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International Journal of Pharmaceutics 216 (2001) 43–49

international journal of pharmaceutics

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# The effect of co-spray drying with polyethylene glycol 4000 on the crystallinity and physical form of lactose☆

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Received 28 September 2000; received in revised form 1 December 2000; accepted 5 December 2000

**Abstract**

The effect of spray drying lactose alone and in the presence of polyethylene glycol 4000 was investigated. Lactose was added to distilled water to give concentrations of 10, 20, 30 and 40g/100ml at room temperature and each spray dried in turn. Identical samples were prepared to which polyethylene glycol (PEG) 4000 was added (12% by weight of lactose) prior to spray drying. Microcalorimetric and X-ray diffraction studies showed that spray drying lactose solutions produced completely amorphous material due to rapid solidification during the spray drying process, whereas lactose suspensions yielded partially crystalline products due to crystalline material that remained in suspension. However, all the PEG/lactose (12%w/w) co-spray dried products were found to be crystalline. It can be inferred that the solidification rates of the lactose in the presence of PEG must have been slower than that of lactose alone which allowed PEG and lactose to crystallise. The PEG/lactose products that were spray dried from solution consisted of α-anhydrous, α-monohydrate, β-lactose and PEG extended chain polymorph, whereas those formed from suspension PEG/lactose samples consisted of only α-anhydrous, α-monohydrate and extended chain PEG crystals. PEG probably caused the more concentrated lactose suspensions to crystallise slowly due to the strong hydrogen bonding between PEG and water, which allowed growth on the α-lactose seed crystals. 

*Keywords:* Amorphous; Crystallisation; Co-spray drying; Lactose; Spray drying; Microcalorimetry; Differential scanning calorimetry; Thermoravimetric analysis

## 1. Introduction

Spray drying is known to produce predominantly amorphous material due to rapid solidification (Sebhatu et al., 1994). The detection and control of the amorphous portion of powdered material is of utmost importance. For example, it has been shown that different physical forms of

☆ This paper is dedicated to Professor J.M. Newton on the occasion of his 65th birthday.

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0378-5173/01/$ - see front matter 
PII: S0378-5173(00)00693-1

lactose can result in changes in drug deposition from dry powder inhalers (e.g. Larhrib et al., 1999) and changes in compaction due to variation in mechanical properties (Inghelbrecht and Remon, 1998). Consequently, it is important to know which physical forms of materials may be present as a result of changes in the formulation content and/or the method of processing.

It is not uncommon in pharmaceutical technology to spray granulate formulations that comprise of lactose and polyethylene glycol (PEG) 4000 as excipients. During spray granulation amorphous forms of the excipients or drugs may be produced and these could revert to the thermodynamically stable crystalline forms on storage. Given that lactose is a widely used diluent in solid dosage forms and that PEG 4000 can be used as a binder in granulations, it is surprising that little data exists in the literature regarding the impact of spray drying lactose in the presence of PEG 4000. The properties of spray dried lactose are reasonably well understood (Chidavaenzi et al., 1997).

In the molten state, PEG 4000 chains are randomly orientated. As the melt cools, nucleation can occur by either homogeneous or heterogeneous mechanisms. The effect of additives on the crystallisation of PEG could result in the added component having one of two effects. Firstly, the additive can be present as crystalline particles, where it may act as a nucleating agent and thus increase the number of nuclei present in the polymer melt. Secondly, the added material could act as an inhibitor of crystallisation by hindering chain diffusion and packing, resulting in a higher percentage of amorphous and imperfectly crystalline material. The crystallisation of PEG (into its different polymorphic forms) and the effect of additives on this process has been studied by Chatham (1985) and Craig (1995). Changes in both the degree of crystallinity and polymorphic form can occur during processing, thus it is necessary to thoroughly characterise the spray dried PEG/lactose samples.

## 2. Experimental

α-Lactose monohydrate was added to distilled water to give concentrations of 10, 20, 30 and 40g/100 ml at room temperature. Each sample was spray dried in turn. Similar samples were then prepared to which PEG 4000 (Honeywell and Stein) was added (12% by weight of lactose). A Buchi 190 Mini Spray Dryer (Switzerland) was used to spray dry the lactose samples or the PEG/lactose suspensions. The experiments were performed at constant process conditions (Table 1), except for the feed rate which was varied in order to minimise fluctuations in the spray dryer outlet temperature.

### 2.1. Assessment of crystallinity

A 2277 Thermal Activity Monitor (TAM) (Thermometric AB, Sweden) was used to assess the crystallinity of the spray dried products using the method of Briggner et al. (1994). Twenty milligrams of each sample was placed in a 3 ml glass ampoule containing a tube with saturated salt solution (sodium chloride) to give 75%RH at 25°C and the power–time response was measured. The area under the power–time curve that was associated with crystallisation of the amorphous content of the sample was used to estimate the degree of crystallinity. Amorphous contents were expressed as a percentage of the response of that obtained following spray drying of a lactose solution (previously shown to be amorphous e.g. Briggner et al., 1994).

### 2.2. Determination of physical form in spray dried lactose and co-spray dried products

Differential scanning calorimetry studies (Perkin–Elmer, DSC 7, aluminium non-hermetically sealed pans, nitrogen flush, calibration with indium) were undertaken at 10°C/min to charac-

Table 1
Parameters used to spray dry lactose and PEG/lactose samples

| Parameters | Controls |
|---|---|
| Airflow rate (dial setting) | 12 |
| Outlet temperature (°C) | 85–90 |
| Inlet temperature (°C) | 185–190 |
| Heating rate (dial setting) | 11.5 |
| Atomiser airflow rate (Normliter/h) | 400 |

Table 2
Summary of feed material (lactose without PEG 4000) and the consequent nature of the spray dried product. Standard deviations are in parenthesis, $n = 4$ (Adapted from Chidavaenzi et al., 1997)

| Feed conc (g/100ml) | % in solution in feed | Amorphous content in product | Crystalline α-anhyd in product | Crystalline β-lactose in product | Crystalline α-monohydrate in product |
|---|---|---|---|---|---|
| 10 | 100 | 100 (1.3) | 0 | 0 | 0 |
| 20 | ca100 | 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) | 0 | 5 (0.3) |

terise the reference (as received) and the spray dried samples.

The lactose monohydrate content in the spray dried samples was quantified using a thermogravimetric analyser (TGA 2950, TA Instruments, open pan) using a scanning rate of 10°C/min. The quantity of lactose monohydrate in the samples was determined by integrating the area under the derivative curve in the 100–150°C temperature region. The retained water content in the spray dried samples was also assessed from the mass loss below 100°C.

The anomeric content in the spray dried and the reference materials were analysed using X-ray diffraction (XRD; Phillips, X-ray Diffractometer). Diffraction peaks at 10.6° and 12.6°($2\theta$) were used to confirm the presence or absence of crystalline β or α-monohydrate respectively. The diffraction peaks of the PEG/lactose spray dried samples were also compared with that of the reference (as received) PEG 4000.

In order to assess the particle size and morphology of the PEG/lactose products photomicrographs were taken using a (Phillips XL20, Scanning Electron Microscope).

## 3. Results and discussion

### 3.1. Spray dried lactose

The data for spray dried lactose have been reported previously (Chidavaenzi et al., 1997), however, to aid comparison with the PEG/lactose data they are summarised here. The 10g/100ml lactose solution yielded amorphous lactose due to rapid solidification, whereas, the sample at equilibrium solubility (20g/100ml) yielded a solid form that was 91% amorphous lactose, probably due to nucleation sites that may have remained. The 30 and 40g/100ml lactose suspensions produced spray dried products consisting of a much higher amorphous lactose content than the amount that was dissolved (Table 2). The crystalline part of these products was found to be anhydrous α-lactose, except for the 40 g/100ml sample which consisted of both anhydrous α-lactose and α-monohydrate (Chidavaenzi et al., 1997).

### 3.2. PEG/lactose samples

In order to assess the amorphous content of the spray dried PEG/lactose samples, they were exposed to 75% RH in an isothermal microcalorimeter. However, for all of the spray dried PEG/lactose products a baseline response was obtained, indicating that the samples contained no detectable (crystallisable) amorphous material. This could either be due to the fact that there was no amorphous material present, or that the amorphous form had been stabilised as a solid solution and thus could not crystallise. The initial expectation was that a solid solution (or semi-solid matrix of some kind) had formed. However, studies using XRD and differential scanning colorimetry (DSC) revealed that the PEG/lactose samples were indeed crystalline. For the 10 and 20 g/100 ml PEG/lactose samples, X-ray diffraction peaks at 12.6° and 10.6°($2\theta$) were observed which

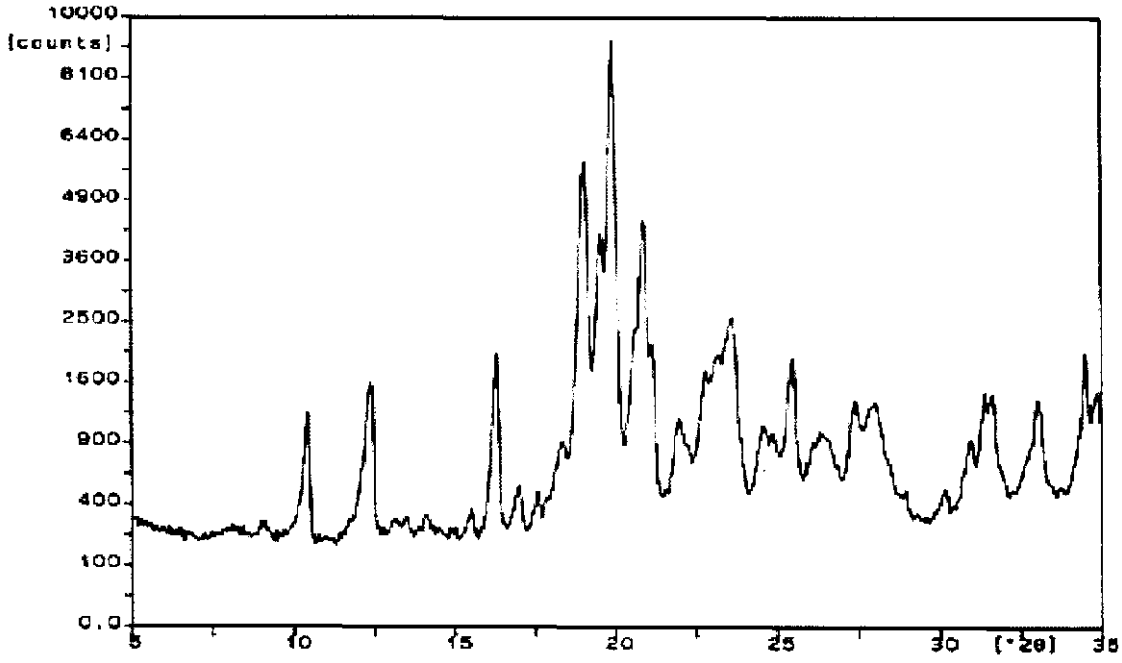


Fig. 1. XRD data for the 10 or 20 g/100 ml PEG/lactose samples showing the presence of crystalline α or β-lactose and the PEG extended chain crystals.

were attributed to the presence of crystalline α-monohydrate and β-lactose respectively (Fig. 1). The diffraction peaks for PEG were similar to those of the reference material (not shown), indicating that the polymer fraction in the spray dried PEG/lactose samples was the extended chain crystalline form (the melting endotherm at 57°C has been attributed to small PEG crystals with a high degree of imperfection; (Chatham, 1985).

The XRD findings were supported by DSC data (Fig. 2) which showed a PEG melt (extended chain) at 57°C, a dehydration peak for α-monohydrate lactose at 120°C, an anhydrous α-melt at 216°C, a β-melt at 235°C.

When the 30 or 40 g/100 ml PEG/lactose samples were characterised by DSC, a flat broad endotherm at 115°C and a large melt at 216°C were observed (Fig. 2). The endotherm at 115°C was attributed to dehydration of a monohydrate (presumably slightly disrupted as the hydrate loss is usually seen as a sharp peak at a higher temperature), whereas the peak at 216°C was attributed to the melt of anhydrous α-lactose. The absence of a melt in the 230–240°C temperature region indicated the absence of crystalline β-lactose in the sample. A melting endotherm of straight chain PEG crystals at 57°C was also observed. No other melts were observed showing that other PEG polymorphs were absent (e.g. the once folded form would melt at 52°C, and no peak was observed in this region). It can be concluded that the cooling conditions employed during the spray drying process must have been reasonably slow, to allow nucleation to the most stable PEG poly-

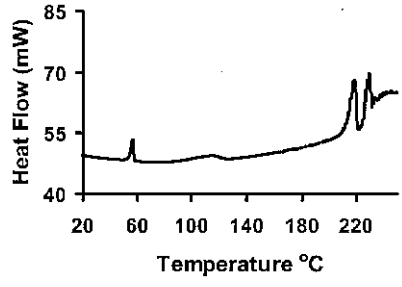


Fig. 2. A DSC data for the 20 g/100 ml PEG/lactose co-spray dried samples similar to that for the 10 g/100 ml sample.

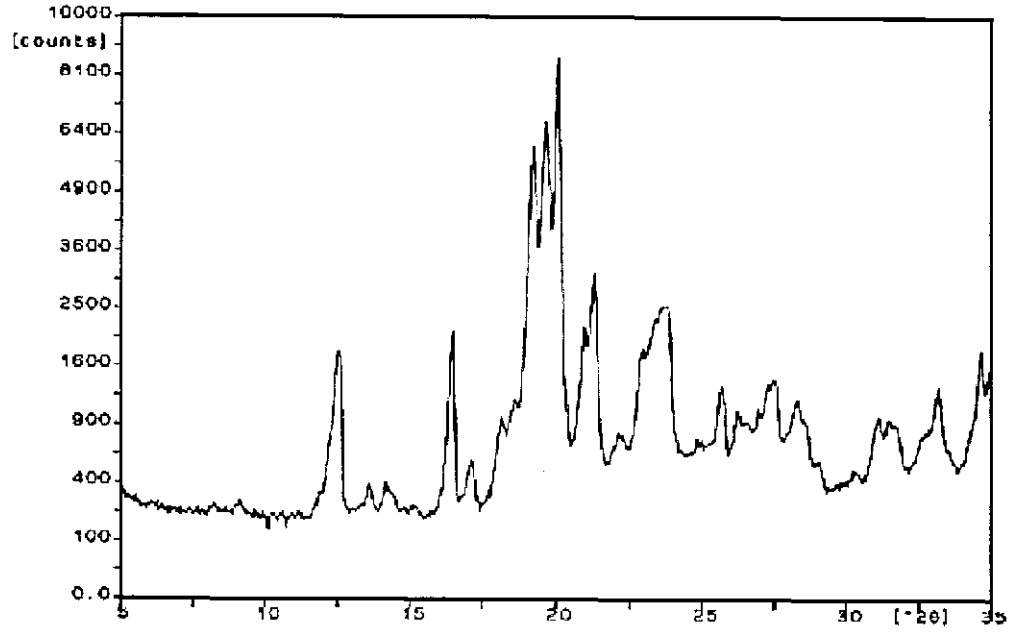


Fig. 3. XRD data for the 30 or 40 g/100 ml PEG/lactose samples which shows the presence of α-anhydrous lactose and extended chain PEG crystals but no β-lactose as shown by the absence of a diffraction peak at 10.6° ($2\theta$).

morph. The DSC findings for the 30 or 40 g/100 ml PEG/lactose samples were substantiated by XRD data (Fig. 3) which showed diffraction patterns that were consistent with that of anhydrous and monohydrate α-lactose, whereas no peaks were observed at diffraction angle ($2\theta$)10.6° (characteristic of β-lactose). It can be concluded that PEG caused the higher lactose concentrations to crystallise in a manner which allowed complete β-α mutarotation during the spray drying process. This could be due to a slower drying process (due to PEG-water hydrogen bonding) and the presence of α-lactose seed crystals.

In order to assess the monohydrate content in the spray dried PEG/lactose samples thermogravimetric investigations were undertaken. The % weight loss of a full monohydrate would be 5%w/w of the lactose mass, thus the moisture loss in the 100–150°C region was related to that for a full monohydrate in order to determine the monohydrate content in the spray dried products. There was no significant ($P < 0.05$) difference in the monohydrate content for the spray-dried PEG-lactose irrespective of feed concentration, in all cases the hydrate weight loss was equivalent to 20% of the sample mass being a monohydrate. Thus the crystalline lactose fraction in the 12%PEG/lactose samples was predominantly in the anhydrous form. This is probably due to the fact that the water was attracted to the PEG rather than being available to form a hydrate with the lactose. The mass (water) loss in TGA experiments in the region 20–100°C was always in the range 0.5 to 1.1%. This water was presumably associated with the PEG and did not induce a change to the monohydrate form.

As the formation of crystalline particles was unexpected, particles were prepared with lower PEG contents (1, 2 and 4% with respect to lactose content). In each case the material formed was found to be crystalline. In each case there was no β-lactose present (checked using X-ray diffraction and DSC). The monohydrate content of the lactose did change, being approximately 40, 48 and 86% for the 4, 2 and 1% PEG contents respectively (compared to 20% monohydrate in the sam-

ple that had 12% PEG). Consequently, reducing the PEG content retains crystallinity, forces crystallisation as only the α form, but allows progressively more monohydrate to form as the PEG content decreases. Long term stability of the anhydrous form has not been investigated, however storage at 75% RH and 25°C for 7 days did not cause any change in hydrate levels. Storage at 75%RH and 40°C, however, resulted in rapid conversion to the monohydrate form (within 1 day). It is probable that the PEG protects from water ingress at 25°C, but as 40°C is close to the PEG melting point there must be sufficient molecular mobility to allow water to access the lactose crystals.

Scanning electron micrographs demonstrated that crystalline PEG spherulites appeared to be present on the surface of the particles (Fig. 4). Spray dried lactose (micrograph not shown) has the appearance of perfectly formed spheres with smooth surfaces. For PEG/lactose (Fig. 4) small spherulites were observed with a distorted and twisted appearance and obvious signs of crystallinity.

The fact that co-spray drying PEG 4000 with lactose produced predominantly crystalline products was surprising, as additives generally inhibit nucleation. Based on the evidence from studies of indomethacin/PVP co-spray dried systems (Corrigan et al., 1985), PEG/lactose solutions or suspensions were expected to produce amorphous material. The additive would possibly inhibit nucleation during the spray drying process by a mass transport step or an orientation and incorporation step (Van Scoick and Carstensen, 1990).

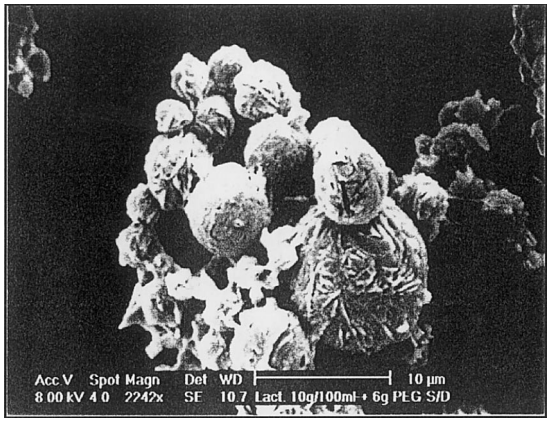


Fig. 4. Micrographs depicting the morphology of the 10 g/100 ml spray dried PEG/lactose particles.

A possible reason for the absence of amorphous material in spray dried PEG/lactose samples is that the solidification rates of PEG /lactose molecules were slower than that of lactose alone, which enabled the PEG and lactose molecules to crystallise during the spray drying process. This hypothesis is substantiated by the fact that PEG has been shown to hydrogen-bond with water (Graham et al., 1989). It is reasonable to assume that the prevalence of such interactions in PEG/lactose/water systems reduced the rapidity of water evaporation during the spray drying process to an extent that nucleation occurred.

## 4. Conclusions

It can be concluded that PEG caused lactose to crystallise during the spray drying process, whereas, spray dried lactose alone was predominantly amorphous material. Spray drying PEG/lactose solutions yielded crystalline α-monohydrate, α-anhydrous and crystalline β-lactose. Spray drying of PEG/lactose suspensions (containing residual lactose particles) yielded only anhydrous-lactose and α-monohydrate. PEG was found to be in its stable extended crystal form in all cases.

The mechanism by which lactose crystallises in the presence of PEG during the spray drying is not understood fully, but is likely to relate to the high affinity with which PEG hydrogen bonds water, which can be expected to slow the drying process.

It was found that PEG caused crystallisation to α lactose even at concentrations as low as 1% PEG to lactose. The only effect of changes in PEG concentration were to alter the proportion of monohydrate and anhydrous forms. The anhydrous form was stable to elevated humidity for at least a week, but was unstable at elevated temperature.

## Acknowledgements

EPSRC and SmithKline Beecham for funding OC

## References

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.

Chatham,S.M., 1985. Characterisation of molten filled hard gelatin capsules. PhD thesis, University of London.

Chidavaenzi, O.C., Buckton, G., Koosha, F., Patrak, R., 1997. The use of thermal techniques to assess the impact of feed concentration on the amorphous content and polymorphic forms present in spray dried lactose. Int. J. Pharm. 159, 67–74.

Corrigan, O.I., Holohan, E.M., Reilley, M.R., 1985. Physicochemical properties of indomethacin and related compounds co-spray dried with polyvinylpyrollidone. Drug. Dev. Ind. Pharm. 11, 677–695.

Craig, D.M.Q., 1995. A review of thermal methods used for the analysis of the crystal form, solution thermodynamics and glass transition behaviour of polyethylene glycols. Thermochimica Acta 248, 189–203.

Graham, N.B., Zulfar, M., Nwachuku, N.E., Rashid, A., 1989. Interaction of polyethylene oxide with solvents: 2. Water–poly(ethylene glycol). Polymer 30, 528–533.

Inghelbrecht, S., Remon, J.P., 1998. The roller compaction of different types of lactose. Int. J. Pharm. 166, 135–144.

Larhrib, H., Zeng, X.M., Martin, G.P., Marriott, C., Pritchard, J., 1999. The use of different grades of lactose as carrier for aerosolised salbutamol sulphate. Int. J. Pharm. 191, 1–14.

Sebhatu, T., Angberg, M., Ahlneck, C., 1994. Assessment of the degree of disorder in crystalline solids. Int. J. Pharm. 101, 237–247.

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