ELSEVIER

International Journal of Pharmaceutics 159 (1997) 67–74

international
journal of
pharmaceutics

The use of thermal techniques to assess the impact of feed concentration on the amorphous content and polymorphic forms present in spray dried lactose

Owen C. Chidavaenzi [a], Graham Buckton [a,*], Fariba Koosha [b], Ram Pathak [b]

[a] *Centre for Materials Science, School of Pharmacy, University of London, 29–39 Brunswick Square, London, WC1N 1AX, UK*
[b] *SmithKline Beecham Pharmaceuticals, Yew Tree Bottom Road, Great Burgh, Epsom, Surrey, UK*

Received 15 January 1997; received in revised form 14 August 1997; accepted 15 August 1997

Abstract

The influence of feed concentration (covering solutions and suspensions) on the physical forms of lactose obtained by spray drying was investigated. Isothermal microcalorimetry was used to assess the heats of crystallisation of the amorphous materials, which enabled the determination of the % amorphous content. Differential scanning calorimetry (DSC) provided qualitative data for the lactose polymorphs that were present in the spray dried products. Lactose monohydrate content was determined thermogravimetrically. The lactose which was dissolved was solidified as the amorphous form, due to the rapid drying conditions. The amorphous contents for the suspension feed concentrations were higher than the amount of lactose dissolved, which was due to a milling effect on the suspended lactose particles in the atomiser. The milling resulted in formation of amorphous material by solid state transition, or enhanced solubility or more likely a combination of both. Only the sample with the highest feed concentration contained small amounts of lactose monohydrate due to incomplete dehydration of the lactose in suspension. The presence of anhydrous lactose was due to the high inlet air temperatures causing dehydration of the lactose monohydrate which was in suspension. Variation of feed concentration during spray drying leads to products with different % amorphous contents and different proportions of crystalline forms. Beta lactose was not detected, either because it was absent or present in quantities below the detection limits of the thermal methods. The spray drying process is now better understood as a process that leads to loss of crystallinity in materials, possibly by a combination of rapid solidification of dissolved material and solid state transitions due to milling effects in the atomiser. © 1997 Elsevier Science B.V.

Keywords: Amorphous; Polymorphism; Lactose; Spray drying; Crystallisation; Microcalorimetry; Differential scanning calorimetry; Thermogravimetric analysis

---

* Corresponding author.

PII S0378-5173(97)00272-X

1. Introduction

1.1. Spray drying

Spray drying is a technique of importance in pharmaceutical industry, however the nature of the process is such that physical and chemical changes can occur in materials. The process involves the transformation of feed material from a fluid state into a dried particulate form by spraying the material into a drying air stream. Materials undergoing spray drying are processed via the following stages; atomisation of feed material, spray–air contact, drying of the spray material and separation of the material from the air stream. The process operational variables include; inlet air moisture, inlet temperature, feed rate, outlet temperature, air flow rate, feed concentration and atomisation pressure. A detailed description of spray drying is available elsewhere (Masters, 1990). Increasing the atomiser pressure creates smaller droplets at constant feed rate, resulting in high density fine particles. An increase in feed rate at constant operating conditions produces generally coarse spray particles and a wet product, due to inefficient drying. The nature of the spray dried product also depends on the properties of the feed material, where an increase in feed solids increases feed viscosity, which in turn produces coarse sprays on atomisation. An increase in feed solids usually results in an increase in particle size and bulk density. However, an increase in feed temperature may reduce feed viscosity causing a decrease in droplet size produced in the atomiser. This may improve atomisation efficiency of the process due to a slight reduction of the initial feed warm up period (Masters, 1990). The impact of feed concentration on the amorphous content and the different forms of the spray dried product, has seldom been studied in great detail. It is for this reason that this investigation was undertaken.

1.2. Characteristics of amorphous lactose

Pharmaceutical manufacturing techniques such as spray drying can produce materials in the amorphous state. Because the amorphous state is metastable with respect to the crystalline form, phase transformations are likely to occur within the shelf life of the pharmaceutical product. These transformations usually result in loss of quality and potency in the product (Van Scoik and Carstensen, 1990).

Amorphous lactose produced by spray drying was found to have compaction properties which differed significantly from that of its crystalline forms (Vromans et al., 1986). Amorphous lactose is physically unstable above its glass transition temperature (T_g) which is above most operating conditions. Numerous publications have demonstrated the physical instability of amorphous lactose at various relative humidities (e.g., Briggner et al., 1994; Buckton and Darcy, 1995, 1996; Sebhatu et al., 1993) due to the absorbed water plasticising the lactose such that T_g falls to or below room temperature. The critical relative humidity at which T_g falls below 25°C is quoted in most publications as around 48% RH. The effects of small quantities of moisture are not easily quantified; therefore, there is an uncertainty about the long term stability of amorphous lactose in pharmaceutical dosage forms. It was thought previously that glassy materials were stable below their glass transition temperature. However, molecular mobility at up to 50°C below the T_g of indomethacin, sucrose and polyvinyl pyrrolidone has been reported by Hancock et al., 1995. Such mobility may take place in amorphous lactose, which may have serious implications for the stability of products.

Although many studies have been undertaken on spray dried lactose, the impact of the feed concentration on the percentage amorphous content and the different lactose forms has been largely overlooked. It is thus the aim of this investigation to probe the effect of variation in feed concentration on the physical properties of the product.

2. Materials and methods

2.1. Materials

α-Lactose monohydrate (ex Smithkline Beecham, Great Burgh, Epsom, UK, batch E00131) was used to prepare the spray dried samples and as a reference material for TGA, microcalorimetry and DSC experiments, β-lactose (Sigma, USA) was used in DSC experiments as a reference material.

2.2. Spray drying

Feed samples were prepared to give concentrations of 10 g/100 ml, 20 g/100 ml, 30 g/100 ml and 40 g/100 ml in distilled water. A Buchi 190 spray drier was used to prepare the samples from the different feed concentrations. The spray drying variables (Table 1), were kept constant, except for the feed rate which was varied for each feed concentration so as to minimise fluctuations in the outlet temperature.

The materials were collected and immediately desiccated over silica gel. The particle sizes of feed material and spray dried products were measured using laser diffraction (Malvern 2600C).

2.3. Isothermal microcalorimetry measurements

The microcalorimeter used was the 2277 Thermal Activity Monitor (TAM) (Thermometric AB, Sweden), which consisted of four independent channels. The technique has high sensitivity, being able to detect heat changes as small as 10^{-6}°C. The heat flow signal ($\mathrm{d}\,Q/\mathrm{d}\,t$ in mW) is monitored as a function of time. Thus, by integrating the heat flow curves at a specific time, the heat evolved or absorbed can be obtained. Each sample was accurately weighed (approximately 20 mg) in a 3 ml glass ampoule, after which a tube containing a saturated solution of sodium chloride was added to give 75% RH at 25°C. The ampoules were sealed and temperature equilibrated for 30 min. A blank experiment was undertaken by sealing an identical ampoule and salt solution without powder present. The use of a freshly sealed blank ampoule minimises heat effects due to relaxation of the rubber stopper of the ampoule, evaporation from the salt solution and the baseline drift which is associated with environmental heat changes (Briggner et al., 1994). Experiments were carried out to investigate the percentage amorphous content in the spray dried samples by analysing the crystallisation peaks using the mean of at least three experimental runs.

Table 1
Parameters used to spray dry lactose at different feed concentrations

Parameters	Controls
Air flow rate (dial setting)	12
Outlet temperature (°C)	85–90
Inlet temperature (°C)	185–190
Heating rate (dial setting)	11.5
Atomiser air flow rate (Normliter/h)	400

2.4. Differential scanning calorimetry (DSC)

Differential Scanning Calorimeter (Perkin Elmer, DSC 7) was used to characterise the test samples and the reference material. The DSC sample weights were between 3.5 and 5.0 mg. Sealed aluminium pans were used and measurements were made in an atmosphere of nitrogen, with a heating rate of 20°C/min over a temperature range of 30–250°C. The instrument was calibrated using indium and the auto balance was also calibrated prior to weight measurements. At least three measurements were taken for each sample.

2.5. Thermogravimetric analysis (TGA)

Use of TGA (2950 Thermogravimetric Analyser, TA instruments) allowed the quantification of the lactose monohydrate content in the samples. This was achieved by analysing a derivative peak of the weight loss curve. The samples were heated over a temperature range of 30–250°C at a heating rate of 20°C/min. Four measurements for each sample were taken.

3. Results and discussion

A typical response of the spray dried material following exposure to 75% RH in the isothermal microcalorimeter is given in Fig. 1. The reference material, α-lactose monohydrate was tested under

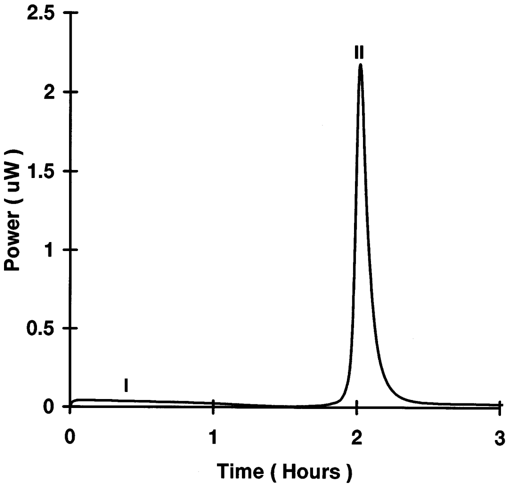

Fig. 1. A microcalorimetric trace showing an amorphous collapse peak (I) and a crystallisation peak (II) for spray dried lactose (20 g/100 ml) 20 mg at 75% RH, 25°C.

the same conditions and gave no crystallisation response, which confirmed that the material was 100% crystalline (best approximation). Two peaks are seen in Fig. 1, it was believed previously (e.g., Sebhatu et al., 1993; Briggner et al., 1994) that the first peak represented the absorption of water vapour in the amorphous structure. However, recent developments in this area of study led to the view that the first peak is more likely a heat change due to the collapse of the amorphous structure (Buckton and Darcy, 1996). This recent notion is consistent with the opinion that vaporisation and absorption have an equal and opposite response, which cancel each other. The second peak is due to the crystallisation of the amorphous lactose. The shape of the second peak demonstrates that the crystallisation process is rapid and co-operative. This co-operative process proceeded after a critical moisture concentration was reached, which was sufficient to lower the glass transition temperature (T_g) of amorphous lactose to below the operating temperature (T). When the T_g of the materials was lowered to T or below, increased molecular mobility facilitated crystallisation.

It was expected that the materials spray dried from a 10 g/100 ml lactose solution would be totally amorphous, as rapid evaporation would cause fast solidification thus giving the material no opportunity to crystallise. A value of 50 mJ/mg (Fig. 2 was obtained by integrating the area under the crystallisation peak for this sample. This value is consistent with that obtained elsewhere for a totally amorphous lactose sample (Briggner et al., 1994), thus this sample is regarded as amorphous.

The material spray dried from a 20 g/100 ml feed sample (which is at the equilibrium solubility of lactose at 25°C), was found to contain 91% amorphous material (obtained from the ratio of the area of the crystallisation peak to that of the amorphous sample), which was within the expected range given the possibility that some nucleation sites may remain, as this solution is approximately at equilibrium solubility.

The results for the feed containing 30 g/100 ml and the 40 g/100 ml (Table 2) samples were surprising as the measured amorphous content was higher than expected. The 30 g/100 ml sample contained about 67% of the lactose in solution with the remainder in suspension. It was expected that the percentage amorphous values would reflect the percentage lactose that was in solution. The lactose in suspension was expected to emerge from the system as either α-monohydrate or anhydrous crystalline forms. However, the 30 g/100 ml feed yielded a powder with 89% amorphous content, which was substantially higher than expected. The 40 g/100 ml feed had approximately 50% of the lactose in solution and 50% in suspension. However, the calculated value for amorphous content was 82% which again is much higher than that which was dissolved in the feed material. A possible explanation for the elevated amorphous contents of the suspension feeds is that atomisation pressure in the spray nozzle may have had a milling effect on the lactose that was in suspension. This pressure dependant milling effect may have resulted in the reduction of lactose particle size giving increased apparent solu-

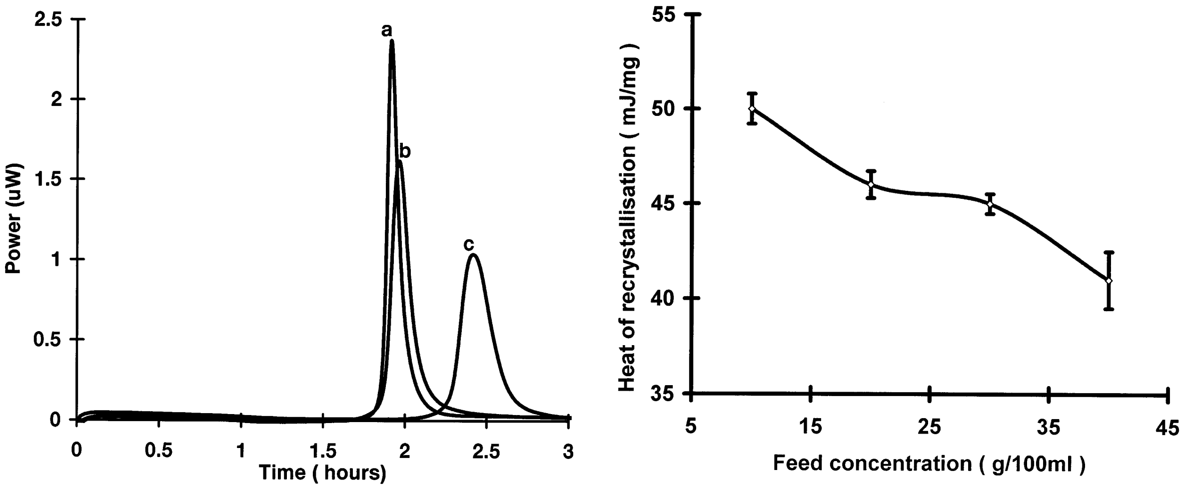

Fig. 2. (a) Typical microcalorimetric traces to show the crystallisation responses for the 40 g/100 ml (peak a), 20 g/100 ml (peak b) and 10 g/100 ml (peak c) products (30 g/100 ml trace not shown for clarity of the figure). Products with the highest amorphous content have the longest lag time prior to the crystallisation response, a plot of the mean area under the curve for each sample is given in (b). (b) A plot of mean area under the crystallisation curve (at 75%RH, 25°C) against feed concentration ($n = 4$, error bars represent standard deviations).

bility (Buckton and Beezer, 1992), solubility would be further influenced by the change in temperature of the feed as it passes through the spray nozzle. The effect of temperature in the nozzle affecting solubility is unlikely to be the only effect as if this explanation was totally responsible for the changes in amorphous content, then the 20 g/100 ml sample would have been expected to be totally amorphous (as it was at equilibrium solubility at 25°C), whereas it remained at 91% amorphous. It is however possible that changes in temperature in the nozzle become more significant when the suspended material load increases, perhaps due to particle–particle attrition. An alternative explanation is that interparticle attrition and abrasion, under the influence of the atomiser centrifugal pressure, resulted in the physical disruption of the lactose crystal structure, giving a solid state transition to the amorphous form.

Changes in particle size were measured and are presented in Table 3. The feed material has a much larger size than any of the spray dried products. Based on these data some milling does take place during passage through the atomiser. The 10 g/100 ml feed produced the smallest size product (Table 3) with the sizes for the products produced from other feeds being essentially identical (within experimental error). It can be concluded from these data that the presence of plentiful nucleation sites (which would be expected to exist in all except the 10 g/100 ml feeds) has resulted in larger particles, by allowing earlier solidification than for the material which was completely dissolved.

From the available evidence it is probable that a combination of the above explanations (solubility changes and solid state transitions) may be the reason for the unexpectedly high amorphous contents in the suspension feed products.

3.1. Determination of the lactose polymorphic forms present in spray died lactose

The characterisation of polymorphs in the spray dried lactose samples was undertaken using DSC, TGA and microcalorimetry results.

From the isothermal microcalorimetry results it was established that a 10 g/100 ml sample contained 100% amorphous lactose, which meant that there was no crystalline material (best approximation) present. This observation was supported by

Table 2
Summary of the feed material and the consequent nature of the spray dried product

Feed Conc. (g/100 ml)	% in solution in feed	Amorphous in product (%)	α-anhydrous in product (%)	Mono-hydrate in product (%)	β-anhydrous in product (%)
10	100	100 (1.3)	0	0	0
20	ca. 100	91 (1.3)	9 (1.4)	0	0
30	67	89 (1.0)	11 (1.0)	0	0
40	50	82 (3.3)	13 (3.1)	5 (0.3)	0

The standard deviations are in parenthesis, $n = 4$.
The data for β-lactose are open to error as they are derived from the absence of a visible melt at the appropriate point on the DSC traces. It is reasonable to assume that a small part of the anhydrous material may indeed be present as β-lactose, but if this is so it is below the detection limit.

the DSC trace for this sample which showed no lactose monohydrate dehydration peak in the 140–150°C temperature range (see Fig. 3 for a DSC trace for reference material) and no β-lactose melting peak at about 235°C. The TGA derivative curve showed no evidence of weight loss associated with hydrate water. These data supported the isothermal microcalorimetry and as such it was concluded that the 10 g/100 ml samples contained no crystalline lactose.

The product from 20 g/100 ml feed contained 91% amorphous lactose, therefore the remaining 9% could potentially consist of one or all of the lactose polymorphs. The absence of any DSC melting peak at 235°C demonstrates that there are no detectable amounts of β-lactose in the sample. The monohydrate dehydration peak was also absent, but there was a melting peak at 216°C (Fig. 3). The TGA derivative trace showed no weight loss associated with hydrate water, which indicated that there was no detectable lactose monohydrate in the sample. It is therefore, concluded that the 20 g/100 ml sample contained no lactose monohydrate and no β-lactose. By reasonable deduction, the 20 g/100 ml sample was thought to contain 9% anhydrous α-lactose and 91% amorphous lactose. The observed DSC peak (Fig. 3) was in keeping with the literature value of 216°C for anhydrous lactose (Lerk, 1983). The 30 g/100 ml sample was found to contain 89% amorphous lactose and 11% anhydrous α-lactose using a similar logic. It should be noted, however, that the absence of a melting peak on the DSC does not prove total absence of the β-lactose as there is a certain threshold quantity required to allow detection, as such the above estimates are best approximations.

Table 3
The particle sizes (μ) of the starting α-lactose monohydrate and the spray dried products produced from different feed concentrations

	10% undersize	50% undersize	90% undersize
Starting material	9.2 (3.5)	22.8 (6.0)	46.0 (11.4)
10 g/100 ml feed	3.3 (0.6)	7.2 (0.3)	16.4 (5.0)
20 g/100 ml feed	3.4 (0.2)	11.2 (0.4)	23.5 (1.1)
30 g/100 ml feed	3.5 (0.3)	12.6 (1.0)	24.6 (1.7)
40 g/100 ml feed	3.8 (0.3)	13.9 (0.2)	25.9 (0.1)

Standard deviations are in parenthesis, $n = 4$.

The 40 g/100 ml sample, showed a TGA secondary weight loss derivative peak (see Fig. 4), which was consistent with the lactose monohydrate reference material. The derivative peak represented a loss of 0.0355 mg of water ($0.0355 \times 10^{-3}/18$ moles of water). This number of moles was equivalent to the number of moles lactose monohydrate (1:1 molar ratio). The % lactose monohydate content was then expressed as a % weight of the analysed sample. The lactose monohydrate content in the 40 g/100 ml sample was calculated to be approximately 5%. However, the dehydration peak was not visible on the DSC

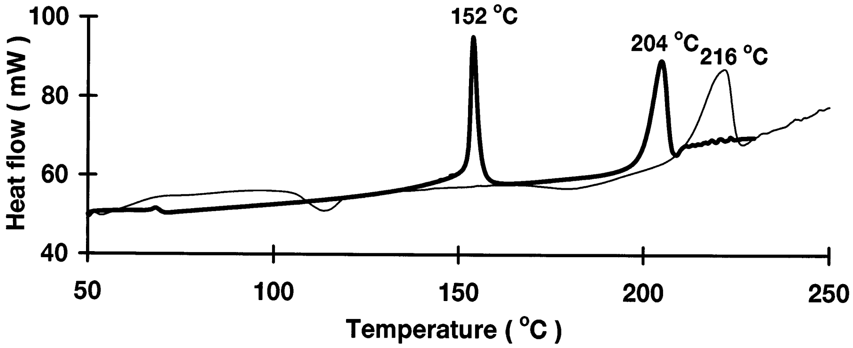

Fig. 3. A DSC trace for lactose monohydrate (reference material) showing a dehydration peak (152°C) and melting peak (204°C) (Bold line) and a typical scan for spray dried lactose (20 g/100 ml) showing the absence of β-lactose melting peak and no lactose monohydrate dehydration peak (however a T_g is seen as a baseline disruption at ca 120°C and a melt at 216°C is observed).

trace for the sample, this may be due to the low sensitivity of the DSC to detect the presence of small amounts of lactose monohydrate (Angberg et al., 1991). The DSC trace for this material also showed no β-lactose melting peak and exhibited a melting peak at 216°C, which could represent the melting peak for either lactose monohydrate and anhydrous lactose. Based on the evidence available it is concluded that the material obtained from the 40 g/100 ml feed consisted of 5% lactose monohydate, 82% amorphous lactose and about 13% anhydrous lactose. The presence of lactose monohydrate in this sample may be due to the high feed rates which were necessary to control the outlet temperature. The feed rates for the other samples were comparatively low, therefore, in the other samples it would have been easier for lactose to be dehydrated to form anhydrous lactose.

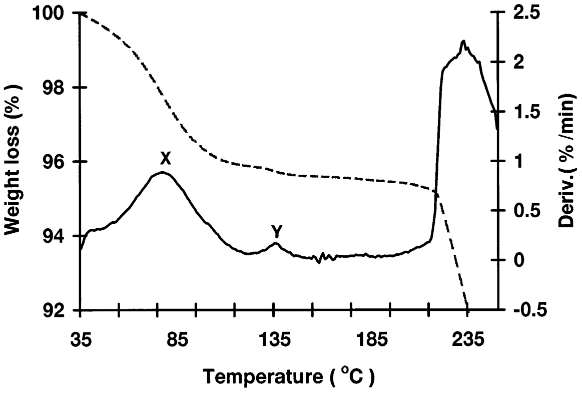

Fig. 4. TGA weight loss curve for spray dried lactose (40 g/100 ml) showing a derivative peak corresponding to loss of absorbed (X) and hydrate (Y) water.

Whilst it should be remembered that the accuracy of the thermal analysis means that small amounts of other polymorphs will not have been detected, clear differences in the physical form are observed depending upon the feed concentration, these differences are summarised in Table 2. Substantial differences in product are possible depending upon both spray drying conditions and the concentration of the feed material.

4. Conclusion

The concentration of feed material was found to have a significant effect on the properties of the spray dried materials. An increase in lactose content in the feed solution or suspension in the more concentrated preparations resulted in a decrease in percentage amorphous lactose in the spray dried products. Under the conditions used, the lactose in solution solidified in an amorphous state. However, at higher feed contents it was observed that suspended lactose was also converted from crystalline to amorphous material. Processes in the atomiser, followed by rapid solidification, cause the lactose in suspension to become amorphous through solid or liquid transitions or more likely a combination of both. At higher feed solids incomplete dehydration of the suspended lactose particles may occur, which may result in some lactose monohydrate in the products.

By selecting the appropriate feed concentrations spray dried lactose can be manufactured with various polymorphic proportions which suit the desired tabletting properties.

Acknowledgements

This work was funded by EPSRC and Smithkline Beecham (Great Burgh, Epsom, UK) to whom we are grateful.

References

Angberg, M., Nystrom, C., Castensson, S., 1991. Evaluation of heat-conduction microcalormetry in pharmaceutical stability studies III. Crystallographic changes due to water vapour uptake in anhydrous lactose powder. Int. J. Pharm. 73, 209–220.

Briggner, L.-E., Buckton, G., Bystrom, K., Darcy, P., 1994. The use of isothermal microcalorimetry in the study of changes in crystallinity induced during the processing of powders. Int. J. Pharm. 105, 125–135.

Buckton, G., Beezer, A.E., 1992. The relationship between particle size and solubility. Int. J. Pharm. 82, R7–R10.

Buckton, G., Darcy, P., MacKellar, A.J., 1995. The use of isothermal microcalorimetry in the study of small degrees of amorphous content of powders. Int. J. Pharm. 117, 253–256.

Buckton, G., Darcy, P., 1996. Water mobility in amorphous lactose below and close to the glass transition temperature. Int. J. Pharm. 136, 141–146.

Hancock, B.C., Shamblin, S.L., Zografi, G., 1995. Molecular mobility of amorphous pharmaceutical solids below their glass transition temperatures. Pharm. Res. 12, 799–806.

Lerk, C.F., 1983. Physico-chemical properties of lactose. Proceedings of the 22nd International Colloquium on Industrial Pharmacy, Ghent, pp. 59–89.

Masters, K., 1990. Spray Drying Handbook, Longman, New York.

Sebhatu, T., Angberg, M., Ahlneck, C., 1993. Assessment of the degree of disorder in crystalline solids by isothermal microcalorimetry. Int. J. Pharm. 104, 135–144.

Van Scoik, K.G., Carstensen, J.T., 1990. Nucleation phenomena in amorphous sucrose systems. Int. J. Pharm. 58, 185–196.

Vromans, H., Bolhius, G.K., Lerk, C.F., van de Biggelaar, H., Bosch, H., 1986. Studies on the tabletting properties of lactose. VII. The effect of variations in primary particle size and percentage of amorphous lactose in spray dried lactose products. Int. J. Pharm. 35, 29–37.