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The use of isothermal microcalorimetry in the study of changes in crystallinity of spray-dried salbutamol sulphate

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Abstract

Isothermal microcalorimetry has been used to monitor the recrystallisation of spray-dried salbutamol sulphate. The drug recrystallises in water vapour, by a cooperative process. The cooperative nature demonstrates that the water must first absorb to saturate the entire powder bed before recrystallisation occurs. Consequently, recrystallisation is slower for low humidities, due to a slower arrival of water vapour. The data have been compared with previous data for recrystallisation of spray-dried lactose. The heat change for the crystallisation was significantly lower for salbutamol sulphate than for lactose. In terms of apparent enthalpy of crystallisation, the large exothermic responses are indicative of the fact that the crystal form is the thermodynamically stable state. The salbutamol which had been recrystallised at the lower humidities showed that the process, whilst being rapid, was discontinuous. In each case, the exothermic recrystallisation was followed by an endothermic response for the expulsion of water as the amorphous region recrystallised. There was a repeating sequence of crystallisation, followed by water expulsion, followed by further recrystallisation. With each repeat of the cycle the responses decreased in size. This ability to follow crystallisation in real time provides a novel insight into the process.

Keywords: Isothermal microcalorimetry; Crystallization; Spray drying; Processing; Surface energy; Inhalation; Salbutamol; Lactose

1. Introduction

Briefly, isothermal microcalorimetry is a technique whereby a sample is held in a cell which is thermostated to one temperature, such that any processes which occur in the cell can be monitored either by heat gain from, or heat loss to, a heat sink. As (almost) all processes (physical or chemical) cause a change in heat, notionally all processes can be followed using this technique (for further details see Buckton and Beezer (1991) or Briggner et al. (1994)).

Isothermal microcalorimetry has found comparatively little use in the field of physical pharmacy. In terms of crystal properties, recent publications have shown that it is possible to follow mutarotation of lactose in real time using isothermal microcalorimetry (e.g., Angberg et al., 1992). It has also been shown that it is possible to

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monitor the recrystallisation of amorphous lactose using this technique (Briggner et al., 1994; Sebhatu et al., 1994). There are, however, very few data available on such applications (see Buckton and Beezer, 1991).

The crystal properties, and degree of crystallinity of pharmaceutical powders are important for many types of dosage form; however, these are especially critical for inhalation technology. This is primarily because the surfaces of materials are often greatly affected by processing, and inhalation products need severe processing conditions to obtain the necessary micronised particles (Buckton et al., 1988). For products which are inhaled as a dry powder the surface properties will influence the ease of dosing (i.e., flow and cohesive nature), and the lung deposition. Lung deposition will only be achieved if powder aggregates are broken into individual particles during inhalation, to achieve the sizes that are needed for deep lung penetration (i.e., sub 5 μm). For suspension aerosols, surface energies of powders will influence (and can be used to predict) the ease of dispersion into the propellant, the extent of aggregation and the losses due to adhesion to the container wall (Parsons et al., 1992).

In a previous publication (Parsons et al., 1992) we have shown that the influence of gross differences in powder surface properties (i.e., the behaviour of totally different materials) on the behaviour of drugs in model inhalation systems, can be explained (and predicted) easily by use of surface energy terms (derived from contact angle experiments). There are occasions, however, when it is hard to obtain accurate contact angle results for powdered systems. This is especially true with highly water soluble hydrophilic materials. Salbutamol sulphate is a material onto which most liquids yield very low contact angles which, consequently, are hard to measure with accuracy. Recently (Briggner et al., 1994), we have reported that microcalorimetry can be used to monitor the recrystallisation of amorphous lactose, and have suggested that the differences in surface energy produced by processing are due to the extent of disruption that is caused to the surface (i.e., how amorphous it becomes). Similar observations have been presented by Sebhatu et al. (1994).

The interaction of water with amorphous solids has been discussed by Saleki-Gerhardt et al. (1994) in terms of a plasticising effect. Amorphous materials convert to the thermodynamically stable crystalline state when the glass transition temperature of the amorphous state is plasticised (by the absorbed water) to room temperature or below (Hancock and Zografi, 1994). Recently, Ward and Shultz (1994) have studied salbutamol sulphate by a range of techniques including differential scanning calorimetry, solution calorimetry and water vapour sorption analysis. Water vapour sorption analysis showed a sharp weight loss of the micronised sample at a critical moisture content. This observation was not seen on repeated studies of the same sample, and can be concluded to relate to the crystallisation of the amorphous content of the powder (which was induced due to processing).

The purpose of this publication is to report on characteristics of the recrystallisation of spray-dried salbutamol using isothermal microcalorimetry, and to compare the results with the data that we have already published for lactose.

2. Methods

A sample of salbutamol sulphate (ex 3M Health Care) was spray-dried from solution in water in a Buchi 90 spray drier. The material was desiccated immediately after drying, and found to show only an amorphous halo by powder X-ray diffraction (i.e., it was taken to be amorphous [1]).

The spray-dried and the feed material were investigated using a Thermal Activity Monitor (Thermometric AB, Sweden), at 25°C. The powder was weighed (20.00 mg) into a 3 ml glass

[1] The powder cannot be described as absolutely amorphous as the sensitivity of powder X-ray diffraction (PXRD) is not sufficiently good to prove this point. It is in fact a statistical certainty that some molecules will be ordered in the powder mass. The detection cut off for amorphous material in a crystalline sample is about 10% (Saleki-Gerhardt et al., 1994) and it may well be that up to 10% of the sample could be crystalline whilst still being seen as amorphous by use of PXRD.

ampoule, after which a tube was added containing a saturated salt solution. The powder, ampoule, and saturated salt solution were all pre-equilibrated in an oven at 25°C prior to assembly. The ampoule was sealed and then equilibrated in the calorimeter for 5–10 min before lowering into the measuring site. The output from the calorimeter was recorded using a microcomputer, in the form of rate of change of heat (dq/dt = power) as a function of time.

The effect of different humidities (i.e., different saturated salt solutions, giving humidities of 80, 75, 65, 54% RH) on the recrystallisation was investigated.

3. Results and discussion

The calorimetric data for recrystallisation of the amorphous material in the spray-dried salbutamol are collated in Fig. 1. The feed sample, which was used to prepare the spray-dried material resulted in a flat baseline when investigated in the calorimeter (not shown), implying that it was already crystalline and that the amorphous nature was induced during spray drying. The amorphous nature for the spray-dried sample was proved by use of powder X-ray diffraction, which revealed that the original sample was indeed crystalline and that the spray-dried sample showed no evidence of crystalline structure.

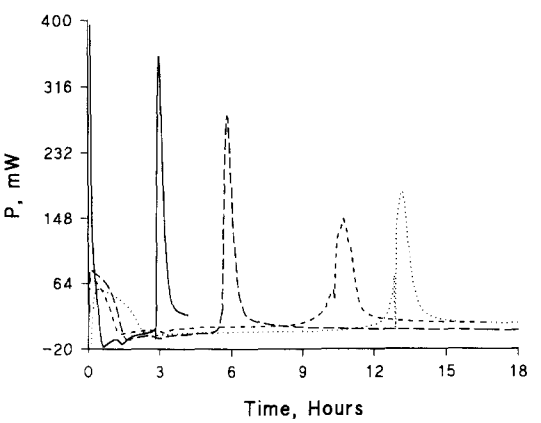

Fig. 1. Typical microcalorimetric outputs (power (P) as a function of time) for spray-dried salbutamol sulphate, using a powder loading of 20 mg, with (———) 80% RH; (— — —) 75% RH; (- - - - -) 65% RH and (....) 54% RH.

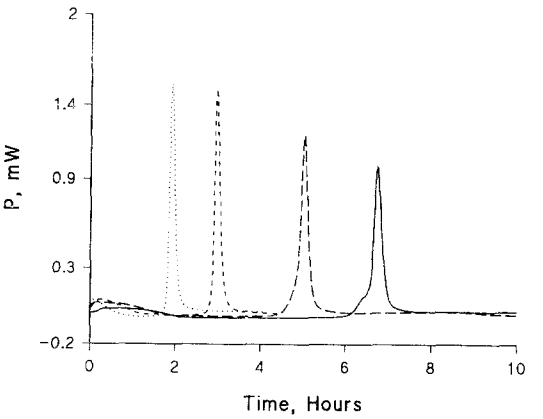

Fig. 2. Typical microcalorimetric outputs (power (P) as a function of time) for spray-dried lactose, using a powder loading of 20 mg, with (...) 85% RH; (— — —) 75% RH; (- - - - -) 65% RH and (———) 53% RH. (Reproduced from Briggner et al., 1994).

The responses in Fig. 1 have some similarity with those observed for spray-dried lactose (Briggner et al., 1994), shown as Fig. 2. The similarities are that the recrystallisation is a cooperative event, in that there is a lag time, then a very sudden response when all the amorphous material in the sample recrystallises at one time. This cooperativity must mean that the water vapour is absorbed by the solid, and subsequently redistributed throughout the powder bed, until the point when the bed is completely saturated with water, after which the next addition of water vapour results in the onset of recrystallisation. A further similarity with the lactose data is the fact that the lag period prior to recrystallisation is increased with decreasing humidity. This is consistent with the argument that the bed must be saturated prior to recrystallisation, and provides evidence that the supply of water vapour will be slower at lower relative humidities.

The area under the curve of the power time response gives the total heat output for the process. For recrystallisation of spray-dried lactose the response was the same for each experimental condition (in the range 45–50 mJ mg^{-1}). For the salbutamol samples, the heat output was 25.6, 25.5 and 27.6 mJ mg^{-1} for the responses at 75, 65

and 54% RH respectively (the response at 80% RH has not been measured as it did not return to baseline). On a molar basis 20 mg represents 0.069 mmol of salbutamol sulphate and 0.055 mmol of lactose, which would mean that the recrystallisation energies are approx. −370 and −850 kJ mol^{-1} for salbutamol sulphate and lactose respectively. These high exothermic values for the apparent enthalpies of crystallisation, testify to the fact that the thermodynamically stable state for most systems is the crystalline form. The absolute values for these apparent enthalpies of crystallisation do not seem unreasonable in relation to standard values that are observed of enthalpies of fusion of organic materials, however, Sebhatu et al. (1994) found that the apparent enthalpy of crystallisation was lower from isothermal microcalorimetry measurements than it was from oscillatory differential scanning calorimetry investigation of identical sugar samples. It is not possible to confirm such observations for salbutamol sulphate, as this drug melts with decomposition, thus distorting the enthalpy term obtained from differential scanning calorimetry (data not reported).

A distinct difference between the recrystallisation of lactose and salbutamol sulphate is seen in the shape of the peaks obtained from the isothermal microcalorimeter at lower relative humidities. The peaks of the individual responses are presented on a larger scale in Fig. 3–6. A response for the spray-dried lactose has also been reproduced on a larger scale for comparison (Fig. 7). With each of the responses for the salbutamol sulphate, the recrystallisation event has multiple peaks. At high humidities (Fig. 3 and 4) the peak is seen as two distinct sections, an initial small peak followed by a second substantial response. At lower humidities, the peak is more obviously discontinuous, for example in Fig. 5, an initial exothermic peak is seen, followed by a sharp endothermic response, then a more rounded exotherm with at least two shoulders. Fig. 6 shows a similar response to that in Fig. 5. These observations were not noted for spray-dried lactose (Fig. 7), although a retrospective examination of the data does reveal that a shoulder is present on the response at 53% RH (Fig. 2).

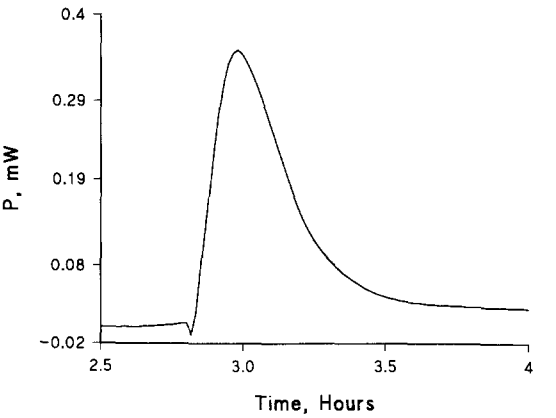

Fig. 3. Response shown in Fig. 1 for recrystallisation of salbutamol sulphate with 80% RH vapour, on an enlarged scale, to reveal further detail.

The explanation for these multiple responses is that the powder absorbs water into the amorphous regions, which cause the molecules to be made sufficiently mobile to allow recrystallisation. As recrystallisation occurs, the absorbed water will be expelled from the structure, which will be an endothermic process. Thus the recrystallisation starts (exothermic response) which causes the expulsion of water (endothermic), and it would appear that this process repeats to a lesser extent after the first dramatic endothermic desorption response. As the response reported above is the net area under the curve, it is the sum of en-

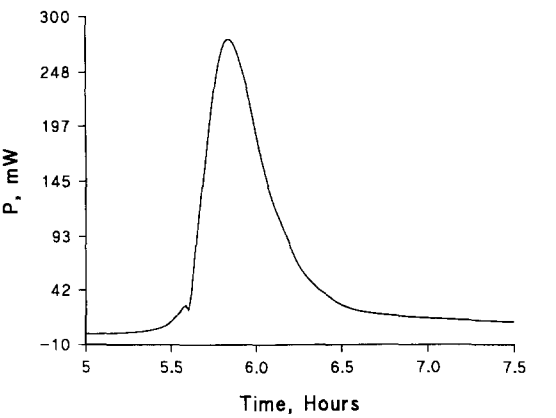

Fig. 4. Response shown in Fig. 1 for recrystallisation of salbutamol sulphate with 75% RH vapour, on an enlarged scale, to reveal further detail.

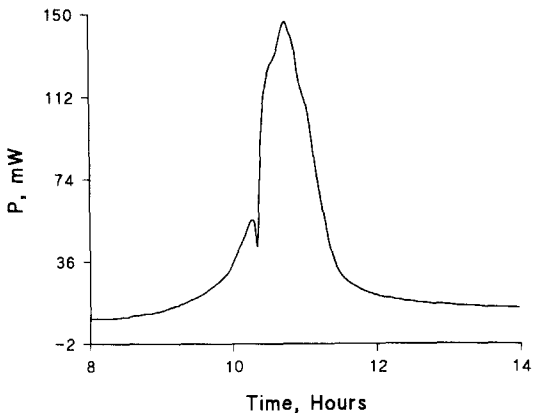

Fig. 5. Response shown in Fig. 1 for recrystallisation of salbutamol sulphate with 65% RH vapour, on an enlarged scale, to reveal further detail.

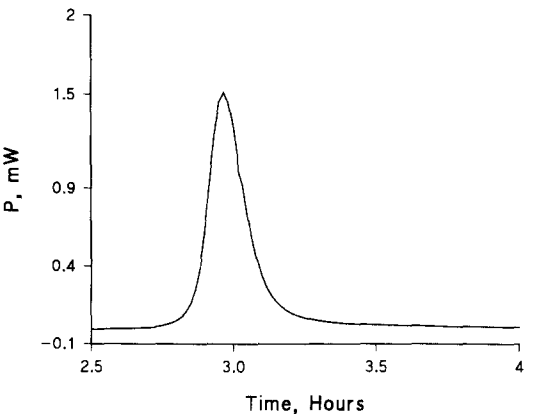

Fig. 7. Recrystallisation of spray-dried lactose (from Briggner et al., 1994) reproduced on a larger scale.

dotherms and exotherms, thus the result was termed an apparent enthalpy of crystallisation. The water vapour which is expelled from the amorphous regions during crystallisation will initially raise the humidity within the ampoule, but subsequently condensation will result in the humidity being recontrolled by the saturated salt solution. The events of desorption of the water from the powder and condensation will thermodynamically be approximately equal and opposite, but they will not necessarily be kinetically synchronised. The approximate balance in the enthalpy terms (for desorption and then condensation of the water) would lead to the conclusion that the net area under the curve will be a reasonably accurate indication of the enthalpy of crystallisation of the amorphous content of the powder. It is probable, therefore, that the multiplicity seen in the peaks at low humidities reflect these kinetic imbalances, superimposed on the crystallisation event. These multiple components of the recrystallisation event are noted most clearly when the process is occurring at the slowest rate (i.e., at low humidity). If the process can be slowed still further, by changing the experimental conditions, then more detail should be available on the mechanism of crystallisation. Consequently, these multiple peaks provide an intriguing insight into the nature of the crystallisation event. It is probable that the multiple peaks also exist for lactose (as demonstrated by the low humidity response in Fig. 2), but the recrystallisation event will have to be slowed (by changing powder load and/or humidity) for them to be seen.

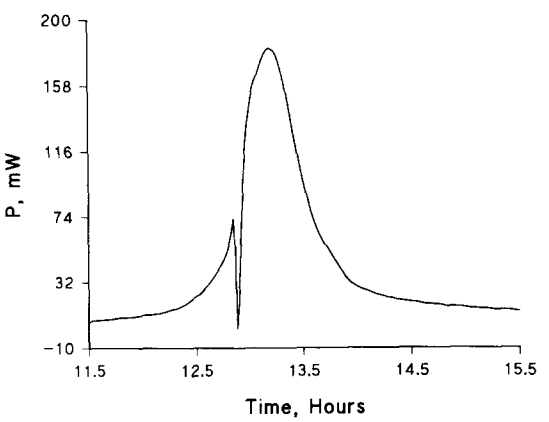

Fig. 6. Response shown in Fig. 1 for recrystallisation of salbutamol sulphate with 54% RH vapour, on an enlarged scale, to reveal further detail.

4. Conclusion

Isothermal microcalorimetry offers a technique by which the amorphous content of materials can be characterised. It has already been shown (Briggner et al., 1994) that the sensitivity of the calorimetric approach will better than that

of X-ray diffraction, and thus there are advantages for use of this technique for studies of small amounts of, processing induced, amorphous material. These processing induced changes are often critical to product performance.

A further issue that has been addressed for the first time in this publication, is that the 'real time' response in the calorimeter gives the opportunity to monitor the crystallisation process as it happens. The data presented here demonstrate a sequenced process whereby recrystallisation starts, water is expelled, further recrystallisation occurs, more water is expelled etc. Each sequential step in this response is smaller than the previous one. The prospects to investigate fundamentals of crystallisation, and factors which influence it are extremely good.

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