature. PET was supplied by Goodfellows. The amorphous form of the protease inhibitor, Saquinavir, was also later run in order to study a model amorphous drug that could demonstrate the pharmaceutical application of the new development in MTDSC. Amorphous Saquinavir, (molecular mass 671), was obtained from Roche Pharmaceuticals (Welwyn Garden City, UK) and used as received after passing though a 125 micron sieve.

Results and discussion

Prototype development

In development of the first prototype accessory, the required parameters for the instrument became apparent. For the early designs, which simply passed nitrogen over the DSC sample pans through a narrow-bore tube, all the transitions of quenched PET were observed with little baseline drift. However, this was accompanied by poor signal control because the amplitude increased dramatically at high underlying temperatures. This was identified as being due to the cooling effect of the gas being greater as the underlying temperature of the DSC cell rose. Therefore, some pre-warming of the gas to equilibrate it close to the temperature of the DSC cell was required. This was achieved very simply by including a small chamber in the design that exposed the nitrogen briefly to the heated environment of the cell. The chamber is shown in Fig. 2a. The very brief equilibration time was sufficient to remove the dependence of the modulation amplitude upon the underlying temperature. All the later designs incorporated this modification.

The problem of the symmetry of the design was highlighted by an intermediate design. In this, a prototype only, one of the machined 'cylinders' was present, situated over the sample pan. The reference hole in the new lid was covered simply by a solid aluminium cylinder, which only blocked the hole and did not pass into the DSC cell. The non-symmetrical arrangement produced a very pronounced drift in the underlying baseline. This drift was removed when two identical 'cylinders' were used over the sample and reference pans in the later designs. Further optimization was achieved by adding the new second lid, and incorporating the needle valve and mass-flow meter arrangement in the gas-flow line. The secondary lid prevented thermal loss from the cell and produced good results with a stable underlying baseline, showing very clearly all the transitions for PET. The lid arrangements are shown in the flow diagram of the gas-flow line in Fig. 1. Addition of the needle valves allowed fine-tuning of the flow rates. Both were adjusted to produce exactly the same mass-flow rates measured by the Krohne meters, thus the amounts of gas passing over the sample pan and reference pan can be assumed to be equal.

Assessment of the final design

Figure 3 is a typical example of the results obtained from the final design set-up. The sample was fully quenched PET, which was subjected to an underlying heating rate of 5°C min^{-1}. Gas switching consisted of a 6 s nitrogen flow 'on' period, followed by a 6 s nitrogen flow 'off' period. Repeating this switching routine continuously gave a 12 s heat flow modulation period, that was constant throughout the experiment, from a starting temperature of 25 to the end point of 300°C. This approach could be expected to result in the generation of a square wave, although in practice one observes an approximate sine wave due to damping within the plumbing. The cycling flow rates measured by the Rotameter positioned directly before the T-piece had a maximum of 90 and a minimum of 0 cm^3 min^{-1}. The shape of the heat flow modulation was close to sigmoidal. Figure 3 clearly shows all of the transitions for PET, (the glass transition, recrystallization and melting), with very little baseline drift apart from the

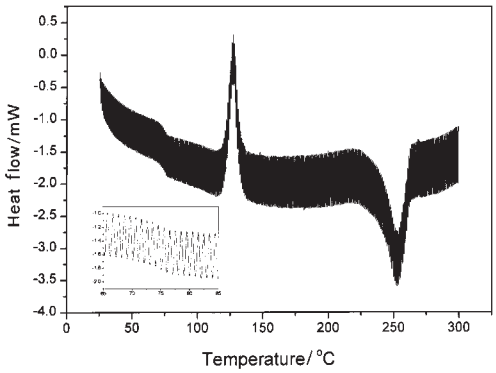

Fig. 3 Response with PET, a 5°C min^{-1} underlying heating rate and a 6 s on/off switching cycle producing a 12 s modulation period

initial swing at the beginning of the heating cycle, typical of most DSC experiments, due to heat capacity effects of the DSC cell. There is a significant change in the heat flow amplitude through the various transitions, implying that the sample is actually responding to the temperature modulation. For example, through the glass transition, the heat flow amplitude increases by 5±0.5%. Therefore, there will be a detectable difference in the heat capacity signal through the glass transition, because the 'complex' heat capacity is determined from the ratio of the heat flow and heating rate amplitudes. The increase in the heat flow amplitude determined here compares to an increase of 30±0.5% through the glass transition of PET measured with conventional MTDSC, using a similar heating rate of 5°C min^{-1}, and a 0.5°C modulation amplitude with a 20 s period. The difference in the amplitude increase through the glass transition region is to be expected, because the glass transition is a kinetic phenomenon and will have a different response to the different modulation frequencies used in the two experiments. This difference reflects the jump in the instrumental time-scales, relative to identical relaxation times for the sample, because the PET in both experiments was quenched with identical cooling rates. The increase in the amplitude step would suggest a difference in the change of heat capacity through the glass transition region for the two PET samples. This is impossible because the two samples were identical. The observation occurs because the response from the gas-flow modulation experiments was not calibrated for heat capacity, the raw modulating heat flow was the signal recorded. Once a suitable calibration procedure is developed, this discrepancy will be eliminated. The purpose of the present report is to illustrate the feasibility of gas-flow modulation for MTDSC measurements and calibration issues will be dealt with in subsequent studies.

A closer inspection of the results reveals that, for this experiment, with an underlying heating rate of 5°C min^{-1}, there were 9 modulations through the glass transition of PET, representing a significant improvement on conventional MTDSC. The lowest period possible, using conventional MTDSC with the same 5°C min^{-1} underlying heating rate, was 20 s. Experiments with lower periods would not equilibrate when using modulation temperature amplitudes comparable to the values observed with the forced gas-flow accessory and so the runs could not begin their temperature programme. For the conventional MTDSC experiments, using a modulation period of 20 s, the maximum number of modulations through the glass transition of PET was 5.

Further reduction in the modulation period was possible. Figure 4 shows an enlarged view of the glass transition of PET using an on/off gas-flow switching cycle of 3 s. This produced a constant modulation period of 6 s with a 5°C min^{-1} underlying heating rate, in addition to the other experimental parameters used in the example shown in Fig. 3. Again, there was an increase in the heat flow amplitude (9±0.5%) through the glass transition. This is slightly higher than the amplitude increase observed for the lower frequency experiments shown in Fig. 4 with a modulation period of 12 s. An increase in the raw modulated heat flow amplitudes was also observed for PET, using conventional MTDSC. In experiments with an underlying heating rate of 5°C min^{-1} and an amplitude of 0.5°C, a period 40 s gave an increase of 22±0.5% in

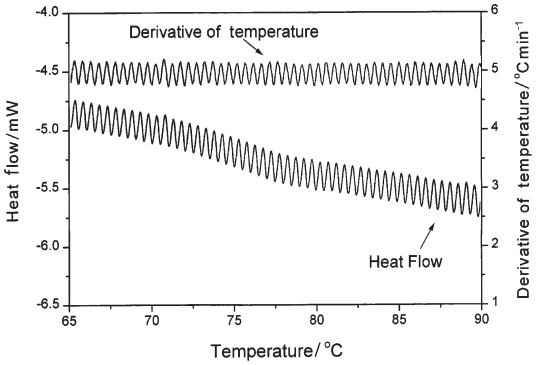

Fig. 4 Response with PET, a 5°C min^{-1} underlying heating rate and a 3 s on/off switching cycle producing a 6 s modulation period, enlarged view of the glass transition region

the amplitude through the glass transition and, when the period was reduced to 20 s, the increase grew to 30±0.5%.

The temperature derivative shown in Fig. 4 represents the temperature of the sample pan, monitored by the DSC cell's own thermocouple mounted underneath the sample pan in the constantan disc. The cyclic nature of the sample temperature derivative, which is equivalent to the instantaneous heating rate, reveals that the sample experiences a temperature modulation. Closer examination of Fig. 4 shows that the modulation of the sample temperature has a constant period of 6 s.

Figure 5 shows a typical response from the thermocouples that were placed on the surface of the sample and reference pans. Nitrogen was only delivered to the sample pan. A 5°C min^{-1} underlying heating rate with a 6 s on/off switching programme was used on a sample of fully quenched PET, producing a constant modulation period of 12 s. The nitrogen flow rate oscillated between 0 and 150 cm^3 min^{-1}. The two K-type thermocouples were in contact with the sample and reference pans, respectively, positioned so that their tips rested on the lids of the aluminium pans, measur-

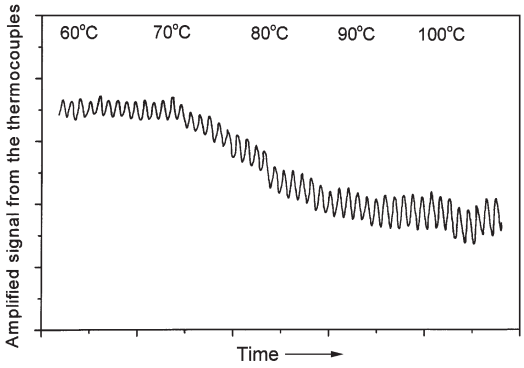

Fig. 5 Response from the thermocouples

ing the differential temperature between the sample and reference. Figure 5 reveals that the amplitude in the differential response, going through the glass transition region, increases by approximately 25%. This change is too great to be a true measure of the heat capacity change, thus asymmetries are causing a baseline shift. However, this does show that the glass transition can be easily detected at this relatively high frequency. This further confirms that the sample (rather than the cell) is responding to the temperature modulation and also implies a significant improvement in the sensitivity of the data derived from this technique.

Further experiments, not shown, indicated that the lower limit of the modulation cycle for a sample of PET is 2.4 s. At this point, the shape of the modulated heat flow is poor, with a saw-tooth waveform with a slightly erratic period. It was felt that this was not due to the concept of the design but the GSA's poor control of the switching cycle at these high frequencies. The GSA is not specifically designed to operate at high switching-frequencies and the solenoid response-time may prevent ideal control at cycles below 2.4 s. Future work on optimizing the gas-flow modulation system, perhaps with a specific flow-switching design, will hopefully lower the minimum modulation period. The initial objective of the present project was solely to explore the possibility of modulating temperature by means of a gas-flow impinging on the sample, hence the shape of any modulation cycle was to be a later concern. However, this preliminary study has shown that the simple design, shown in Figs 2a and 2b, will produce near-sinusoidal temperature modulations. Such a waveform will be due to gas-compression, lag, and flow effects within the tubing and the 'cylinders'. A problem occurs, however, at the long periods above 100 s, when the modulation takes the form of a square wave, following the simple gas-flow on/off routine. Again, a new cyclic type of switching device will have to be developed to solve this issue, possibly based on a peristaltic action.

The experiment shown in Fig. 6, using Saquinavir, had an underlying heating rate of 5°C min^{-1} with a 3 s on/off gas-switching cycle, producing a constant temperature modulation period of 6 s, (compared to a minimum of about 30 s using the existing MTDSC equipment). Initially, before the start of the run, the needle valves were adjusted to produce equal flow rates of nitrogen delivered to the sample and reference pans, respectively. Once the switching programme was operating, the flow rates to the sample and reference remained equivalent, oscillating between a maximum of 50 and a minimum of 11 cm^3 min^{-1}, as shown by the mass-flow meters. The powdered Saquinavir gave a reasonable response, although at this high frequency the shape of the modulation was slightly saw-tooth in nature. On inspection of the Lissajous figure, the Saquinavir data had reached a 'steady-state' before the glass transition. However, the shape was not as smooth as a typical response from a sinusoidal temperature programme. In fact, the ellipse had slightly square ends, indicative of a contribution from a saw-tooth waveform. Again future improvement of the gas-flow switching device is likely to improve the shape of the Lissajous figure. The peak in the heat flow signal for Saquinavir is an accompanying endothermic relaxation to the glass transition. Observation of an endothermic relaxation is extremely common with amorphous pharmaceutical materials and a similar endothermic relaxation peak has been

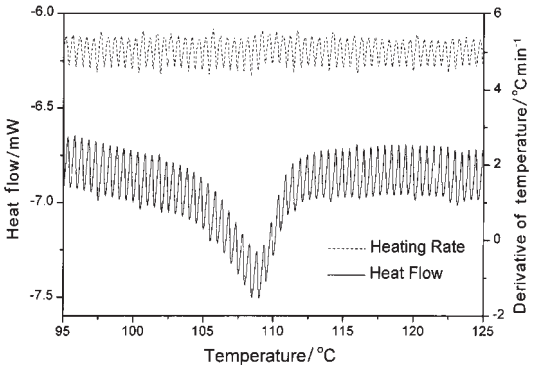

Fig. 6 Response with Saquinavir, a 5°C min^{-1} underlying heating rate and a 3 s on/off switching cycle producing a 6 s modulation period

previously reported for Saquinavir [8, 13]. This shows that observation of relaxation phenomena is possible with the FGFA. Investigations of the responses of relaxation peaks as a function of modulation frequency are limited with MTDSC at the moment, because of the narrow working range of frequencies. Thus, although the results for Saquinavir are limited and the system is far from completely optimised, the present work indicates the possibility of a novel tool for extending the frequency range of MTDSC.

Conclusions

The present study shows that the essential practical requirements for the use of gas-flow modulation for high-frequency temperature modulation, are: an appropriately sealed, tunable gas supply to both sample and reference pans (good results can sometimes be achieved by supplying the gas-flow only to the sample pan); an effective method for high-frequency cycling of the gas-flow rate; a small aperture which delivers the gas supply directly over the pan; a temperature equilibration chamber to reduce the dependence of the modulation amplitude on the underlying temperature of the DSC cell; symmetrical thermal mass on the accessory, and a thermocouple touching the pan lid to directly monitor the temperature of the sample.

Saquinavir provided the opportunity to investigate a relevant pharmaceutical amorphous material, with all the problems inherent in such samples, e.g. a powdered sample with the possibility of poor thermal contact, and a narrow glass-transition obscured by an endothermic relaxation. PET allowed the observation of a number of different transitions within the same experiment, namely, a glass transition, an exothermic crystallization and a melting endotherm.

The results presented here indicate that the gas-flow accessory design can achieve modulation periods from 12 down to 6 s easily. The lower limit for a sample of PET was 2.4 s. This is a frequency limit of approximately 0.5 Hz. The limit in frequency of the conventional TA Instruments 2920 MTDSC, at comparable heating rates and amplitudes, is 0.05 Hz. Therefore, the technology developed here raises the

possible attainable frequency by an order of magnitude. Thus, the present work, while sub-optimal in detail, is extremely encouraging and provides strong evidence that the gas modulation approach holds considerable promise. Ultimately the aim is to provide all of the benefits of the MTDSC approach, but with the productivity associated with conventional DSC.

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