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The use of isothermal microcalorimetry in the study of changes in crystallinity induced during the processing of powders

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Abstract

Isothermal microcalorimetry has been used to follow recrystallisation of amorphous regions of powder surfaces. Lactose monohydrate was taken as a model powder, and was processed by spray drying and micronisation. Spray drying produced an amorphous powder (as shown by X-ray diffraction), which was found to recrystallise when exposed to humidities over 50% RH. The recrystallisation process was extremely cooperative, with the entire sample recrystallising almost instantaneously, rather than a gradual process over the period of exposure to the water vapour. Similar results were noted when micronised material was investigated. The amount of amorphous material produced during micronisation was directly proportional to the intensity of the process. It proved possible to quantify the % amorphous content of powder sample with a resolution of at least 1%, which is considerably better than other techniques. The amorphous regions of the lactose crystallised as either α- or β-lactose. The difference between these samples could be detected by X-ray diffraction, and also could be seen by isothermal calorimetry, as the β-regions mutarotated to α-lactose. The application of isothermal microcalorimetry to studies of crystal properties of powders provides a quantitative characterisation of many aspects of crystallinity and crystal transition. The data obtained can subsequently be used to characterise the properties of the material, and to show how and when crystallisation will occur, and to aid predictions of the product of the crystallisation process. The demonstration of these applications provides a huge potential for the use of isothermal microcalorimetry in this field of study.

Key words: Isothermal microcalorimetry; Crystallinity; Processing; Powder; Surface properties; Amorphous material

1. Introduction

1.1. Isothermal microcalorimetry

Calorimetric techniques have been in existence for many years, however, the use of thermal methods in the pharmaceutical sciences has been limited. Most workers have concentrated on the use of scanning calorimetry, whilst isothermal techniques have seen comparatively little application.

Isothermal microcalorimetry is based on the fact that almost all physical and chemical processes are accompanied by a heat exchange. The instrument (as used in this study) consists of a water bath, which serves as a large heat sink. This heat sink is maintained at a pre-set temperature

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(in the range of 5–95°C) to an accuracy of 10^{-4}°C. The measuring channels (of which there can be four within one instrument, thus allowing four independent experiments to be undertaken simultaneously) are housed in the heat sink, and are formed of a holder for a sample and reference cell. Each holder is surrounded by heat conducting thermopiles. The cells are lowered into the loading position from outside the calorimeter, via intermediate temperature equilibration positions. When the cells are in place, they are maintained at isothermal conditions, such that any processes which occur within the cell (which liberate or absorb heat) will result in a flow of heat either into the cell from the heat sink, or from the cell to the heat sink. The comparison of the sample and reference cells allows the elimination of certain changes in temperature of the heat sink, such that changes in temperature of the order of 10^{-6}°C are detectable as an out of balance signal. Numerous cell types are available for the calorimeter, allowing many different types of experiment to be designed. Given that almost all processes produce heat, it is the design of the experiment, and the interpretation of results, which are critical to a successful outcome.

Applications of microcalorimetry in the field of physical pharmacy have been reviewed by Buckton and Beezer (1991).

1.2. Powder crystallinity and processing effects

It has long been recognised that the behaviour of powders will change depending upon their processing history. Different milling processes have been found to alter contact angles measured on the same solid (Hansford et al., 1978), and the enthalpy of water vapour sorption was found to vary for samples of a drug milled by different individual or sequential milling processes (Buckton et al., 1988). It is obvious that the milling processes changed the orientation of molecules on the surface of the powder particles, and thus altered the surface energies. It has been shown in numerous publications that powder surface energy can be linked to interactions that occur within formulations (e.g., Rowe 1989, 1990; Parsons et al., 1992). It has been observed, empirically, by many workers in industrial practice, that processing induced changes in materials can result in changes in the behaviour of powders in formulations. A major reason for changes in powder behaviour is that the surfaces of crystals become amorphous during processing. Amorphous material behaves in a different manner to crystalline materials, and thus influences interactions, including the powders cohesiveness and adhesion between the powder and other phases. Until this time, the fact that processing can be critical to the behaviour of certain products has not led to significant published work on the effect of processing on powder properties.

It has been shown that isothermal microcalorimetry is a suitable technique to follow crystal transitions in powders. Angberg et al. (1991a,b, 1992) investigated the mutarotation of lactose in the calorimeter, which was induced by changes in atmospheric humidity. It was apparent from these publications, that it was possible to estimate the proportions of the different forms of lactose that were present in the sample, and to investigate how storage conditions, and the presence of other formulation components (e.g., microcrystalline cellulose) affected the mutarotation process. The energies associated with crystallisation processes are sufficiently large, that they can be detected with great ease using a calorimeter. For example, differential scanning calorimeters are able to detect very large peaks for crystal heats, and transitions, whereas isothermal microcalorimeters can have a specific sensitivity which is four orders of magnitude greater than conventional scanning instruments (Buckton and Beezer, 1991).

The aim of this study is to probe the potential for application of microcalorimetry in the study of changes in crystallinity which have been induced by processing.

2. Method

2.1. Material preparation

Samples of lactose monohydrate (DMV) were prepared by either micronisation in an air jet mill

(Airfilco Micronizer Fluid Energy Mill, chamber pressure range from 4 to 7 bar) or by spray drying in a Buchi 190. All samples were desiccated immediately after processing.

2.2. Microcalorimetry

The samples were investigated using a Thermal Activity Monitor (Thermometric AB, Sweden), at 25°C. In each case the powder was weighed into a 3 ml glass ampoule, after which, a tube was added containing a saturated salt solution. The ampoule was sealed and equilibrated in the calorimeter for 5–10 min before lowering into the measuring site. The output from the microcalorimeter was recorded using a microcomputer, and was in the form of rate of change of heat (dq/dt) (i.e., power) as a function of time (a p-t curve).

Experiments were undertaken to investigate: (i) the effect of variations in powder load in the cell; (ii) changes in humidity (i.e., changing the salt in the saturated salt solution); (iii) changes in the surface area of the saturated salt solution, which involved (a) adding two tubes of saturated salt solution to the same cell, thus doubling the available surface area or (b) placing the saturated salt solution in the calorimeter cell and the powder in the inner tube; (iv) the effect of pre-storage of the powder at a defined humidity (rather than being transferred directly from dry conditions) prior to transfer to the calorimeter cell; (v) the effect of changes in pressure during micronisation.

2.3. Variation in microcalorimetric method

In all the microcalorimetric experiments, the start is defined as the time when the cell has reached temperature equilibrium, and is lowered into the measuring position of the calorimeter. The data acquisition started at the onset of the calorimetric experiment for the spray dried material. However, for the micronised materials the data aquisition began at the time of sealing the cell. It follows that the curves for the micronised and spray dried materials differ slightly (by a time displacement of approx. 10–15 min). From a calorimetric point of view, however, the experiments are directly comparable.

Unless otherwise stated during the discussion, spray dried materials were investigated using a saturated salt solution in a glass tube of liquid surface area of 19.6×10^{-6} m^2. Micronised materials were investigated using a saturated salt solution reservoir with a surface area of approx. 10×10^{-6} m^2.

2.4. Powder X-ray diffraction

Samples were investigated before and after calorimetric runs using a Scintag XDS200 X-ray diffractometer, in order to compare crystallinity.

3. Results and discussion

3.1. Investigations of spray dried lactose

The spray dried material was investigated by X-ray diffraction, and was found to be completely amorphous lactose (Fig. 1).

A typical microcalorimetric trace is shown in Fig. 2, for which 20 mg of powder was loaded into the cell, and equilibrated with a saturated salt solution producing 85% RH (relative humidity). The trace has an initial small peak running for about 1 h, which can be attributed to a wetting stage. The wetting of the powder by the vapour is seen as a comparatively small peak as the microcalorimeter is detecting all processes which occur within the cell. As the water reservoir (saturated salt solution) and the powder are both housed within the cell there will be a response for vaporisation of the water which will be similar in magnitude, but opposite to the sorption enthalpy. It follows that vaporisation and sorption are almost equal and opposite and result in a small composite peak. This is a good example of experimental design, as if the water vapour were generated remote from the measuring site the wetting response would be very large (see, for example, Sheridan et al., 1993), and would potentially obscure the recrystallisation peak which is the area of interest in this study.

The second peak in Fig. 2 is a very large response at about 2 h. The shape of this peak is indicative of a very rapid cooperative process. The decay of the response could not be faster, within instrumental response time, and thus the peak corresponds to a process of high heat output, which has occurred over a very short period of time. If the sample is removed after this peak, and then subjected to X-ray diffraction analysis, it is seen to have recrystallised (Fig. 3). The physical form of the recrystallised powder is that it has fused into one lump of material, rather than existing as a free flowing powder. When this material was removed from the cell, if it was placed in a new cell with a saturated salt solution, no peak was observed. If the material was gently ground in a pestle and mortar, and placed in a new cell with a saturated salt solution, no response was observed.

The evidence overwhelmingly points to a recrystallisation process which occurs throughout the entire powder bed simultaneously. It is very surprising that such a level of cooperativity exists within the powder bed. It must be concluded that the water vapour is taken up by the powder at the surface, and then transported into the powder bed. Only when the entire bed is saturated does the recrystallisation occur, and when it happens it

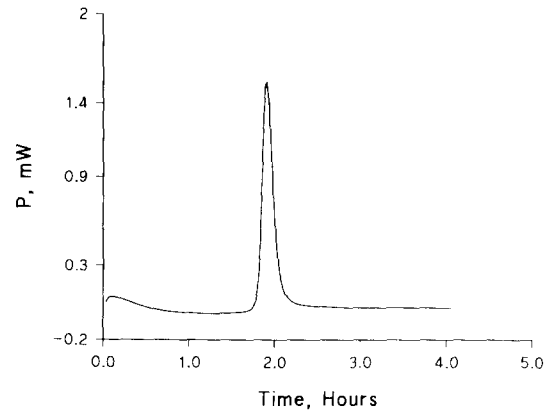

Fig. 2. Typical microcalorimetric output of power (P) as a function of time, for spray dried lactose (20 mg powder, 85% RH, 25°C).

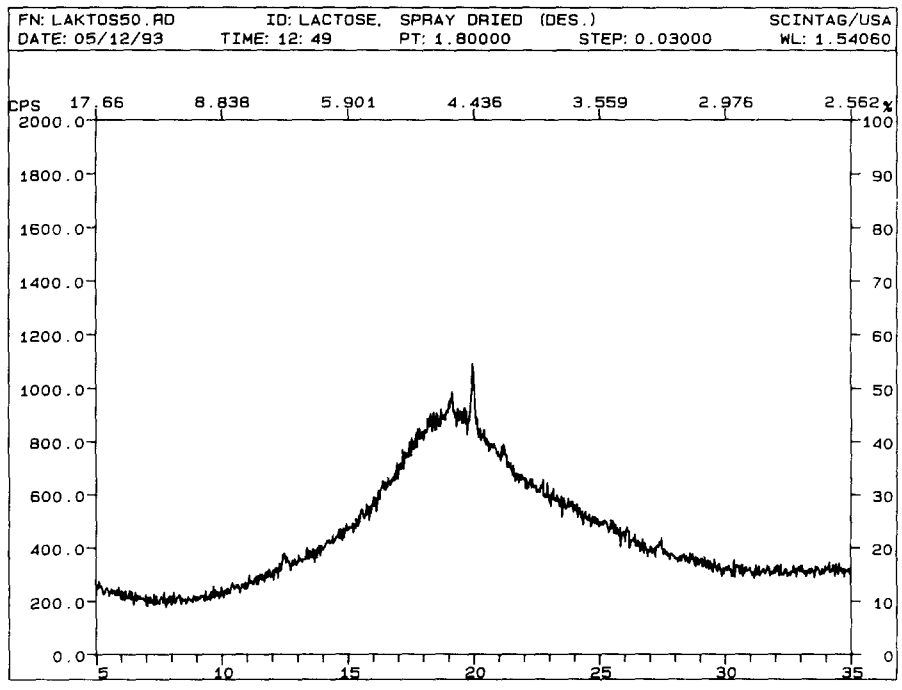

Fig. 1. Powder X-ray diffraction pattern for spray dried lactose.

occurs essentially simultaneously throughout the bed of powder. To investigate this observation further, different loadings of powder were placed in the cell.

The responses in Fig. 4 are for spray dried lactose placed in the cell at 85% RH, using 10, 30 and 50 mg of sample, larger quantities of sample resulted in responses which were too large to be recorded by the instrument, as the output is already on the lowest sensitivity setting. In Fig. 4, it can be seen that the effect of sample loading is to alter the time taken for the recrystallisation to occur, from just over 1 h for 10 mg, to about 6 h for 50 mg. If the areas under the curve are measured for each peak (which is equivalent to the total heat output for the process), and expressed as mJ/mg, then the result is almost identical for each loading (44.9, 46.9, 47.8 mJ/mg for the 10, 30 and 50 mg samples, respectively). It is probable that the results for the 30 and 50 mg samples are more accurate, as a larger area was measured, and the trace was well displaced from the wetting peak. The longer time required for

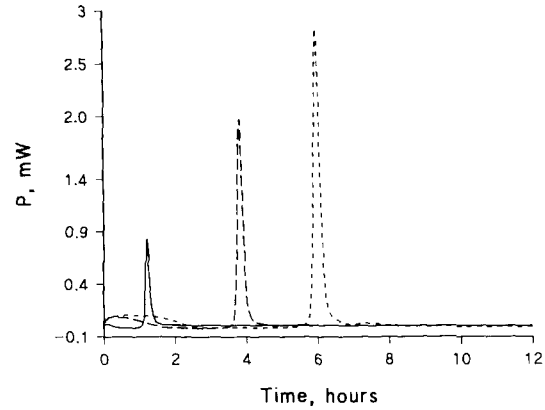

Fig. 4. Typical microcalorimetric outputs (power (P) as a function of time) for spray dried lactose, using powder loadings of 10 (———), 30 (— — —) and 50 (- - - - -) mg (85% RH, 25°C).

crystallisation to occur for increases in powder weight is in line with the view that the powder bed must be fully saturated before the instantaneous cooperative crystallisation occurs (which will take longer for increased weights of powder

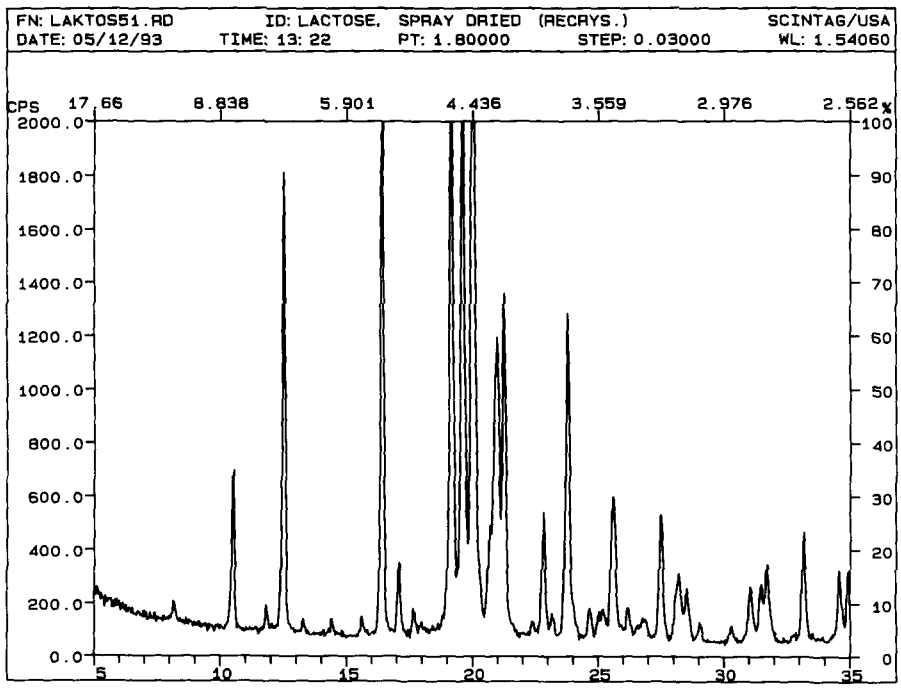

Fig. 3. Powder X-ray diffraction pattern for spray dried lactose, after a typical microcalorimetric run, sample removed immediately after the recrystallisation peak.

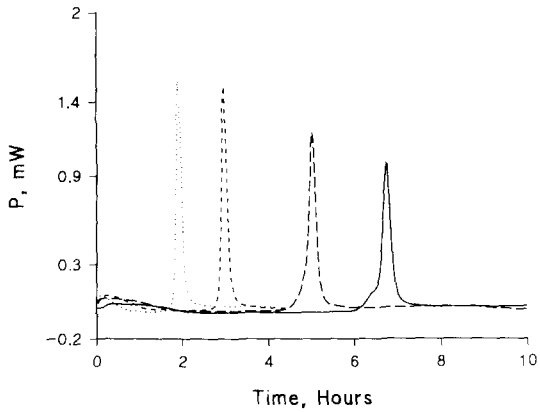

Fig. 5. Typical microcalorimetric outputs (power (P) as a function of time) for spray dried lactose equilibrated at 85 (· · · · · ·), 75 (- - - - - -), 65 (— — —) or 53% (———) RH (20 mg powder, 25°C).

beds). At this stage the significance of this finding to bulk material (where the powder bed may be many kilos) has not been investigated, however, the batch size may be expected to relate to the time required before recrystallisation occurs.

If it is accepted that the delay in onset of crystallisation for larger loadings of powder is due to the delay in saturating the powder bed, it is probable that the lag period will be related to both the humidity of the air, and the rate of supply of the water vapour to the air (to replace that which has been sorbed by the powder).

The effect of changing the RH of the air in the cell is demonstrated in Fig. 5, where sample weight is maintained at 20 mg, and the RH is varied (85, 75, 65, and 53% RH). The recrystallisation peaks are still always rapid, demonstrating the same cooperative process, but are delayed by approx. 2, 3, 5 and 7 h at the respective decreasing humidities. If the areas under the curve are calculated in each case, they equal 46.0, 46.8, 53.0 and 50.3 mJ/mg (for 85, 75, 65 and 53% RH, respectively). The similarity between these values, and those for different powder loadings indicates that the crystallisation process is identical in each

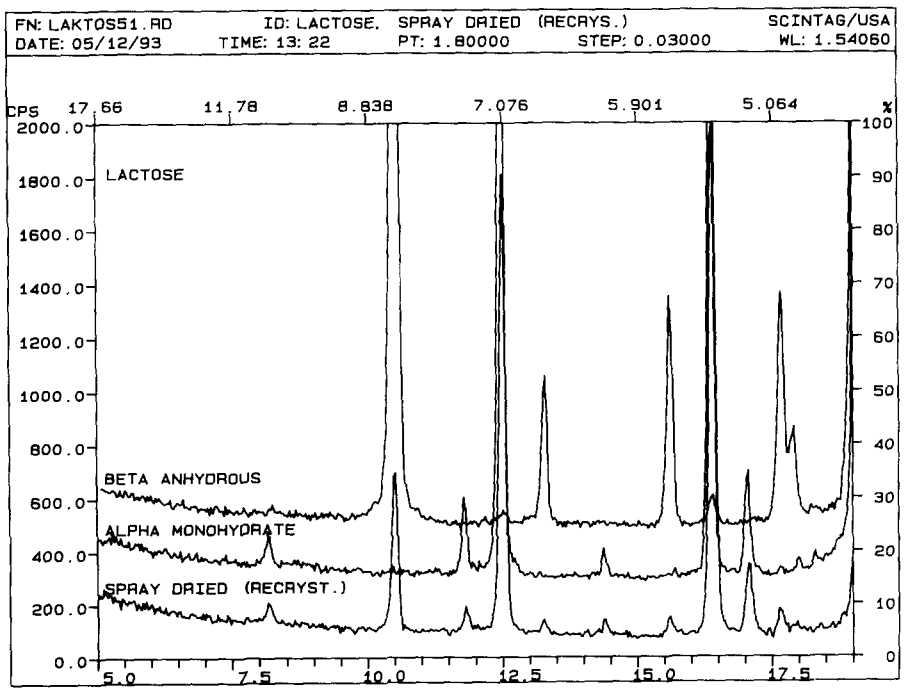

Fig. 6. Powder X-ray diffraction patterns for α-lactose monohydrate, β-lactose (anhydrous), and the spray dried sample removed from the microcalorimeter immediately after the recrystallisation peak.

case. There is a slight broadening of the recrystallisation peaks as the humidity is decreased, which may reflect a finite time for the final water sorption to occur during the crystallisation process. Within the time frame of an overnight experiment (up to 20 h), there were no recrystallisation peaks observed at humidities of 47% or below.

Experiments were undertaken to investigate the effect of the surface area of the saturated salt solution, and the powder bed. If the saturated salt solution was added in two tubes (rather than one, thus doubling the surface area) the recrystallisation occurred more rapidly (not shown). If the powder was placed in the two tubes, and the saturated salt solution was placed in the cell, the recrystallisation was significantly delayed (by almost 2 h from the standard method, when using 20 mg of powder). It can be concluded that the delay in observing a recrystallisation peak is due to both the available surface area of the saturated salt solution and the powder bed (if both are large the delay is short, if either is reduced, the delay is increased).

The recrystallisation process for spray dried lactose was found to produce a mixture of the α- and β-lactose (Fig. 6). Comparison with the X-ray diffraction peaks for pure α- and β-lactose allows a calculation of approximate proportions of the two in the recrystallised sample, which is about 15% β. If the sample is retained in the microcalorimeter after the recrystallisation peak, the β-lactose will transform to α-lactose monohydrate. Angberg et al. (1991a,b, 1992) have shown that this process can be followed calorimetrically. An enlargement of the scale after the main recrystallisation peak shows that the mutarotation process can be seen to occur (Fig. 7). At this stage, no attempt at quantification has been made, but it is clear that it is possible to estimate the proportions of α- and β-lactose in the recrystallised material from the size and shape of the subsequent transition peaks.

3.2. Micronised material

The micronised samples were of lower amorphous content than the spray dried sample. In an attempt to quantify the quantity of amorphous material present, samples were prepared with mixtures of totally amorphous, and totally crystalline material, such that the amorphous content was known. Fig. 8 shows data for such mixtures with different amounts of amorphous material. The traces represent samples which have been estimated to have 0, 24.7 and 48.8% amorphous material. In Fig. 8, the sample weight was similar in each case (39 mg), and the relative humidity was 75%. The higher the content of amorphous

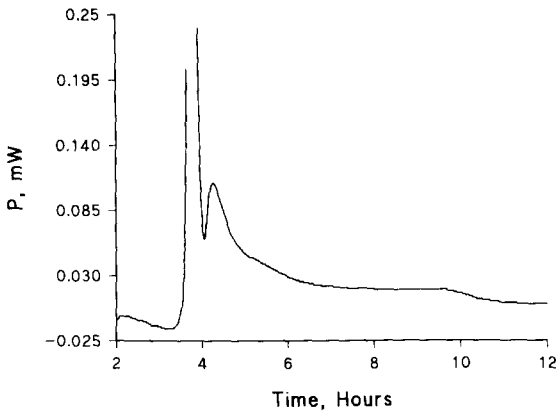

Fig. 7. Microcalorimetric output shown with an enlarged scale, revealing mutarotation of β- to α-lactose, following the recrystallisation peak (from 20 mg of spray dried lactose, recrystallised in the microcalorimeter using 75% RH vapour).

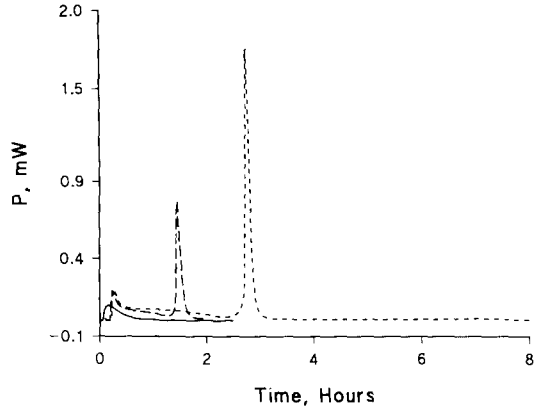

Fig. 8. Typical microcalorimetric outputs for mixtures of amorphous and crystalline lactose (39 mg, 75% RH, 25°C): ——— 0, — — — 24.7 and - - - - - - 48.8% amorphous content.

material the longer the delay before recrystallisation. The differences in magnitude for the response (area under the curve), are directly proportional to the degree of crystallinity. The degree of crystallinity for any sample can be calculated according to the general equation:

% amorphous material in sample

$$= 100 \times (Q - \text{blank})/(Q_a) \quad (1)$$

where Q is the heat output for the test sample, and Q_a denotes the heat output for a totally amorphous sample (assuming that the same RH is used, and that the loading of powder is identical, or normalised).

The blank response in Eq. 1 relates to the output obtained by loading the cell into the calorimeter. In order to obtain a quantitative value for the degree of crystallinity of a sample, this loading process must be standardised. The variables which must be considered are (i) the temperature differential between the outside environment and the calorimeter, before loading into the equilibration position, and (ii) the length of time at the equilibration point, before lowering into the measuring site (assuming that the RH, the dimensions of the surface area of the hydrostat, the surface area of the powder and the powder loading are standardised). The greater the temperature differential between ambient and the calorimeter, the longer the time needed at the equilibration point. As materials with low amorphous contents will recrystallise rapidly, it is essential to minimise the equilibration time. If the time at the equilibration stage is held constant at 5 min, then the calorimetric output for the loading of a cell containing totally crystalline material can be evaluated. The data in Fig. 9 show the relationship between room temperature (ambient) and the temperature of the microcalorimeter (25°C) on the measured output on lowering the cell into the measuring site. It can be seen that it is vital to control ambient conditions if reproducibility is to be achieved. If the blank response is to be zero, the extrapolation would suggest that pre-equilibration at 27.5°C would be most appropriate. There is a parallel line for 'old' cells, which are those in which the

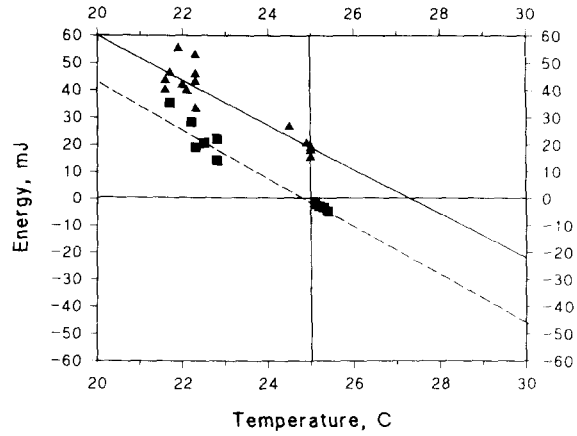

Fig. 9. The effect of the ambient – microcalorimeter temperature differential on the blank response for newly filled cells (triangles), and previously equilibrated (squares) cells (where the cells contain a tube containing the saturated salt solution (85% RH), and a standard weight of totally crystalline lactose (150 mg), 25°C).

internal environment (RH) has had time to come to equilibrium prior to the experiment. These reused cells are not an appropriate model by which to determine the blank response for the true experimental conditions.

The data in Fig. 10 show that a linear relationship exists between the % amorphous content and the heat output (J/g) obtained during the crystallisation process. This line intercepts the y-axis at the point equal to the blank response. As, by definition, the blank response can readily

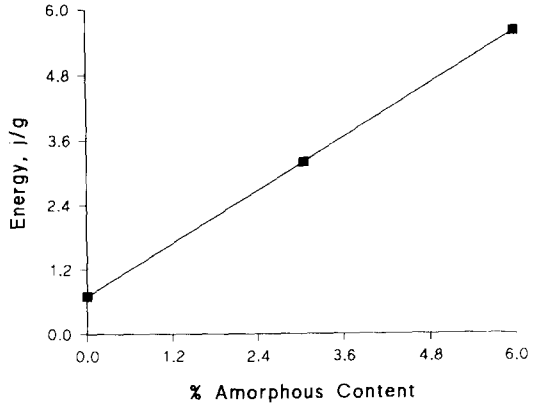

Fig. 10. Relationship between the % amorphous content and the microcalorimetric heat output.

be measured, it follows that any degree of crystallinity can be measured. All that is necessary is to produce the relationship equivalent to that in Fig. 10, which can be by reference to X-ray diffraction data for highly amorphous samples. The advantage of the microcalorimeter is that the resolution is much greater than that obtainable for X-ray diffraction experiments. For X-ray diffraction, a lower cut off in detection may be at about 3% amorphous material, but the calorimetric data can routinely define the crystallinity down to at least 1% amorphous material (below which the response may become similar to the blank).

There are enormous advantages in being able to define the degree of crystallinity in these lower regions. The low amorphous content is likely to exist at the surface of the particles, and it is the surface which will be involved in interactions (and indeed reactions), so even though a small % of the bulk is amorphous, a large % of the surface may be affected, and thus the significance is potentially great.

As was noted in section 1, the processing history of a powder will tend to affect its degree of crystallinity (and hence its cohesive and adhesive interaction potential). The data in Fig. 11 are recrystallisation exotherms obtained from samples of lactose from the same batch, which have been milled at either 7, 6, 5 or 4 bar in the fluid energy mill. As with all the micronised samples,

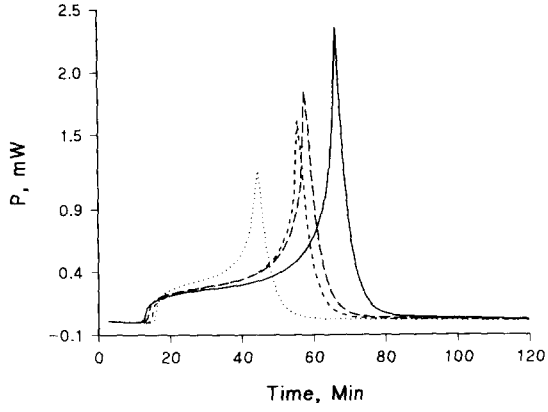

Fig. 11. Calorimetric output for samples of lactose which have been milled under different pressures in the fluid energy mill. (———) 7 bar; (— — —) 6 bar; (- - - - - -) 5 bar; (· · · · · ·) 4 bar.

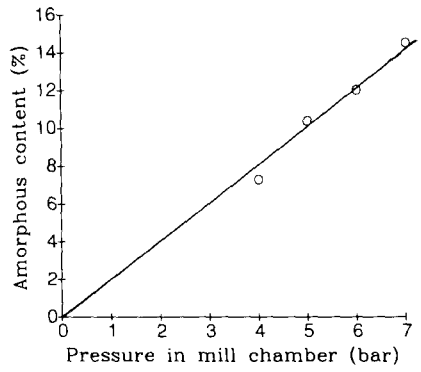

Fig. 12. The relationship between the pressure used during fluid energy milling, and the amorphous content of the product.

the trace consists of a very small peak (about 20 μW) after about 5 min, which is due to air disturbance caused by lowering the cell into the equilibration position of the calorimeter, then a rise to a second peak at about 15 min when the cell is lowered into the measuring position. This second peak exhibits a quasi-plateau which is due to water sorption, which continues until the major recrystallisation peak is seen (which is sharp and rapid). The contributions from air disturbances, friction and temperature imbalance (the blank effect) decline rapidly and are insignificant after approx. 5 min. The time to peak (where the meaning of the word peak is crystallisation peak), the peak height, and the area under the curve all increase as the air pressure is increased, demonstrating that there is a direct correlation between air pressure and the amount of amorphous material which is produced. It is straightforward to quantify the amorphous content, by use of Eq. 1. The amorphous content of the materials was determined to be 14.5, 12.0, 10.4 and 7.3% for the samples milled at 7, 6, 5 or 4 bar. The relationship between pressure and the amorphous nature of the product is shown in Fig. 12, there is a linear relationship ($r^2 = 0.994$) between this processing parameter and the amorphous nature of the product. The existence of this simple relationship (for this material) notionally will allow a prediction of the nature of the product from the conditions of milling. The effect of milling time has not been investigated at this stage.

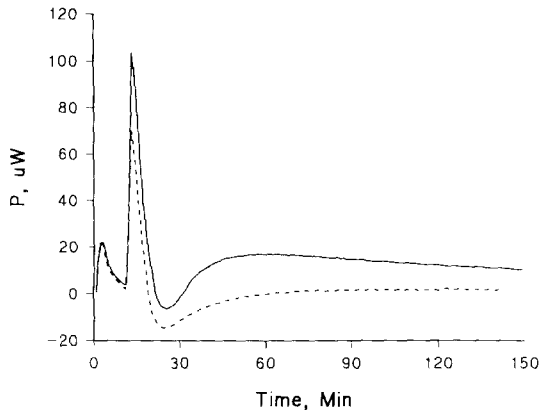

Fig. 13. Calorimetric output for two samples of micronised lactose, which had been stored for 24 h at either 50 (———) or 75% (— — —) RH, prior to sealing into the cell at 75% RH and lowering into the calorimeter.

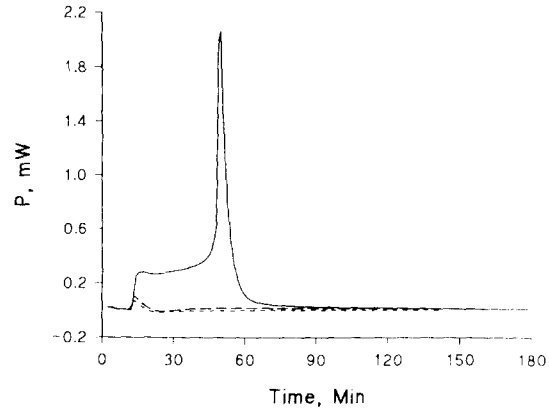

Fig. 14. Data from Fig. 13 reproduced on identical scale to the recrystallisation response. The samples shown here are the same batch stored dry (———), and stored at 50 (— · — · —) or 75% (- - - - - -) RH prior to loading into the calorimeter at 75% RH.

The traces in Fig. 13 reveal the effect of pre-storing the micronised lactose at different humidities prior to adding it to the calorimeter. The samples stored at 50 and 75% RH both showed the standard initial peak for addition to the equilibrium position (approx. 20 μW), followed by a peak which will correspond to the disruption due to lowering into the measuring site, and temperature out of balance factors, which were rapid and which started on an exponential decay (peak height 50–100 μW). The samples behaved in an identical manner up to this point (irrespective of whether they had been exposed to 50 or 75% RH environments), differing only slightly in peak height due to differences in sample load weight. However, subsequent to the sample introduction peak (which finished after about 30 min), there was a further response for the samples which had been stored at 50% RH, which was not seem for samples which were stored at 75% RH. The origin of this long response can only be speculated, but clearly demonstrates that the pre-treatment at 75 and 50% RH results in different physical states of lactose. It can be seen from Fig. 14, by comparison of the responses from samples which were added to the calorimeter dry with those from the same batch which were pre-exposed to higher humidities, that the storage at 50 and at 75% RH has resulted in complete recrystallisation of the amorphous region (prior to loading into the calorimeter).

Experiments were also performed in which micronised lactose samples were pre-treated by storage at 40% RH for different periods of time, prior to calorimetric investigation. After storage, the samples were immediately transferred into

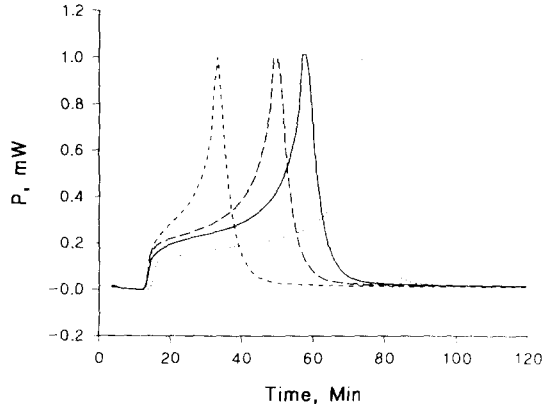

Fig. 15. Microcalorimetric traces for samples which had been pre-stored at 40% RH prior to adding to the cell of the calorimeter at 75% RH. Exposure times were (- - - - - -) 115, (— — —) 58, (———) 29, and (· · · · · ·) 0 min. Sample weights varied in the range 163–167 mg. Calculated amorphous content was 10.6% in each case.

the calorimetric cells at 75% RH. The calorimetric output is shown in Fig. 15. The duration of the quasi-plateau region is reduced following extended pre-treatment. The size of the recrystallisation peak is, however, unaffected. Since storage of the micronised lactose at 40% RH results in some water uptake, these experiments clearly demonstrate that water sorption occurs during the quasi-plateau period.

4. Conclusion

Microcalorimetry offers an extremely valuable approach to the study of recrystallisation and crystal transition processes in the solid state. These experiments are undertaken isothermally at ambient conditions, unlike other techniques (such as differential scanning calorimetry) which utilise elevated temperature. The microcalorimetric observations are made in 'real-time' and give kinetic information concerning the recrystallisation of the material. It is possible to quantitate the amorphous material in the sample to a resolution of 1% amorphous content, or less. We are not aware of any other analytical technique which cam match this level of resolution.

It is possible to utilise the calorimetric approach to quantify the effects of processing on the degree of crystallinity of materials. It has long been noted that such processing effects are important in controlling the behaviour of powders, but it has remained difficult to adequately quantify surface adaptation, until now.

The effect of pre-storage at different humidities can be used to provide fundamental information about the properties of lactose.

This demonstration of the application of microcalorimetry opens up an enormous potential for research in powder properties.

5. Acknowledgement

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