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The role of modulated temperature differential scanning calorimetry in the characterisation of a drug molecule exhibiting polymorphic and glass forming tendencies

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Abstract

The thermal properties of the drug sulfapyridine were studied using a combination of differential scanning calorimetry (DSC), modulated temperature differential scanning calorimetry (MTDSC) and thermo optical analysis with a view to examing the combined use of these methods as a characterisation strategy. Conventional DSC indicated that quenched sulfapyridine exhibited a series of transitions on reheating at 10°C min^{-1} which were ascribed to a glass transition (56.9°C), cold crystallisation (103.7°C), a solid-solid transition (131.4°C) and metastable and stable polymorphic melting (177.3 and 186.3°C). MTDSC studies were able to show the glass transition with much greater clarity in the reversing signal than was possible using the conventional technique, while it was also possible to observe the phase angle which again allowed clearer visualisation of the Tg. Thermooptical analysis confirmed the interpretation of the DSC and MTDSC data, showing the formation of spherulitic crystals which converted to a needle-shaped morphology on heating, these being ascribed to metastable and stable polymorphs respectively. The study has therefore demonstrated that using the three techniques in combination allows unique insights into the glass transitional and polymorphic behaviour of a drug substance.

Keywords: Differential scanning calorimetry; Modulated temperature differential scanning calorimetry; Heat capacity; Polymorphism; Amorphous; Glass transition; Morphology; Thermo optical analysis

1. Introduction

It is important that polymorphic tendencies are detected for pharmaceutical compounds because of the possible influence upon stability and bioavailability. A number of techniques are available for polymorphism studies with DSC being widely used (Giron, 1995). Typically the melting properties of a compound are measured in the 'as received' state and then again after a known crystallisation/cooling regimen has been applied. If there is an appreciable change in the melting point or there is more than one melting peak then polymorphism is suspected. Another behavioural

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feature is the ability to form a supercooled liquid or 'glass' when cooled from the melt. This can also be detected by DSC in the form of the glass transition temperature (Tg). The Tg is a very important parameter for some pharmaceutical formulations, such as those produced by freeze drying, as it has a direct influence upon the storage stability of the materials.

DSC has some limitations in that if a Tg occurs in the same temperature range as another transition, for example water or solvent loss, the two events can not be separated. Furthermore if only a small amount of amorphous material is present then DSC may not be sensitive enough for it to be detected. MTDSC may provide a solution to these problems. Firstly by separating 'reversing' and 'non-reversing' thermal events, the heat capacity change associated with the Tg can be separated from heat flow changes caused by melting, drying, solvent loss and protein denaturation. Secondly by use of the phase angle curve produced from the MTDSC data analysis, very small Cp changes can be detected which increases the sensitivity of the technique for small amounts of amorphous material and for Tg determination in general. The disadvantage of MTDSC is that the data analysis and interpretation are more difficult than for DSC and also experiment times can be very long because of the much lower heating rates used. Also the choice of experimental parameters requires a certain degree of knowledge not only of the MTDSC technique but also of the general thermal behaviour of the compound under investigation. For this reason MTDSC is almost always used as an additional tool to complement DSC and other measurements.

A useful and relatively simple complementary technique to DSC and MTDSC is thermo optical analysis (TOA) in which the sample is heated on a microscope stage and the crystal structures and transitions can be observed directly and recorded to film or video. Use of all three thermal techniques can provide a comprehensive understanding of thermal transitions taking place.

Theoretical details of DSC and MTDSC are well documented elsewhere (Hutchinson and Montserrat, 1996a,b, 1997; Hutchinson, 1998; Jiang et al., 1998) and therefore are not considered further. The rest of the paper will concentrate on the analysis and interpretation of results obtained with a model compound, sulfapyridine, which was chosen as it is readily available and exhibits many of the properties of interest in this study.

2. Experimental

2.1. Materials and instrumentation

Sulfapyridine was obtained from Dr Theodor Schuchardt GmbH München catalog No. 33237 and used as received. All the thermal analysis measurements (DSC and TMDCS) were performed on a Mettler Toledo DSC821e fitted with a 34 place autosampler and RP100 refrigerated chiller unit. The instrument was calibrated for temperature accuracy using indium and zinc standards. Heat flow calibration was performed with indium. A Tau Lag calibration, which ensures correct reference temperatures when experimental heating rates are used which are different to the rate used for the initial temperature calibration, was performed with indium and zinc. Samples were encapsulated in Mettler Toledo standard aluminium crucibles which were hermetically sealed after weighing on a Mettler Toledo AG245 analytical balance. Control of the DSC and data analysis was performed using Mettler Toledo STARe software version 5.12. TOA measurements were performed using a Mettler Toledo FP90 and FP82 hot stage system and Olympus (Hamburg, Germany) BH2 transmission microscope through crossed polarising filters.

2.2. Methodologies

Conventional DSC measurements were performed at 10 and 20°C per min heating rates on fresh samples of sulfapyridine and also on quenched samples. Quenching was achieved by removing the crucible from the DSC furnace above the melting point and placing onto a large aluminium tray at room temperature. This cooled the sample from 200 to 25°C in ≈ 5 s.

MTDSC measurements were conducted using sine wave temperature programmes defined by

underlying heating rate, amplitude and period. For most measurements a 1,1,1 program (rate, 1°C min^{-1}, amplitude, 1°C, period, 1 min) was used as this gave around 10 cycles through the glass transition region and is a reasonable compromise between sensitivity and experiment time. The Mettler Toledo DSC821e can use other sine waves as well as other wave forms (square waves, saw tooth's, etc.). MTDSC measurements were conducted on quenched sample, as it was found that the sulfapyridine as received has no amorphous content. The quenched samples were prepared in the same way as for the DSC measurements detailed earlier.

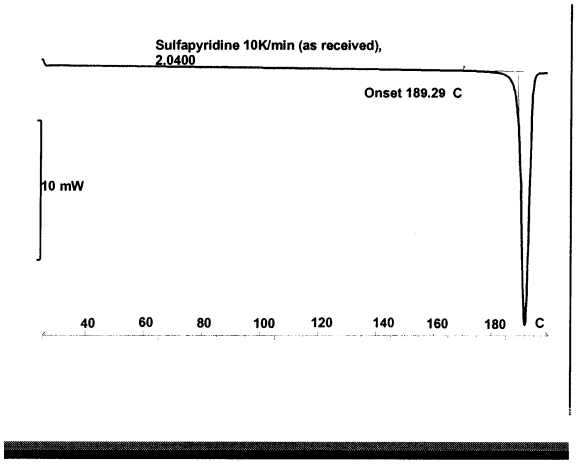

Fig. 1. Conventional DSC of Sulfapyridine measured at 10°C min^{-1}.

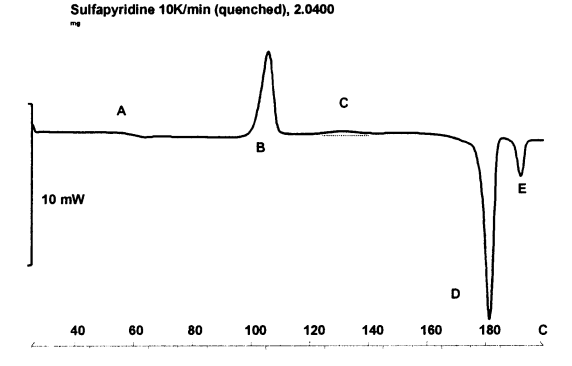

Fig. 2. Conventional DSC of quenched Sulfapyridine measured at 10°C min^{-1}.

TOA measurements were performed using samples which were quenched from the melt by first melting a small amount on a microscope slide, then placing the slide onto a cool aluminium block. The sample cools from 200 to 25 °C in ≈ 10 s. The samples were heated at 5°C min^{-1}.

3. Results and discussion

3.1. Conventional DSC studies

Upon heating from 25 to 200°C at 10°C min^{-1} sulfapyridine as received shows a single melting peak with an onset of 189.3°C (Fig. 1). This indicates that a single crystal form is present and that the purity is high. Heating a fresh sample at 20°C min^{-1} gives the same results and this shows that the DSC system is correctly calibrated for the Tau Lag. First order transitions such as melting are unaffected by heating rate and so would not be expected to change when measured at different heating rates in the DSC.

The quenched sample was then heated at 10°C min^{-1} and shows a number of thermal events. There is a baseline shift (A) at 56.9°C; a strong exothermic peak (B) at 103.7°C; a small exotherm (C) at 131.4°C; a strong endotherm at (D) 177.3°C; and a smaller endotherm (E) at 186.3°C (Fig. 2). These may be tentatively ascribed as follows; the event at 56.9°C may be as a result of a glass transition, followed by cold crystallisation at 103.7°C. The small exotherm at 131.4°C may be because of a solid-solid transition while the two endotherms at 177.3 and 186.3°C may be as a result of metastable and stable polymorphic forms of the drug, respectively. It should be noted that while the presence of two melting peaks was seen for all repeats the relative sizes showed some variation because of the unpredictable nature of the nucleation process. The temperatures and energies associated with these transitions are shown in Table 1. In summary, the DSC results indicate that sulfapyridine when quenched from the melt forms a glass which upon further heating undergoes a number of transitions which would suggest that different crystal forms (polymorphs) are produced.

Table 1
Temperatures and enthalpies of transitions in quenched Sulfapyridine

Temperature (°C)	Transition	Enthalpy (J g^{-1})
56.9	Glass Transition	N/A
103.7	Cold Crystallisation (devitrification)	−65.4
131.4	Solid/solid transformation	−2.6
177.3	Metastable melt	+107.6
186.3	Stable melt	+21.3

3.2. MTDSC studies

MTDSC raw data is a complex heat flow signal which contains the reversing, non-reversing and phase information. This is deconvoluted by the analysis software and normally only the calculated signals are evaluated. Fig. 3 shows the reversing, non-reversing and total heat flow signals for the quenched sample run with a 1,1,1 sine wave. It can be seen that the reversing signal shows the heat capacity change of the glass transition and also a second Cp change associated with the recrystallisation exotherm, a similar change in reversing signal has been noted during the recrystallisation of lactose by Hill et al. (1998). This second Cp change can be explained in terms of the decrease in mobility of the system as the amorphous regions crystallise. The non-reversing signal shows the recrystallisation exotherm and also the small crystal rearrangement exotherm. Because of the lower underlying heating rate of the ADSC measurement compared to conventional DSC (1°C min^{-1} cf. 10°C min^{-1}) the relative peak sizes are different in the two curves. Also because the devitrification and polymorphic rearrangement are kinetic processes they are also affected by the underlying heating rate and so do not appear at the same temperature in the ADSC and conventional DSC curves. Another small endotherm is seen at the same temperature as the Tg and this is the relaxation process. This was not picked out by the conventional DSC measurement but similar events are commonly associated with glass transition temperatures and are well documented.

Fig. 4 shows the phase curve for the same experiment. The phase detects all the transitions, Tg, devitrification and rearrangement but it is interesting that the relative signal strength for the Tg compared to the devitrification is greater than was seen by conventional DSC. This leads to the expectation that the phase curve is very sensitive to Cp changes and so is likely to be able to detect small amounts of amorphous material with an increase in sensitivity when compared to DSC. Whilst this avenue is not explored further here it is planned to pursue this at a later date.

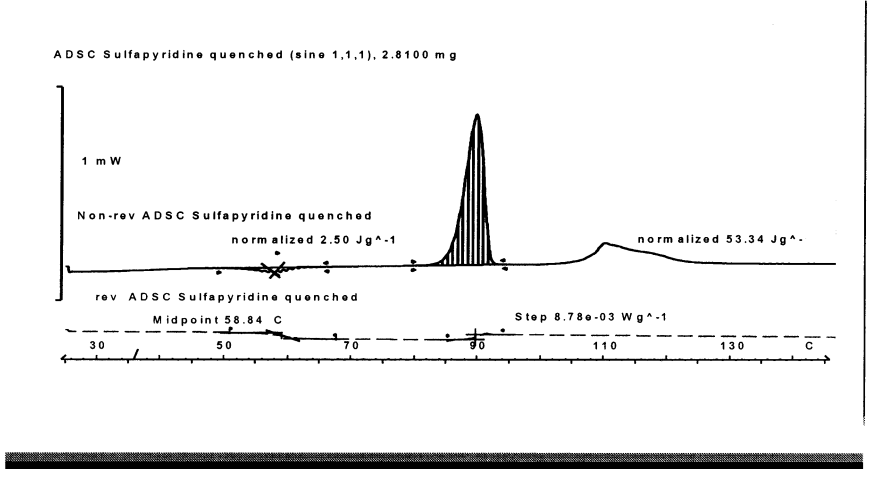

Fig. 3. MTDSC results for quenched Sulfapyridine measured with a 1,1,1 sine wave.

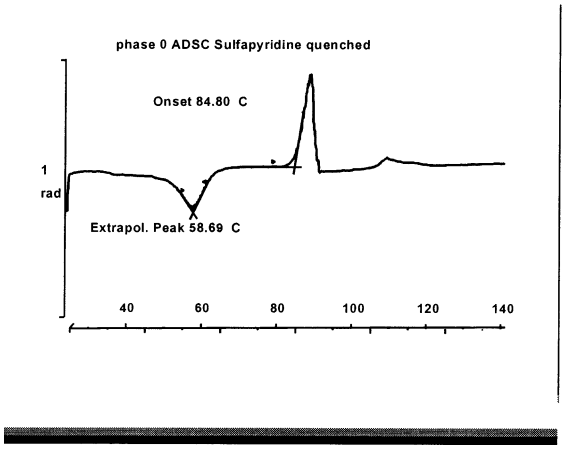

Fig. 4. MTDSC phase angle measurement for quenched Sulfapyridine measured with a 1,1,1 sine wave.

In the area of the melt the MTDSC signal becomes very difficult to interpret because the system is no longer in equilibrium. Further work is underway to gain a better understanding of the meaning of MTDSC data during melting but the melting process is not considered in this study.

3.3. Thermo optical analysis

Viewed under the microscope the glassy form of sulfapyridine gives a dark field through crossed polarising filters. Above the Tg crystal growth can be observed and by 120°C the field of view is filled with spherulitic crystals (Fig. 5). On further heating some of the spherulites are transformed into needle shaped crystals in the range from 130 to 150°C (Fig. 6). Some spherulites remain and these can be seen to melt at around 175°C (Fig. 7). The remaining needle crystals melt around 190°C. This is interpreted in terms of the spherulites being metastable and hence transforming into the stable needle form. Depending upon conditions not all the spherulites transform and the remaining spherulites have a low melting point. The stable needle crystals melt at a higher temperature.

4. Conclusions

Sulfapyridine as received is a stable high purity substance with a single melting peak. On quench cooling a glass is formed which upon heating

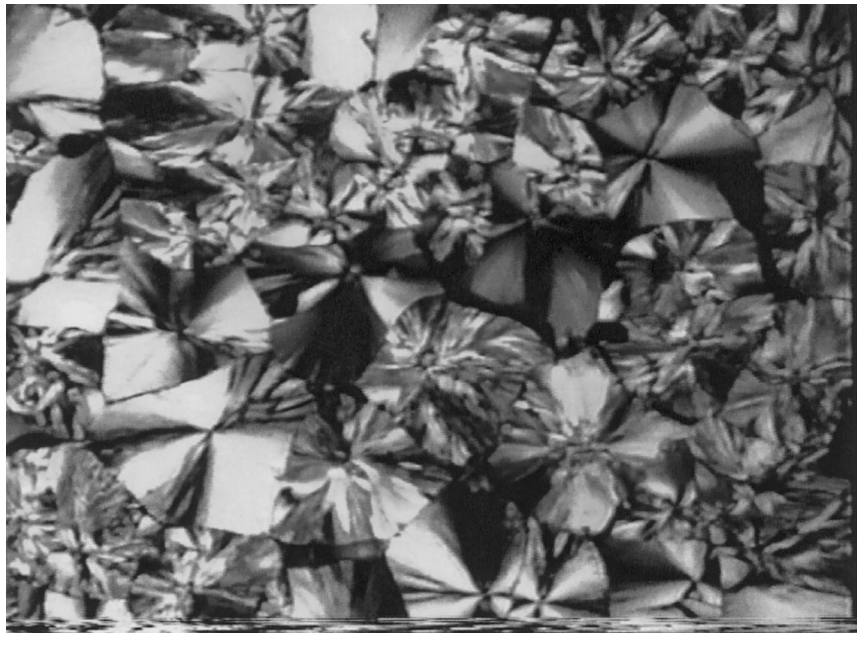

Fig. 5. Spherulitic crystals formed from glass (120°C). Image width equivalent to 2 mm.

Fig. 6. Transformation of spherulites to needles (150°C). Image width equivalent to 2 mm.

Fig. 7. Needle crystals after transformation and melting of spherulites (180°C). Image width equivalent to 2 mm.

passes through its glass transition temperature and then undergoes devitrification and a 'cold crystallisation' process where metastable spherulitic crystals are formed. Upon further

heating some of these crystals undergo a solid/solid transformation where the spherulites convert to stable needle shaped crystals. Remaining spherulites have a lower melting temperature than the needle crystals which themselves melt at the same temperature as the original sulfapyridine sample. DSC and MTDSC are able to detect all the processes which take place but give only indirect information regarding the crystalline transformations. TOA is able to characterise the crystals and can determine all the transition temperatures except the Tg. Therefore in order to have a full understanding of the processes and material structures involved all three techniques are required. The phase information from the MTDSC appears to be very sensitive to changes in Cp and therefore may be very useful in detecting small amounts of amorphous material.

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