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The use of isothermal microcalorimetry in the study of small degrees of amorphous content of powders

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A common observation with powdered systems is that their behaviour is subject to variability if processing conditions are changed. These effects manifest themselves due to different interactions between the processed powder and other phases. It has been suggested (Briggner et al., 1994; Saleki-Gerhardt et al., 1994; Sebhatu et al., 1994) that the main cause of differences in behaviour as a consequence of the processing of powders is due to the disruption of crystalline material to yield amorphous regions. Approaches to the study of crystallinity of powders have generally concentrated on X-ray powder diffraction and infrared spectroscopy, although other approaches have been used, such as density (Duncan-Hewitt and Grant, 1986), and solution calorimetry (Pikal et al., 1978). It has been shown that it is possible to use isothermal microcalorimetry to probe small amounts of amorphous content in powders that have been induced during processing (Briggner et al., 1994; Sebhatu et al., 1994). By extrapolation it has been claimed that it should be possible to detect as low as 1% (Briggner et al., 1994) or 2% (Sebhatu et al, 1994) amorphous content in a sample of powder. The purpose of this paper is to present data which give an indication as to the lower limit of detection that is possible for amorphous content in a powdered sample.

Lactose monohydrate (DMV) was dissolved in water and spray dried (Buchi 90) in order to create amorphous material (this was tested by powder X-ray diffraction (Briggner et al., 1994)). The original crystalline lactose was found to be 100% crystalline (best approximation), in that it did not give a recrystallisation response in the calorimeter. The amorphous and the crystalline powder were both stored under dry conditions (over silica gel) at 25 ± 0.5°C, prior to use. Small quantities of the powders were then added to a small glass jar and tumbled in order to prepare mixes (1 g) containing different amounts of amorphous lactose.

The powder mixtures (800 mg, weighed accurately) were then loaded into a glass ampoule containing a tube of a saturated solution of sodium chloride (to give a relative humidity of 75%). The ampoule, the salt solution and the powders had all been pre-equilibrated to 25°C for

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30 min prior to assembly. The ampoule was then sealed and lowered into the equilibration position of an isothermal microcalorimeter (Thermometric AB, Sweden). After 10 min, the ampoule was lowered into the measuring position of the instrument. This low equilibration time was only possible due to having optimised the equilibration procedure and pre-storage requirements. The instrument was set to record data only after lowering the ampoule into the measuring position, i.e., the recorded time 0 is in fact at least 10 min after the ampoule was sealed. The output of the instrument records power as a function of time, for the net response of any event(s) occurring within the measuring site. For further details of the calorimeter system see Briggner et al. (1994). Mixtures of different proportions of amorphous and crystalline lactose were investigated.

For each recrystallisation response measured in the microcalorimeter, the total heat change was determined by measuring the area under the powder time curve. The area was calculated by use of the 'Digitam 3' software package (Thermometric), which was found to yield comparable results to areas under the curve obtained by a cutting and weighing method. The area under the curve was corrected to a heat by reference to an electrical calibration response. For each sample four replicate investigations were performed, with results quoted as mean values.

The recrystallisation event is seen as a sharp co-operative response, which occurs after an initial small wetting response. Further details of this observation can be seen elsewhere (Briggner et al., 1994).

Data were obtained for progressively lower quantities of amorphous lactose, by mixing amorphous and crystalline material. With each change in proportion, the time to the recrystallisation response decreased, as did the magnitude of the response. In Fig. 1, the responses for mixtures containing 1.25% amorphous material are shown. It can be seen that the sharp recrystallisation peak occurs at just under 2 h. The reproducibility of the experiment is shown in Fig. 1 in that the four replicates shown are almost identical. Halving the quantity of amorphous content to 0.625% resulted in a peak at about 1 h, and gave rise to

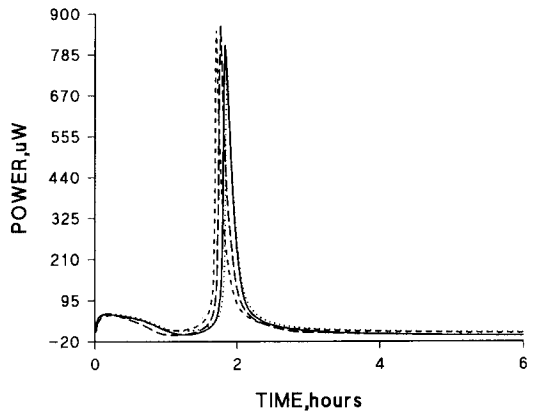

Fig. 1. Four replicate responses for the recrystallisation of a sample containing 1.25% amorphous lactose.

the first signs of deviation from reproducibility, but only with respect to the shape of the recrystallisation response. The areas under the curves for the four traces in Fig. 2 are similar, showing that the response is the same, but the kinetics are variable at this level of amorphous content.

The areas under the curve can be used to give a heat output per mg of amorphous material. Previously, this has been found to be in the order of 50 mJ mg^{-1} for totally amorphous lactose (Briggner et al., 1994), the results here give mean values of 58.9 and 53.9 mJ mg^{-1} (calculated as response per mg of amorphous material, rather than per mg of total sample) for the samples

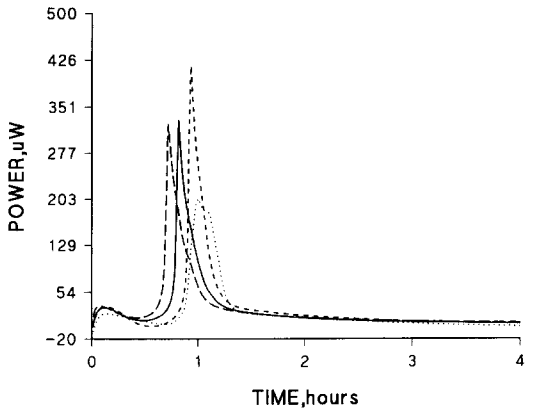

Fig. 2. Four replicate responses for the recrystallisation of a sample containing 0.625% amorphous lactose.

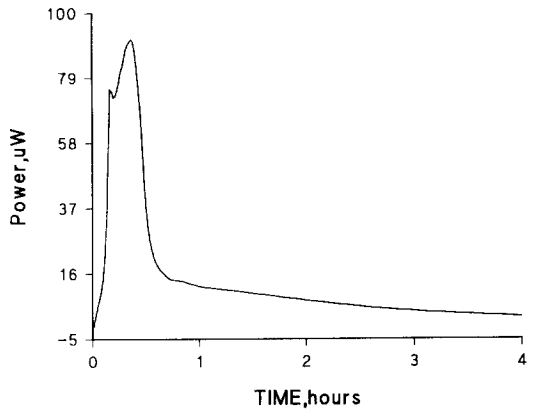

Fig. 3. Response for the recrystallisation of a sample containing 0.313% amorphous material.

containing 1.25 and 0.625% amorphous material, respectively, which are slightly higher, but not inconsistent with our earlier findings. This shows that samples with this low level of amorphous content can be investigated and quantified. There is no reason to suspect that material with this level of amorphous content distributed on the surface of the crystalline powder, rather than the mixtures of amorphous and crystalline material that are used here, should behave in a different manner, but that will eventually need to be checked. The difficulty in checking this finding (with respect to the accuracy of microcalorimetry in quantifying the processing induced changes in crystallinity) will be the absence of techniques, other than microcalorimetry, that can be used to quantify the degree of amorphous material in a processed sample.

Further reduction in the amorphous content (below 0.625%) resulted in a multiple peak (Fig. 3). The area under the curve for the 0.312% amorphous sample equated to 80.9 mJ mg^{-1}, which is rather larger than for the other mixtures. A possible reason for this value being different to the others is the great difficulty in weighing and mixing such small quantities of powder, however, the fact that the response for this mixture is so rapid gives another reason for error in that it is superimposed on the wetting response, thus artificially elevating the size of the recrystallisation event.

As noted, multiple peaks were observed for the samples with 0.312%, and for one of the samples with 0.625%, amorphous content. There are two possible explanations for the observed multiple peak. One option is that the dynamics of one recrystallisation event are being observed, and the other is that several sequential crystal transitions are being followed. The recrystallisation process is initiated by the water plasticising the amorphous material, and allowing sufficient molecular mobility for the recrystallisation to occur. Upon recrystallisation, the water will be expelled from the material. It follows that the multiple peaks may be the onset of recrystallisation (exothermic, positive power output), followed by expulsion of water (endothermic, negative output), followed by a further stage of recrystallisation etc. Superimposed on this will be the fact that the desorbed water will be condensed into the saturated salt solution in order to restore the humidity at 75% RH. The kinetics of this will be significant, as the rapid loss of water (negative power output) from the crystallising (positive power output) material will cause a rise in atmospheric humidity, prior to the response for the condensation (positive power output). It is only with the comparatively small output seen for the material with very low amounts of amorphous material that these multiple peaks are observed. The samples with higher amorphous content can be assumed to be behaving in a similar way to that seen in Fig. 3, but the magnitude of the response is sufficiently great to hide any oscillation between the positive and negative responses.

The second possible explanation for the multiple peaks is that of crystal transitions. It has already been shown that the transition between β- and α-lactose can be followed calorimetrically (Angberg et al., 1992; Briggner et al., 1994). Thus, it could be argued that the data in Fig. 3 (three peaks left to right) reflect crystallisation to anhydrous lactose with superimposed conversion to lactose monohydrate, followed by a small peak (approaching 1 h) for conversion between β- and α-lactose monohydrate. It has already been shown (Briggner et al., 1994) that the spray dried lactose recrystallises to a mixture of α- and β-lactose monohydrate and that a very small peak after the

main recrystallisation can be seen which is the transition to the stable form. The magnitudes of the responses seen in Fig. 3 are not dissimilar to those observed for the transitions between α- and β-lactose (Briggner et al., 1994). This is unlikely to be the total reason for the multiple peaks, as similar behaviour has been seen with salbutamol sulphate (Buckton et al., 1995). A distinct possibility is that the multiple peak response is in fact a combination of both of the above explanations.

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