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The influence of additives on the recrystallisation of amorphous spray dried lactose

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Abstract

Amorphous material in crystals can constitute reactive 'hot spots', which can be centres for chemical degradation or physical transitions, leading to product instability. Problems have been encountered in studying small amounts of amorphous content for powdered systems, due to poor sensitivity of the majority of techniques. Isothermal microcalorimetry has been shown to have good resolution for cases where the amorphous content of the powder can be made to recrystallise in the instrument. In this study amorphous lactose has been investigated, being recrystallised by exposure to air at 75% RH. The lactose has been studied in two layers separated by varying amounts of glass beads (inert carrier), magnesium stearate (hydrophobic excipient), or microcrystalline cellulose (hygroscopic excipient). Significant differences were observed in the time needed to cause recrystallisation when amorphous material was separated by these different additives. Glass beads had only a small effect, but magnesium stearate caused an increased lag time prior to the recrystallisation event. In both these cases the lactose all recrystallised at one time, even though it was divided into two physically separated regions. A layer of microcrystalline cellulose between two layers of amorphous lactose resulted in a long lag time prior to recrystallisation, as it removed considerable amounts of water vapour from the atmosphere, thus preventing saturation of the lactose. By varying the weight of amorphous lactose in the upper and lower layers, and comparing data with the results obtained for homogeneous mixtures, it was possible to postulate a mechanism for the cooperative recrystallisation process. In essence, the water vapour is absorbed into the upper layers of the sample, and then transferred away yielding a concentration gradient through the entire sample in the cell. As the water content gradually increases in the lower layers, the rate of water absorption can become more rapid than the rate at which water is transferred away from the surface. After this time the surface saturates, starts to recrystallise thus liberating a great excess of water vapour, which is sufficient to cause the lower layers of powder to become saturated and also to recrystallise.

Keywords: Amorphous material; Recrystallization; Lactose; Microcalorimetry

1. Introduction

In recent publications the importance of amorphous regions in crystalline solids has been discussed (Ahlneck and Zografi, 1990; Briggner et al., 1994; Saleki-Gerhardt et al., 1994; Sebhatu et al., 1994). It has been noted that the presence of small amounts of amorphous material can affect the interaction between the powder and other components of a formulation, and therefore can

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influence the physical and chemical stability of a product. Many examples of batch-to-batch, and supplier-to-supplier, variability stem from changes in the degree of crystallinity of powders.

We have demonstrated the value of using isothermal microcalorimetry in crystallinity studies (Briggner et al., 1994; Buckton et al., 1995a) and have shown the remarkable sensitivity advantage of this technique. For example, isothermal microcalorimetry is capable of detecting as little as 0.5% amorphous material in a solid, compared to a lower detection cut off of about 10% for other techniques, such as X-ray diffraction. The microcalorimetric approach used involves exposing the powder to a vapour which will result in the recrystallisation of any amorphous material in the sample. The trigger for the recrystallisation is the absorption of the vapour into the amorphous regions, the vapour then acts as a plasticiser until the glass transition temperature of the amorphous material falls to the temperature of the experiment. At this point the material has sufficient freedom of motion to recrystallise.

As microcalorimetry can be used to follow the recrystallisation process in real time, the data that are obtained are of fundamental importance in the study of recrystallisation events. The data available so far demonstrate that the amorphous material in a sample all recrystallises at the same time, rather than being a gradual process. This cooperativity is surprising and indicates that the water is transferred within the powder mass rather than remaining in one region to cause localised saturation. The purpose of this study is to investigate this cooperative recrystallisation process, especially with respect to the influence of other excipients.

2. Method

Spray dried lactose (known to be amorphous, Briggner et al., 1994) was used as the test material. The amorphous lactose was recrystallised in the microcalorimeter by exposing the material to an atmosphere of 75% RH. This was achieved by adding the powder to a glass cell, then adding a small tube containing a saturated salt solution. The ampoule was then sealed and lowered into the microcalorimeter measuring site. The temperature equilibration was achieved in two stages, firstly by pre-equilibrating the powder, glass cell and tube of saturated salt solution (separately) at slightly over 25° C. Secondly, the rapidly assembled sealed cell was lowered into an equilibration position in the calorimeter (at 25° C) for 10 min

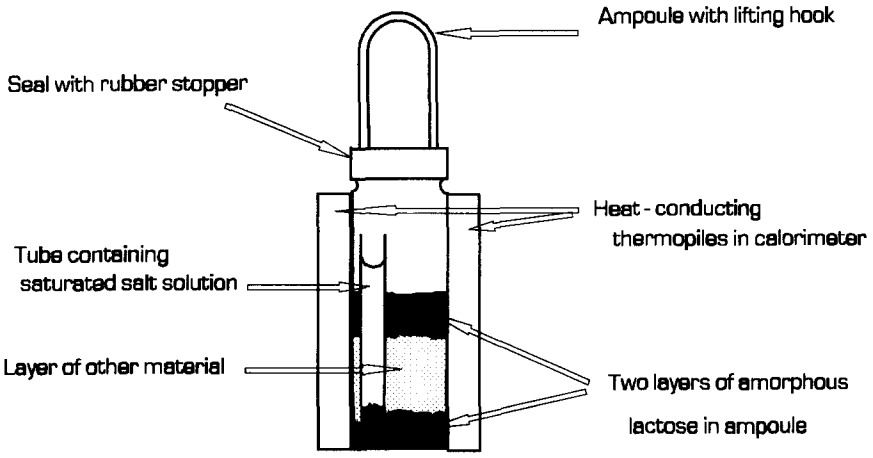

Fig. 1. Diagrammatic representation of the experimental set up, showing the glass ampoule in the measuring site of the calorimeter, containing a tube with the saturated salt solution (to control humidity), and two layers of lactose separated by another material (either glass beads, magnesium stearate or Avicel in this study).

prior to lowering into the measuring site. This procedure resulted in minimal baseline disruption.

The experiments with microcrystalline cellulose (Avicel PH101) were undertaken by accurately weighing half the spray dried lactose (13–14 mg) into the glass cell, covering this with either 170 or 250 mg of Avicel, then adding the second half of the spray dried lactose. Thus, two regions of spray dried lactose were separated by a thick layer of Avicel. Subsequently, the weight of lactose in the lower and upper layers was varied. The same process was used for magnesium stearate, in this case separating the 35 mg lactose with either 93 or 122 mg of lubricant. Finally, two layers of lactose were separated by glass beads (Ballotini, Jencons no. 18, median diameter 66 μm) as an inert barrier. A representation of the experimental method in shown in Fig. 1.

All experiments were repeated at least twice, and reproducibility was extremely good in terms of time of onset and the shape of the response obtained. See the footnote to section 3 for the one exception to this.

3. Results

The use of a sealed ampoule in which the water vapour is both generated and then used (sorbed) is an important experimental condition as the heat change associated with the wetting of the powders is matched by an approximately equal and opposite vaporisation from the saturated salt solution, such that it does not mask the response for the recrystallisation event.

The recrystallisation of the lactose is known to be due to water vapour absorption, and is known to occur when the entire sample is saturated with the water vapour. This is demonstrated in Fig. 2, where the typical sharp cooperative peak is seen when the entire 35 mg of amorphous lactose recrystallises at one time (immediately after total bed saturation by the vapour, in this case after about 5 h). Also shown in Fig. 2 is the response for the recrystallisation of lactose which had been divided into two equal sections, one in the bottom of the cell, and the other on top of 1.145 g of glass beads such that there was a distance of about 0.5 cm between the two regions of lactose.

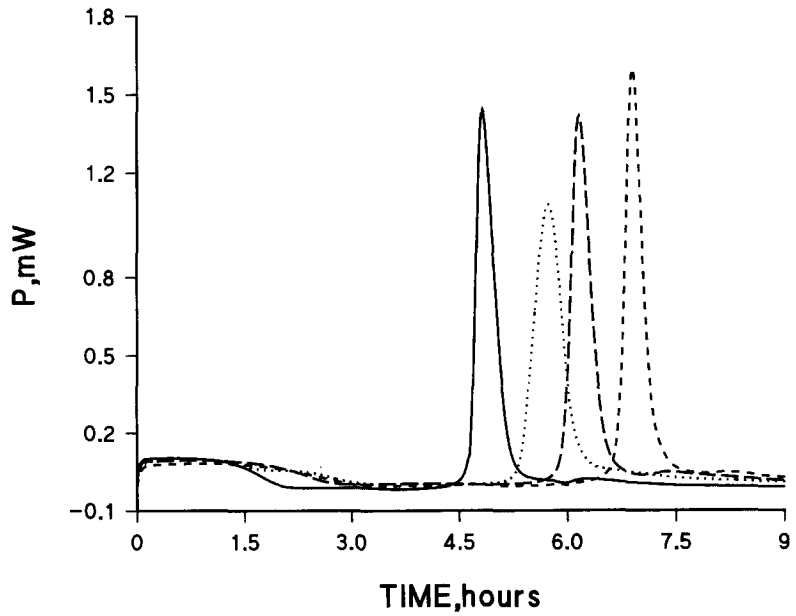

Fig. 2. Microcalorimetric output of power (rate of change of heat with time, P) as a function of time, showing responses for the recrystallisation of amorphous lactose (———), lactose separated into two equal parts by a layer of either 93.1 mg (— —) or 122.3 mg (- - -) of magnesium stearate or 1.14 g of glass beads (· · · ·).

As can be seen (Fig. 2) the response for the recrystallisation event was a single cooperative event, delayed only slightly from that seen when the lactose was present on its own. The peak height was slightly lower for the sample with the glass beads, but the area under the curve was indistinguishable from that of the lactose alone. The wider peak is indicative of a minor change in kinetics for the recrystallisation, with the process lasting slightly longer than for the sample which was not separated by glass beads.

The two other traces in Fig. 2 are for samples where the lactose has been divided into two equal parts, separated by a layer of magnesium stearate of 93.1 or 122.3 mg. It can be seen that the greater the loading of magnesium stearate the longer the lag time before recrystallisation. However, the recrystallisation event is of the familiar sharp isothermal shape, and essentially the same area under the curve in each case. It follows that the presence of a hydrophobic material between the two regions of lactose does not change the cooperativity of the process, with the entire lactose sample recrystallising at one time.

Consideration of the data in Fig. 2 allows some conclusions to be made about the recrystallisation process. The rate of recrystallisation will be influenced by the rate of supply of water vapour, the rate and extent of water absorption by the amorphous material, and the rate of desorption, or moisture transfer within the amorphous sample, which will deplete the local concentration of water in the amorphous region (Fig. 3). From the data in Fig. 2, it can be concluded that the water is either removed from the upper region of amorphous lactose, and transferred to the lower region, at such a rate that the upper region does not become saturated (until the entire system is saturated) (i.e., k_4 is greater than k_3 in Fig. 3), or the water has equal rate of access to the upper and lower levels of lactose in the cell. Given that the nature of the material that separates the two amorphous regions has an effect on kinetics (glass beads fastest, then a weight-related slowing due to magnesian stearate), it is reasonable to assume that it is not true that access to the upper and lower levels of lactose is achieved at an equal rate, thus it is probable that the nature of the

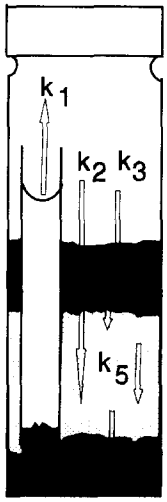

Fig. 3. Diagrammatic representation of the rate constants which control bed saturation with water vapour: k_1 = evaporation from saturated salt solution (may well be rate limiting for entire process, see Briggner et al. (1994) for further discussion); k_2 = transfer through pores in bed (may be rather small in relation to k_3 in the early stages, if the driving force for absorption is strong, but may increase as surface layer moves towards saturation); k_3 = absorption into surface layer of amorphous lactose; k_4 = desorption from surface layer of amorphous lactose; k_5 = transfer through powder bed (similar to k_2, except dealing with only one region; may be complicated by absorption into this powder as would be seen with microcrystalline cellulose); k_6 = absorption into lower layer (would equal k_3 if the concentration above each layer and the rate of supply of vapour were equal in both places). There would also be a desorption rate from the lower level, which would be expected to be small in relation to the absorption until equilibrium is approached.

recrystallisation event is that the rate of loss of water from the upper layer of lactose (due to desorption and transfer through the powder bed and/or pores) is faster than the rate of water arrival to the upper layer. This issue will be considered further in the discussion below.

The data presented in Fig. 4 are for experiments in which the lactose was separated by layers of Avicel. The difference between the lactose alone (single peak at approx. 4 h) and those where the two regions of lactose were separated is substantial, with recrystallisation occurring at between 6 and 9, and 9 and 12 h with the two loadings of Avicel. Furthermore, the samples with

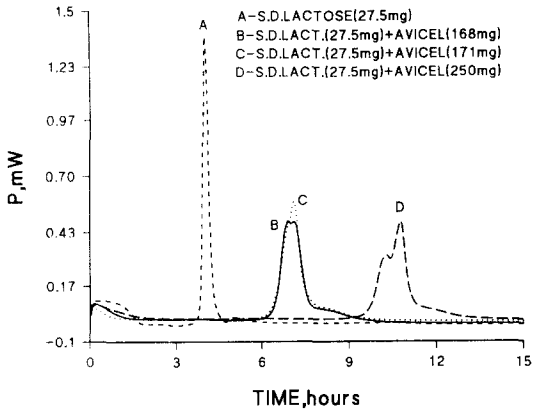

Fig. 4. Microcalorimetric output of power (rate of change of heat with time, P) as a function of time, showing responses for the recrystallisation of amorphous lactose, separated by different weights of Avicel. Avicel alone does not give a recrystallisation response (not shown).

added Avicel show two distinct peaks [1], which could relate to the two regions of lactose recrystallising at similar, but not identical times. The reason for the increased delay in recrystallisation in the presence of Avicel is that the microcrystalline cellulose is effectively acting as a desiccant, thus it takes significantly longer to saturate the powder bed, given that there is an upper limit on the rate of evaporation from a saturated salt solution with a set surface area.

Given that it is possible to see two different peaks for the recrystallisation of lactose when separated by Avicel (Fig. 4), it is interesting to investigate whether these are indeed due to the upper and lower layers, or whether they are just the kind of discontinuities that have been observed with slow recrystallisation of homogeneous samples of other materials (see, for example, salbutamol sulphate (Buckton et al., 1995b)). The data in Fig. 5 are for variations of the distribution of spray dried lactose either above or below a layer of 250 mg of Avicel. The first peak (onset at 9 h) in Fig. 5 is for a sample with a lower layer of 21.4 mg of spray dried lactose and an upper layer of 8.3 mg, whilst the response with an onset at approx. 15 h has a lower layer of 7.1 mg and an upper layer of 20.0 mg spray dried lactose. Both responses show multiple peaks, each with at least two and possible more events being observed. However, it is clear that the first response is essentially a small event followed by a large event, whilst the second is inverted (in proportion to the inversion in weights of lactose in the upper and lower layers). Also shown in Fig. 5 (trace C) is a response for a sample in which the lactose has been uniformly mixed with the Avicel. For this mixture, unlike the results for the situation where the two regions of lactose are separated, the response was a single recrystallisation event (the protracted tail is probably a consequence of β-α mutarotation after recrystallisation, see Briggner et al., 1994). It seems reasonable, therefore, to suggest that the recrystallisation of the two layers is occurring at slightly different times, with the upper layer recrystallising just before the lower layer.

From Fig. 5 it can be seen that the sample with the small amorphous layer on top was the first to recrystallise, followed by the homogeneous mixture, then the sample with the large amorphous layer on top. The reason for these observations may well be that the kinetics of water distribution change depending upon where the water is first absorbed, which will depend upon the relative magnitude of the different rate constants in Fig. 3. For example, for the sample which has the small amorphous layer on top, the sequence could well be that this upper layer saturates (whilst water is also being absorbed by the Avicel and the lower layer of amorphous lactose), and then recrystallises with a subsequent expulsion of water. The water vapour which is expelled will give a rapid increase in the rate of supply of water vapour in the surrounding air and as such will allow the lower layer of lactose to become saturated and recrystallise very soon after the recrystallisation process begins in the upper layer. Con-

[1] There was some variability in the magnitude of the two peaks for samples separated by approx. 170 mg of Avicel. To demonstrate this two different responses are included in Fig. 4. In other respects reproducibility was extremely good for replicate determinations, in terms of time of onset and shape of the transitions. This reproducibility cannot be shown readily in the figures.

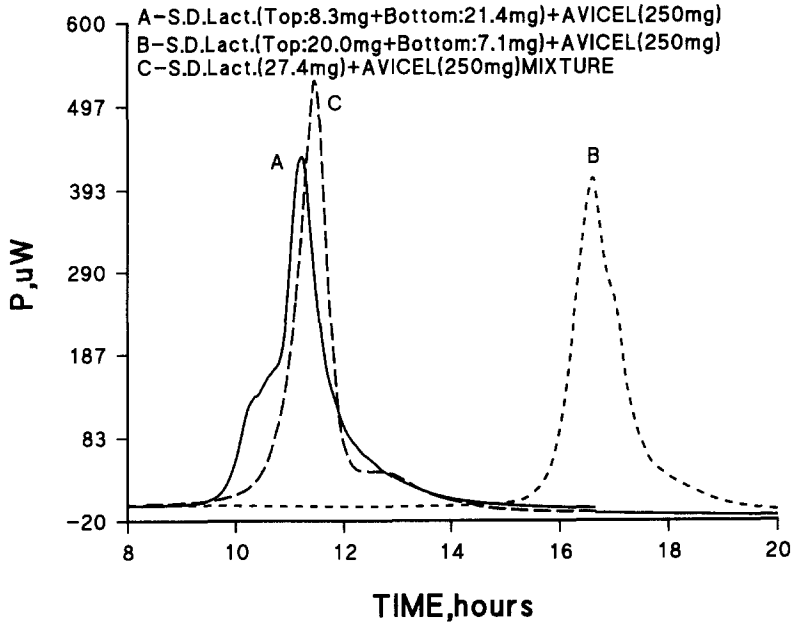

Fig. 5. Microcalorimetric output of power as a function of time for the recrystallisation of amorphous lactose in the presence of 250 mg Avicel PH101. (A) Lower layer of 21.4 mg lactose/Avicel/upper layer 8.3 mg lactose; (B) lower layer of 7.1 mg lactose/Avicel/upper layer of 20.0 mg lactose; (C) homogeneous mixture of 27 mg lactose and 250 mg Avicel.

versely, the sample which has a large amorphous layer on top will take longer to saturate this top layer and as such the sample will take longer to recrystallise (as it will take longer to saturate, i.e., in Fig. 3, k_3 will stay larger for a long time at the expense of k_2 and possibly k_4 and therefore also k_5 and k_6), although when the top layer does recrystallise it will once again trigger the recrystallisation in the lower layer. It follows that the cooperative mechanism for recrystallisation in these ampoules is probably due to rapid availability of water vapour as a consequence of the upper layer crystallising, which then causes the lower layers of sample to recrystallise almost immediately. This means that physically separated samples still give the impression of cooperativity even though there is no physical contact between the powder.

4. Conclusion

From the combined data presented here it is possible to summarise the discussion above to give a working hypothesis for the mechanism for the cooperative recrystallisation process. It is probable that there is a concentration gradient of absorbed water through the sample, with highest amounts of absorbed water at the powder surface and the lowest amounts at the lower levels of powder. The concentration gradient is formed by absorption of water at the surface, and via direct access through pores, however, the equilibration of water in the powder bed is faster than the rate of supply of water vapour, such that the surface does not saturate immediately. After time, the lower layers have sufficiently high water content to reduce the driving force for movement of water such that the rate of absorption in the surface layers may exceed the rate of transfer away from the surface layers. At this time the surface saturates (but the entire sample need not saturate) and starts to recrystallise. The expulsion of water from the surface gives a rapid supply of water vapour which immediately saturates the (already nearly saturated) layers of powder below, which then also recrystallise.

This study provides further fundamental infor-

mation on the transmission of water through powder beds, and on the mechanism of recrystallisation within powder beds. The data also have direct importance with respect to products which include partially amorphous material (either by design or by accident) and different excipients.

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