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The influence of heating/drying on the crystallisation of amorphous lactose after structural collapse

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Abstract

This study was designed to investigate the influence of collapse of amorphous lactose on its subsequent behaviour during drying, or other processes which cause increases in the temperature of the material. Amorphous lactose was prepared by spray drying from aqueous solution. The solid was dried and then exposed to 50% RH for various times in order to induce different amounts of collapse in the amorphous structure. All the samples remained amorphous for the range of exposure times used. During heating in a differential scanning calorimeter, the non-collapsed material crystallised at ca. 180°C to give mostly α-lactose, with some β-lactose present. The collapsed lactose crystallised at ca. 70°C and yielded mostly β-lactose, with some α-lactose monohydrate present. It can be concluded that the collapsed structure will crystallise on drying at lower temperatures than the non-collapsed lactose. The non-collapsed material rapidly loses its sorbed water (this would occur during the early stages of drying), whilst the collapsed lactose loses its water suddenly during crystallisation. Thermogravimetric analysis revealed (generally) three distinct water loss peaks for the collapsed structure, two of which were believed to be due to crystallisation occurring and the final one being the loss of water of crystallisation. The sudden loss of water from the collapsed material will make a substantial contribution to the free water content of a formulation and as such could cause confusion during drying processes. Material which was partially collapsed behaved in an intermediate manner between non-collapsed and totally collapsed samples. © 1997 Elsevier Science B.V.

Keywords: Drying; Lactose; Amorphous; Collapse; Isothermal microcalorimetry; Differential scanning calorimetry; Thermogravimetric analysis; Crystallisation; Water

1. Introduction

It is now acknowledged that the presence of any amorphous material in pharmaceutical formulations can have important consequences.

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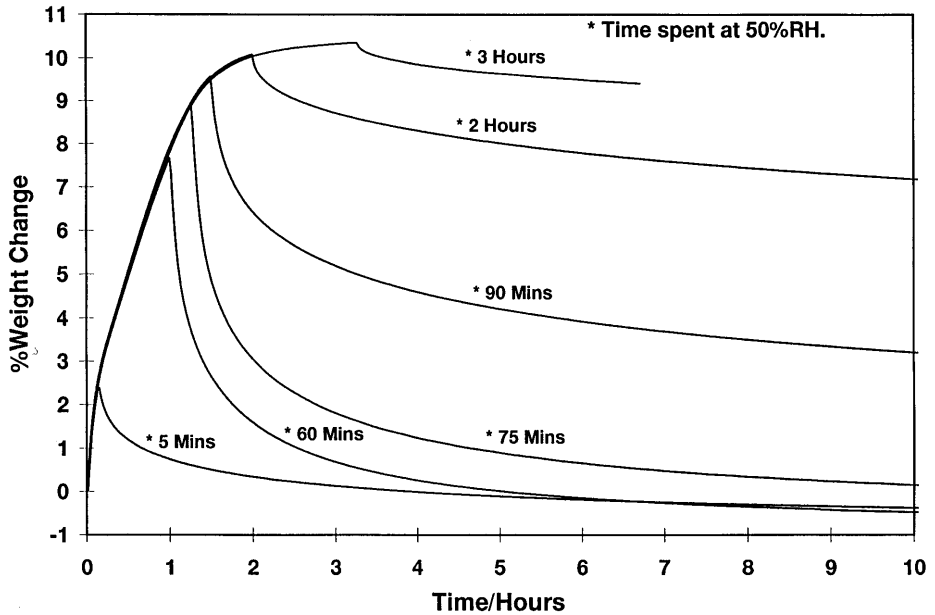

Fig. 1. Water uptake and loss for amorphous lactose. 0–4 h at 0% RH, then various times at 50% RH, followed by return to 0% RH. It can be seen that short (up to 60 min) exposure times to 50% RH result in full and rapid desorption of water (no collapse in structure). Intermediate exposure times (up to 2 h) to 50% RH result in some rapid desorption followed by some slow desorption, due to partial collapse of the structure. Long exposure times (3 h) results in complete collapse with only slow desorption, due to slow diffusion through the collapsed amorphous structure (Reproduced from Buckton and Darcy, 1996).

Amorphous forms of many drugs and excipients can be produced during processing and can revert to the thermodynamically stable crystalline form on storage. The amorphous form will have different physical properties, and as such will interact with other phases (i.e. other formulation components, whether these are powders or liquids) in a different manner to that of the crystalline form. This can be important in many products, for example in certain dry powder inhalations where micronised drug must adsorb reversibly to a lactose carrier. An additional complication in systems which contain amorphous material is that the amorphous 'structure' can change in different conditions (for example, it may collapse when exposed to humid air).

It has been recognised for many years that amorphous materials (if present in particulate, rather than thin film, form) can collapse when above their glass transition temperature, due to the inability of the rubbery material to support its own weight under gravity (structural transitions in carbohydrates have been reviewed by Flink (1983)). Recently, Buckton and Darcy (1996) showed that amorphous lactose exhibited varying degrees of structural collapse depending upon the time for which it was held at 50% RH (Fig. 1). It was noted (Buckton and Darcy, 1996) that water was rapidly absorbed and desorbed by the structure prior to collapse, but water sorption to and from the collapsed structure was slow and controlled by diffusion in the solid, rather than just by the external relative humidity (RH). It is reasonable to assume that the pre-collapsed and collapsed structures will behave differently in pharmaceutical products and further that the large quantities of water associated with the collapsed material may have a detrimental effect on products in which such material is included.

Drying of pharmaceutical products is a critical step in many manufacturing processes, such that a limit of water content is often set. The presence of water in amorphous materials is of importance for two reasons. The first has been addressed previ-

ously in the pharmaceutical literature (e.g. Ahlneck and Zografi, 1990) and relates to amplification. The concept of amplification is that a sample which contains 0.5% amorphous material which is found to contain 0.5% associated water will in reality have most of that water absorbed in the amorphous region (See Buckton and Darcy (1995) for gravimetric data to support this). Thus an apparently small water content if averaged over the entire sample mass, will in reality be a vast water content when localised in a small amorphous region and as such will influence the physical and chemical stability of that region. The second issue is one that we have not seen addressed in the literature and relates to the retention of water in amorphous regions of samples. If water is absorbed in a non-collapsed amorphous structure it will desorb rapidly and be easily dried. If however, the water is in a collapsed region this will not be so (see Fig. 1). It is known (e.g. Skrabanja et al., 1994) that on drying, water which is held in a collapsed amorphous region is only removed by slow diffusion through that region, and not by sublimation. Although there is no published evidence to our knowledge, we are aware of problems which arise during drying of products which contain partially amorphous lactose, whereby the 'free' water content (i.e. that which is measured by 'loss on drying' experiments at temperatures below 100°C) in formulations can drop and then suddenly rise again. The work presented here is an attempt to demonstrate how water can desorb from collapsed amorphous structures during heating/drying and thus give large fluctuations in the free[1] water in the product.

In this study the collapse of amorphous lactose and the nature of water retention within that structure are examined in detail. The data presented here are for a totally amorphous sample, but the trends which are observed are believed to be applicable to samples which contain a small amount of processing induced disorder.

[1] In this context, free water is being used to describe water which is available to interact between powder surfaces to produce a moist powder mass. Water which is held within a collapsed amorphous structure is not readily desorbed and thus not freely available to the powder mass.

2. Materials and methods

Spray dried lactose was prepared using a Buchi 190 with a feed containing 15 g of lactose in 100 ml of water. The processing conditions were (feed rate 2 ml/min, inlet and outlet temperature, 120°C and 75°C, respectively). The amorphous lactose was desiccated prior to study. The amorphous material gave the same area under the curve for crystallisation in a sealed, humidity controlled, ampoule in an isothermal microcalorimeter (Thermometric AB) that was reported previously (Briggner et al., 1994) giving confidence that the material was indeed amorphous.

Amorphous lactose samples (20 mg) were loaded in a humidity and temperature controlled (25°C) microbalance (Dynamic Vapour Sorption (DVS), Surface Measurement Systems). They were exposed to 0% RH for 4 h, which allowed desorption of absorbed water. The RH was then changed to 50% for a defined period of time and the water uptake noted. Following such uptake the samples were removed and rapidly transferred for thermal analysis.

Further analysis was by differential scanning calorimetry (Perkin Elmer DSC7) using ca. 3 mg in non-hermetically sealed pans and scanning from 25 to 250°C at 10°C/min under an atmosphere of nitrogen. Thermogravimetric analysis (TA Instruments) was undertaken using the same conditions of scan rate as for DSC and also with a ca. 3 mg sample load. Isothermal microcalorimetry (Thermal Activity Monitor, Thermometric) was used by sealing the remainder of the sample (ca. 14 mg) in an ampoule with a saturated salt solution to produce a defined relative humidity at 25°C, and measuring the area under the curve for the recrystallisation peak. This area when compared to that produced for the crystallisation of the amorphous starting material provides a quantitative method by which to measure the amorphous content of the sample (Briggner et al., 1994).

3. Results and discussion

Experiments which include a transfer from an environment which is controlled accurately (in

this case the DVS instrument at 25°C and 50% RH) to other instruments (in this case the DSC, TGA and isothermal microcalorimeter) always carry the risk that the absorbed water content will change. Water vapour will rapidly transfer in and out of non-collapsed amorphous lactose when environmental conditions are changed, however, there will be no rapid gain or loss of water in the collapsed amorphous lactose (Fig. 1 and Buckton and Darcy, 1996). In this experiment the TGA water loss measurements gave a check as to the extent of water loss/gain on transfer from the DVS. It was found that some water loss occurred in non-collapsed, but little change was seen in the water content of collapsed samples during transfer.

The duration of exposure to 50% RH in the DVS, prior to transfer to the DSC and TGA ranged from 1 to 9 h. For this time range all the lactose samples remained amorphous at the point when they were removed from the DVS and transferred to the DSC or TGA. This was checked by exposing the material to a controlled humidity in a sealed ampoule in the isothermal microcalorimeter, which in each case resulted in the same crystallisation response as for the starting material (this is as reported previously, Buckton and Darcy, 1996). It was found that the sample would spontaneously crystallise if stored in the DVS at 50% RH for ca. 12.5 h.

Exposure to 50% RH for 1 h resulted in no collapse in structure. Exposure to 50% RH for periods longer than 1 h resulted in gradually increasing amounts of collapse until at 3 h exposure collapse was almost complete. This estimate of the extent of collapse is based on the rate of water desorption upon returning the sample to 0% RH (Fig. 1) which has been discussed previously (Buckton and Darcy, 1996). The extent of collapse is related to the amount of water which has been absorbed, which acts as a plasticiser and lowers the glass transition temperature of the lactose. As the collapse temperature, which is close to the glass transition temperature, falls below room temperature the material will collapse. The water content in the amorphous lactose following exposure to 50% RH for different times can be seen in Fig. 1.

3.1. Changes in DSC and TGA responses following collapse of amorphous structure

3.1.1. The non-collapsed amorphous sample

The DSC traces obtained for samples exposed to 50% RH for different durations, i.e. amorphous lactose with varying extent of collapsed structure, are shown in Fig. 2. It can be seen that the non-collapsed material (exposed to 50% RH for 0 or 1 h) has an exotherm at ca. 187°C, which is the crystallisation of the amorphous material, followed by two melts, one at ca. 215 and the other at ca. 230°C. These melts are typical of those observed for α- and β-lactose respectively (Angberg, 1995). It should be stressed that the sample was amorphous at the start of the DSC run and thus the melts are a consequence of the crystals having formed during the heating of the sample.

The TGA response for the non-collapsed amorphous lactose (0 and 1 h at 50% RH in Fig. 3) shows a broad weight loss (on the derivative plot) up to 100°C. This is the loss of absorbed water.

3.1.2. The collapsed amorphous samples

3.1.2.1. Changes in the crystallisation response. The samples which have some collapsed material (those exposed to 50% RH for over 1 h) can be seen to have different DSC traces from those which are non-collapsed (Fig. 2). The first difference is an exotherm in the region of 70°C. By stopping selected DSC runs after this exotherm (at ca. 90°C) and transferring the sample to sealed humidity controlled ampoules in an isothermal microcalorimeter, it was possible to show that this endotherm was due to a crystallisation of the sample. It was found that samples stored at 50% RH for 1 h (non-collapsed) then heated to 90°C produced a crystallisation response in the isothermal microcalorimeter which was identical to the amorphous starting material. Those stored for 1.5 h at 50% RH then heated to 90°C were ca. 15% amorphous, longer exposure times to 50% RH followed by heating to 90°C resulted in no crystallisation peak in the microcalorimeter, indicating these samples to be crystalline.

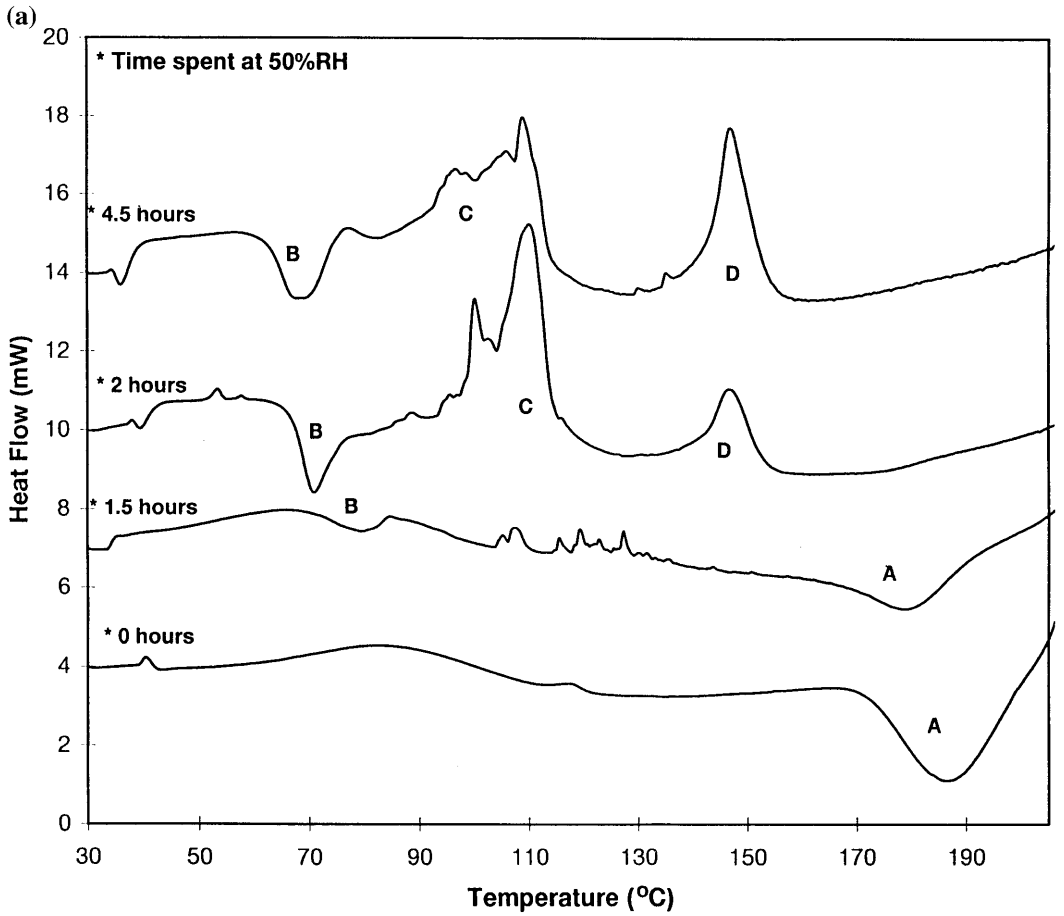

Fig. 2. Typical DSC traces of samples which had been exposed to 50% RH for 0, 1.5, 2, or 4.5 h. (a) for the scan region 30–200°C: A = high temperature crystallisation exotherm, B = low temperature crystallisation exotherm, C = endotherms associated with water loss from the collapsed structure, D = endotherm in region of monohydrate water loss; (b) for the scan region 205–250°C showing different proportions of the α- and β-lactose melts.

It can be seen from Fig. 2 that the non-collapsed material has just one crystallisation exotherm, this being at ca. 187°C. The sample which collapsed partially (i.e. 50% RH for 1.5 h) has a recrystallisation exotherm at ca. 70°C as well as at 187°C. However, those samples which have exhibited substantial collapse have only the 70°C exotherm and no high temperature crystallisation peak. It follows that the samples which have water sorbed into the collapsed amorphous structure crystallise at a lower temperature than those which do not. These observations from DSC are in keeping with the data discussed above for samples investigated in the isothermal microcalorimeter after heating to 90°C.

The TGA data (Fig. 3) for collapsed samples (2 h or more exposure to 50% RH) show a substantial weight loss in the derivate response during crystallisation (i.e. at ca. 70°C).

3.1.2.2. Changes in the region 90–150°C. The DSC and TGA traces for non-collapsed samples are relatively flat in this temperature region, however, with increasing extent of collapse increasingly large multiple endotherms are seen in the DSC. The endotherm at 150°C corresponds to the temperature at which lactose loses its hydrate water. The TGA responses (Fig. 3) show water desorption in discrete peaks which correspond to the peaks seen on the DSC run. The fact that net

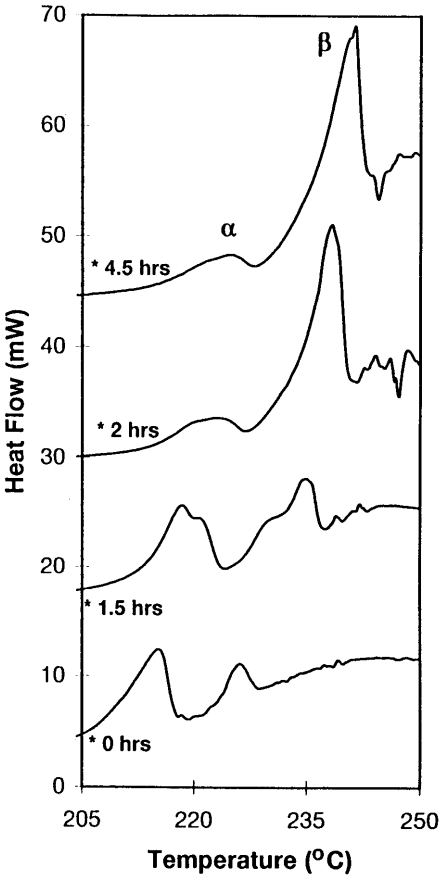

Fig. 2. (*Continued*)

endotherms are seen in this region indicates that these responses are either due to loss of water which was entrapped within the sample (endothermic event) without any crystallisation (exothermic event), or due to a crystallisation event which is superimposed on some disruptive (endothermic) event such as a transient breaking of bonds within the amorphous structure, as well as water loss. If crystallisation is occurring over this temperature range it must be within regions which were not detected as amorphous in the isothermal microcalorimetry experiment described above.

The peak at 150°C became larger as the extent of collapse in the sample increased, however, at its largest it only amounted to a mass equivalent to ca. 1.5% of the total weight of the sample. Clearly, this mass is not equivalent to the amount of water that would be lost if the full sample were a monohydrate (5%).

3.1.2.3. Changes in the melt region. The magnitudes of the enthalpy of fusion for α- and β-lactose are seen to vary, this being indicative of an increased composition of β-lactose when the sample had been collapsed at the start of the DSC run. It is known (Angberg, 1995) that the proportion of α- and β-lactose seen at the end of a DSC run can be different from that which was present at the start due to heat induced maturation. As such it is important not to over interpret these differences, however, the differences are indeed striking. The high β-lactose content in the samples which were collapsed prior to the DSC run is in keeping with the observation that the weight loss at 150°C (see above) was lower than that which would be seen if the sample were 100% α-lactose monohydrate.

3.1.3. General discussion

The above data can be related to two different scenarios of importance during pharmaceutical manufacture:

1. Where amorphous material absorbs water at ambient (uncontrolled) RH leading to differing levels of collapse, and during subsequent processing, the sample is heated above 70°C. In this situation, the collapsed material would be prone to crystallise rapidly, whereas the non-collapsed material would not. The changes in crystallinity may then impact on the product properties.
2. Where the amorphous material has collapsed, but during processing has not been raised above 70°C. The data presented above show that amorphous lactose which has collapsed will desorb water very slowly, whereas non-collapsed lactose allows water to desorb rapidly. If amorphous lactose is subjected to a 'loss on drying' in an industrial process to see if a drying step is complete, any water which is present in non-collapsed lactose would be lost rapidly during the test and would show the sample was not dry. However, if the amorphous material had collapsed, a 'loss on drying' test would only give substantial water loss

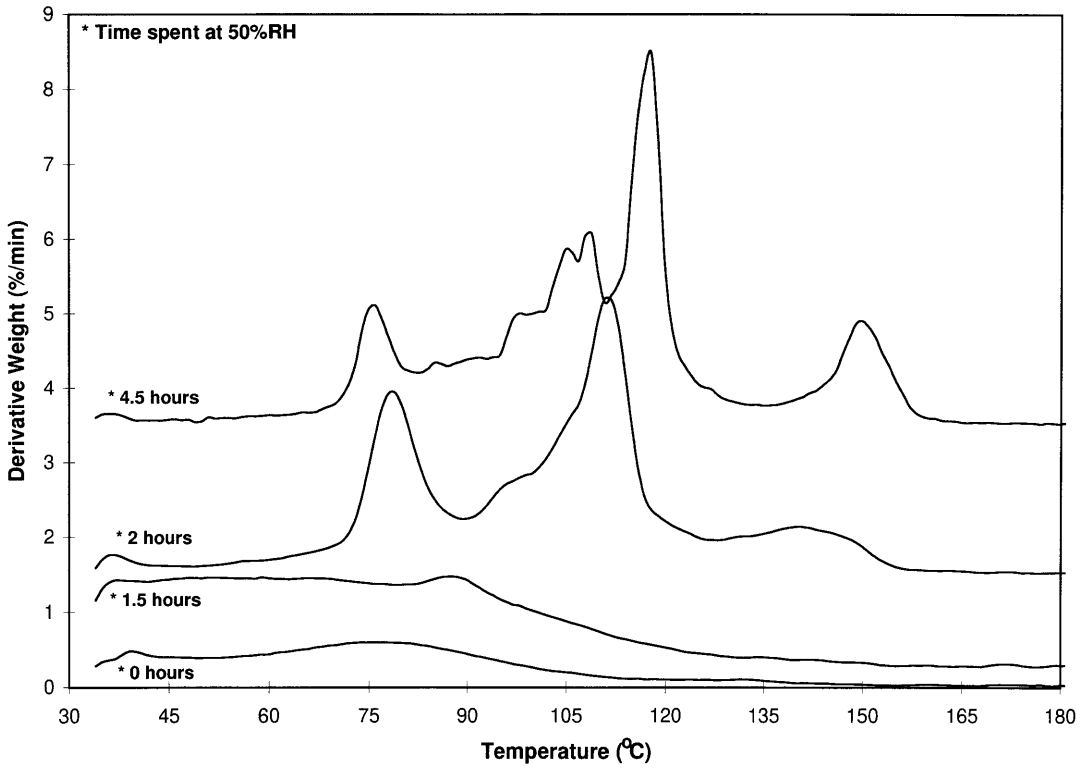

Fig. 3. Typical TGA traces for samples which had been exposed to 50% RH for varying periods of time.

if the sample temperature were raised to above 70°C, and would not achieve complete water loss until the sample was well above 100°C (see Fig. 3). There will be occasions when 'loss on drying' experiments will not raise the temperature of the sample sufficiently to remove water from collapsed regions. As such, water desorption from the sample will be slow, thus it will appear that the sample is dry. At some later time, however, the collapsed structure will crystallise and release its water, thus the sample will appear to be significantly more wet than when previously tested by 'loss on drying'. This has significance for end point determination in drying processes. Other amorphous materials will crystallise from their collapsed state at different temperatures than lactose, and as such it would be necessary to know this before drying processes can be understood fully.

4. Conclusions

There are numerous conclusions as a result of this work, the most important being that heating induces the crystallisation of collapsed amorphous lactose at lower temperatures than non-collapsed material. The collapsed material is critical, as this material will crystallise at much lower temperature (ca. 70°C) than the non-collapsed, and as such may be more prone to change during standard pharmaceutical drying processes. The crystalline product changes depending upon whether the sample was collapsed prior to onset of the drying process. The collapsed material forms some α-monohydrate, but much more β-lactose than would be formed if the sample were crystallised from non-collapsed lactose.

Information on the drying of amorphous materials is important for an improved understanding of the movement of water in products and thus to

set logical end points for drying processes. The improved understanding of the effect of collapse and drying on the crystal forms of lactose has significance for the many products which include lactose as an excipient, as functionality is closely related to the polymorphic form.

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