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The effect of spray drying solutions of polyethylene glycol (PEG) and lactose/PEG on their physicochemical properties

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Abstract

The effect of spray drying polyethylene glycol (PEG) 4000 and lactose/PEG solutions was investigated. Microspherical PEG particles were successfully prepared from ethanol, which allowed lower outlet temperatures than water. The product was crystalline and consisted of rough spheres or rod like particles. In the case of lactose/PEG composites, spray dried from water, the crystallinity of both components was reduced on spray drying, the extent being dependent on the starting composition. Spray dried lactose/PEG with PEG present as 10% by weight was found to be the most amorphous of the systems prepared. Conversion to more crystalline products occurred over time, the rates of conversion being dependent on temperature and humidity. On storage at low humidity (31–34%) amorphous lactose in lactose/PEG spray dried systems converts to anhydrous crystalline lactose while at high humidity (75% RH) the monohydrate is formed. The rate of transformation of amorphous lactose to the crystalline monohydrate form, at high relative humidity, was quantified using the Avrami equation applied both to X-ray diffraction (XRD) peak intensity and heat of fusion data. Crystallisation of lactose appeared to be retarded at low PEG concentrations, where PEG was present predominantly in a non-crystalline state, but was accelerated at higher PEG contents. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Spray dried polyethylene glycol (PEG); Spray dried lactose/PEG composites, stability; Amorphous; Crystallinity

1. Introduction

The physicochemical properties of pharmaceutical solids are important considerations in formulation and these properties can be significantly altered by processing. For example, co-precipitates of hydroflumethiazide with the water soluble amorphous polymer PVP, in appropriate proportions, results in high energy amorphous composites (Corrigan and Timoney, 1975). Co-spray drying these systems extended the composition range over which amorphous systems were obtained and further increased the energy of the systems (Corrigan and Holohan, 1984). Frequently the spray drying process results in high energy amorphous products (Corrigan, 1995) with improved functional properties such as particle size, compaction or dissolution rate. For example it is well known that the spray drying of pure

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lactose produces an amorphous product having significantly altered functional properties compared with those of the conventional crystalline forms of the sugar (Sebhatu and Alderborn, 1999).

It has also been shown that additives can influence the recrystallisation of amorphous spray dried lactose (Buckton and Darcy, 1995), PVP delaying the onset of recrystallisation (Stubberud and Forbes, 1998). In contrast Chidavaenzi et al. (2001) reported that co-spray drying lactose with polyethylene glycol (PEG) 4000 at levels of 12, 4, 2, and 1% of the solids resulted in crystalline products and inferred that the presence of the PEG slowed the solidification rate of the lactose, during the drying process, allowing both components to crystallise. Differential scanning calorimetry (DSC) and X-ray diffraction (XRD) data supported crystallisation of the lactose in α-monohydrate, α-anhydrous and crystalline β forms, the relative proportions being dependent on the concentration of PEG, with the PEG crystallising during the drying process as the extended crystal form.

In this paper, we examine the preparation and properties of spray dried PEG and high energy lactose/PEG composites. The crystallinity of both components was reduced on spray drying, with amorphous material being produced, the amount depending on the feed composition. The physical stability of these systems under different storage conditions was also examined.

2. Experimental

2.1. Materials

α-Lactose monohydrate was purchased from BDH (UK), anhydrous lactose from Sheffield Products (Division of Quest International, USA) and PEG 4000 from Riedel de Haën (Germany). Lactose and lactose/PEG 4000 (containing 5, 10, 20, 30% PEG 4000 by weight of solids) systems for spray drying were prepared using deionised water. The lactose used in the preparation of all solutions for spray drying was lactose monohydrate. To ensure that lactose was fully in solution, total dissolved solids employed were 5 and 10%. PEG 4000 alone was spray dried from 95% ethanol as a 2.5% w/v solution.

Physical mixes were prepared using sub 125 μm mesh sieved powders mixed in a Turbula Mixer™ for 5 min.

All spray dried systems were analysed by DSC and XRD within 1 h of production. They were then stored at various controlled temperature and humidity conditions using incubators and saturated salt solutions (Nyqvist, 1983). Magnesium chloride and sodium chloride were used to create low humidity and high humidity conditions, respectively. The following storage conditions were investigated: 4 °C 34% RH, 4 °C 75% RH, 30 °C 32% RH, 30 °C 75%RH, 45 °C 31% RH, 45 °C, 75% RH.

2.2. Spray drying methodology

Unless otherwise stated in the text, systems were spray dried using a Büchi 190 with inlet air temperature range 118–123 °C, outlet temperature 76–80 °C, pump setting 5 and airflow rate at 600 Nl/h. Some systems were also prepared using a Büchi 191 and required slightly higher inlet temperatures ($\sim$ 125 °C). These systems showed no differences in physicochemical properties.

2.3. Assessment of physicochemical properties

X-ray powder diffraction measurements were made on samples in low background silicon mounts, which consisted of cavities 0.5 mm deep and 9 mm in diameter (Bruker AXS, UK). The Siemens D500 Diffractometer consists of a DACO MP wide-range goniometer with a 1.0° dispersion slit, a 1.0° anti-scatter slit and a 0.15° receiving slit. The Cu anode X-ray tube was operated at 40 kV and 30 mA in combination with a Ni filter to give monochromatic Cu Kα X-rays. Measurements were generally taken from 5 to 35° on the two θ scale at a step size of 0.05° per s for qualitative analysis. For quantitative analysis a step size of 0.02° was used with a count time of 5 s.

DSC (Mettler Toledo DSC 821^e) using closed 40 μl aluminium pans with three vent holes and

thermogravimetric (TG) analysis (Mettler TG 50 linked to a Mettler MT5 balance) using open pans, were performed on accurately weighed samples (5–10 mg). Samples were run at a heating rate of 10 °C/min under nitrogen purge.

Scanning electron microscopy (SEM) was performed using a Hitachi S-3500N variable pressure scanning electron microscope.

Gel permeation chromatography (GPC) was performed using a Plaquagel-OH Mixed 8 μm 300×7.5 mm column (Polymer Laboratories Ltd., UK) with water as the mobile phase. Calibration curves were prepared using PEG narrow standards (Polymer Laboratories Ltd.). 0.2% w/v concentrations of standards and samples were prepared using water as the dissolution medium and volumes of 200 μl were injected in triplicate (method supplied by Polymer Laboratories). Samples were analysed with Waters Millenium 32 software and Minitab™ statistical software version 13.1.

3. Results and discussion

3.1. Pure components

Fig. 1 shows a DSC scan of spray dried lactose. Spray dried lactose was amorphous, as expected, as evidenced by the exotherm in the DSC scan (scan c). A halo and absence of peaks in the powder XRD profile also confirmed that the sample was amorphous (Briggner et al., 1994). Fig. 1 also shows a DSC scan of commercial grade anhydrous lactose with a melting endotherm in the 230 °C region indicative of β-lactose (scan a). A slight depression was evident at approximately 140 °C suggesting that some monohydrate may be present in the commercial sample. The DSC scan of lactose monohydrate shows a dehydration endotherm in the 140 °C region and an α-lactose melting endotherm at approximately 217 °C (Fig. 1 scan b). SEM of the spray dried lactose showed smooth spherical particles approximately 1–4 μm in diameter.

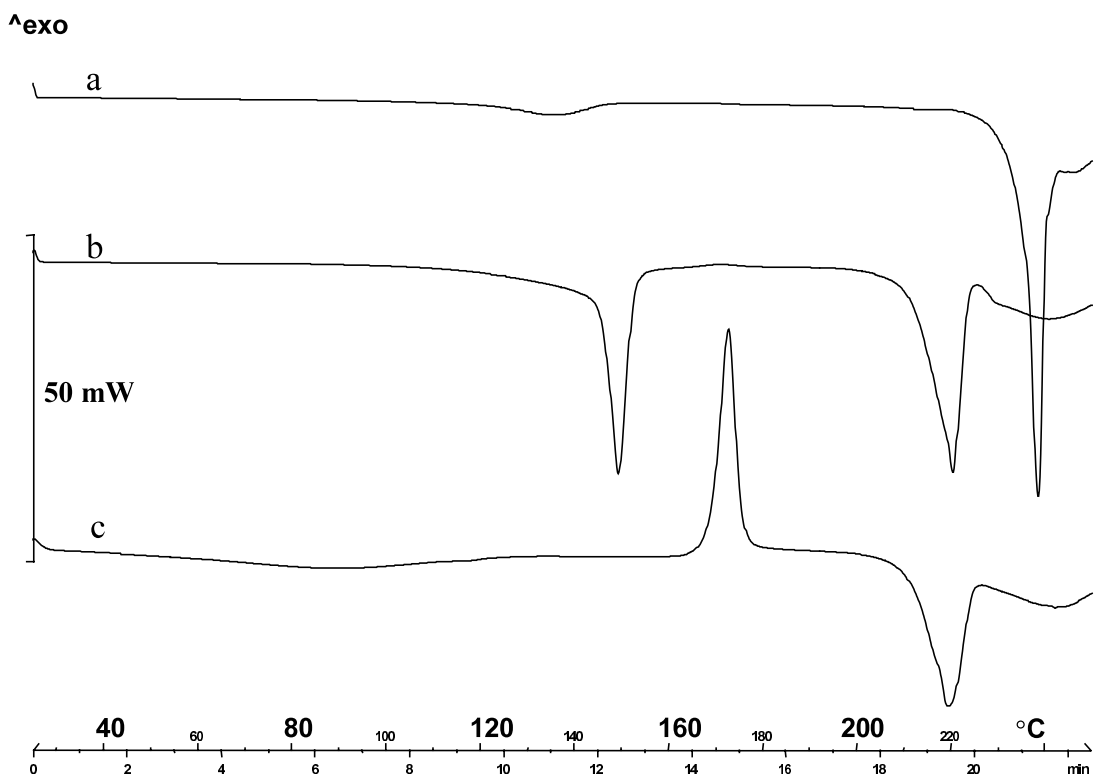

Fig. 1. DSC data for various forms of lactose (a) anhydrous lactose; (b) lactose monohydrate; (c) spray dried lactose.

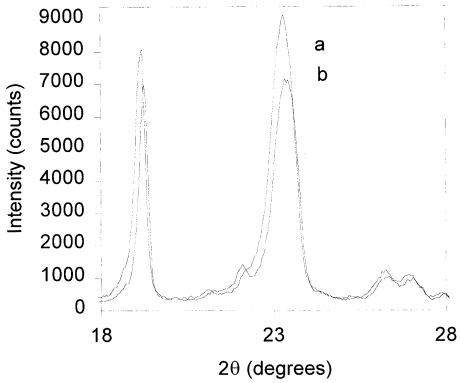

Fig. 2. XRD of (a) commercial sample of PEG; (b) spray dried PEG.

Attempts to spray dry PEG from water were unsuccessful since an outlet temperature below that of PEG's melting temperature was not achieved. Therefore, PEG was spray dried from ethanol 95%, using inlet temperatures of 75–77 °C which allowed outlet temperatures of less than 47 °C to be attained i.e. temperatures which were sufficiently low to allow solidification of PEG.

Fig. 2 shows the XRD scans of PEG before and following spray drying, both showing peaks indicative of crystallinity. The reduction in magnitude of the XRD peaks in the spray dried sample (Fig. 2, scan b), together with a reduction in enthalpy change for the melting endotherm by DSC was consistent with some reduction in PEG crystallinity on spray drying. XRD showed peak intensities of 8039 counts per second (CPS) at 19.2°(2θ) and 9120 CPS at 23.4° for non-spray dried compared with lower CPS of 6959 and 7108 for the spray dried PEG. The enthalpy changes by DSC were 192 J/g ($\pm$ 2.35 J/g) for the commercial PEG, and 173 J/g ($\pm$ 0.65 J/g) for the spray dried sample. Therefore, it appears that a reduction in crystallinity of $\sim$ 10–15% was achieved on spray drying.

PEG 4000 is known to exist in extended or once folded chain conformations, the latter being metastable with respect to the former (Chatham, 1985; Kambe, 1980). Once folded chain PEG melts at a lower temperature, approximately 5 °C lower by DSC than the extended form (Chatham, 1985; Kambe, 1980). Double peaks are observed by DSC when the sample consists of mixtures of once folded and extended chain PEG (Chatham, 1985; Kambe, 1980). DSC analysis of the spray dried PEG sample resulted in a single peak having a slightly lower PEG melting temperature than non-spray dried PEG. This could be due to the presence of amorphous polymer and/or PEG being present in the once folded chain form.

Fig. 3 shows scanning electron micrographs of spray dried PEG. Particle morphology was highly dependent on the processing conditions. Thus, depending on the spray drying conditions, either sphere-like particles with nodules or twig-like particles were produced. The sphere-like particles were produced when the outlet temperature was 45–46 °C, and these were quite large, approximately 50–70 μm in diameter. Their surfaces were not smooth, as is often the case with spray dried products, but were rather 'convoluted', of large surface area, appearing like aggregates of attached smaller particles (Fig. 3). If the outlet temperature was greater than 47 °C melting occurred, while outlet temperatures of 41–44 °C tended to produce elongated twig-like particles (Fig. 3).

The molecular weights by GPC of the commercial PEG and spray dried PEG were as follows: Mn; 2626 ($\pm$ 33.5) and 2644 ($\pm$ 65.6), Mw; 3856 ($\pm$ 110) and 3824 ($\pm$ 28.1), Mp; 4114 ($\pm$ 120) and 4084 ($\pm$ 27), respectively. There was no significant difference in molecular weights before and after spray drying of PEG, indicating that the heat involved in the spray drying procedure did not result in any significant polymer chain scission/breakdown (two sample t-tests; $P > 0.05$).

3.2. Lactose/PEG systems

The XRD pattern of co-spray dried lactose/PEG (5%) is shown in Fig. 4. The spray dried composite contained crystalline β-lactose indicated by peaks at 10.5 and 17.7°, peaks not shown by α-lactose monohydrate or anhydrous α-lactose. The maximum intensity β-lactose peaks (at 19.2 and 21°) are close to the maximum peak intensities of α-lactose monohydrate, stable anhydrous α-lactose and unstable anhydrous α-lactose at

19.9, 19.4 and 19.0°, respectively (Buma and Wiegers, 1967). PEG also shows a peak at 19.2°. This spray dried composite contained amorphous PEG as indicated by the reduction in peak intensity in the 23.3° region compared with the physical mix, also shown in Fig. 4 (scan c). Co-spray dried lactose/PEG 4000 (5%) shows a peak at 19.2 consistent with the presence of β-lactose and possibly some crystalline PEG. Crystallisation of PEG on storage is also evident (Fig. 4, scan b).

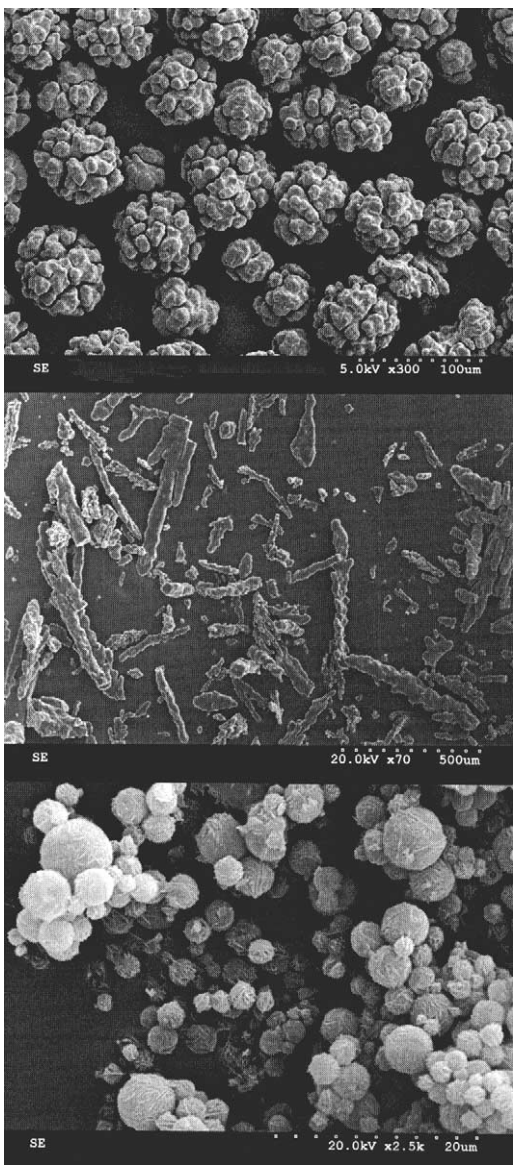

Fig. 3. Scanning electron micrographs of spray dried PEG (top and middle) and spray dried lactose/PEG 10% (bottom).

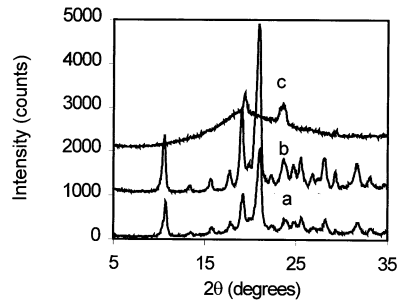

Fig. 4. XRD of lactose/PEG 4000 (5%). (a) Spray dried lactose/PEG 5%; (b) spray dried lactose/PEG 5% stored for 16 days at 4 °C 34% RH; (c) physical mix of amorphous lactose/PEG 5%.

The DSC of spray dried lactose/PEG (5%) is shown in Fig. 5 (scan a). No distinct PEG melting peak was observed in comparison to the physical mixes (Fig. 5, scan e and f), indicating the absence of detectable crystalline PEG. An exotherm is present, consistent with recrystallisation of amorphous lactose. The lactose melting endotherm occurs at approximately 231°C indicative of the melting of β-lactose at this temperature.

The XRD scan of spray dried lactose/PEG 4000 (10%) is compared with a range of physical mixtures of equivalent composition in Fig. 6. The spray dried system is practically amorphous, just showing low intensity broad peaks in the ranges 12–13 and 19–20°. These peaks could indicate traces of crystalline stable α-anhydrous lactose (Buma and Wiegers, 1967). No β or monohydrate lactose forms were evident initially. Crystalline PEG is also apparently absent.

The DSC scans of lactose/PEG 4000 (10%) is included in Fig. 5 (scan b). A very slight depression in the PEG melting endotherm region is observable by DSC, which could be attributed to some of the once folded chain conformation (Chatham, 1985). Alternatively the presence of the large amount of a second component (lactose) could also lower the position of the melting endotherm. On storage it was observed that the PEG melting endotherm shifts to a higher temperature which would be consistent with conversion to the more stable extended chain form. An

exotherm due to recrystallisation of amorphous lactose was observed and the lactose melting endotherm occurred at 214 °C consistent with α-lactose. A scanning electron micrograph of the spray dried sample, the most amorphous of the lactose-PEG composites prepared, is shown in Fig. 3. The product, relative to pure PEG, consists of relatively smooth microspheres of a much smaller size, being 2–5 μm in diameter consistent with Chidavaenzi et al. (2001) who reported spray dried lactose/PEG particles with a particle size of roughly 2–10 μm in diameter. The lactose/PEG composite particles are similar in size to those obtained on spray drying pure lactose but are less smooth.

The DSC and XRD scans of spray dried lactose/PEG 4000 (20%) are included in Figs. 5 and 7, respectively. This system was more crystalline than that prepared with 10% PEG. Spray dried lactose/PEG 4000 (20%) consists mainly of amorphous lactose with some crystalline α-anhydrous lactose and some crystalline PEG. The DSC shows a low PEG melting point (which could be indicative of once folded PEG). A small exotherm indicative of amorphous lactose and an endotherm corresponding to melting of α-lactose are also evident. The enthalpy change, due to the melting of PEG, was not as large as that of the corresponding physical mix.

DSC and XRD scans of spray dried lactose/PEG 4000 (30%) are also included in Figs. 5 and 7, respectively. This system showed similar characteristics to the 20% PEG system with both crystalline α-anhydrous lactose and amorphous

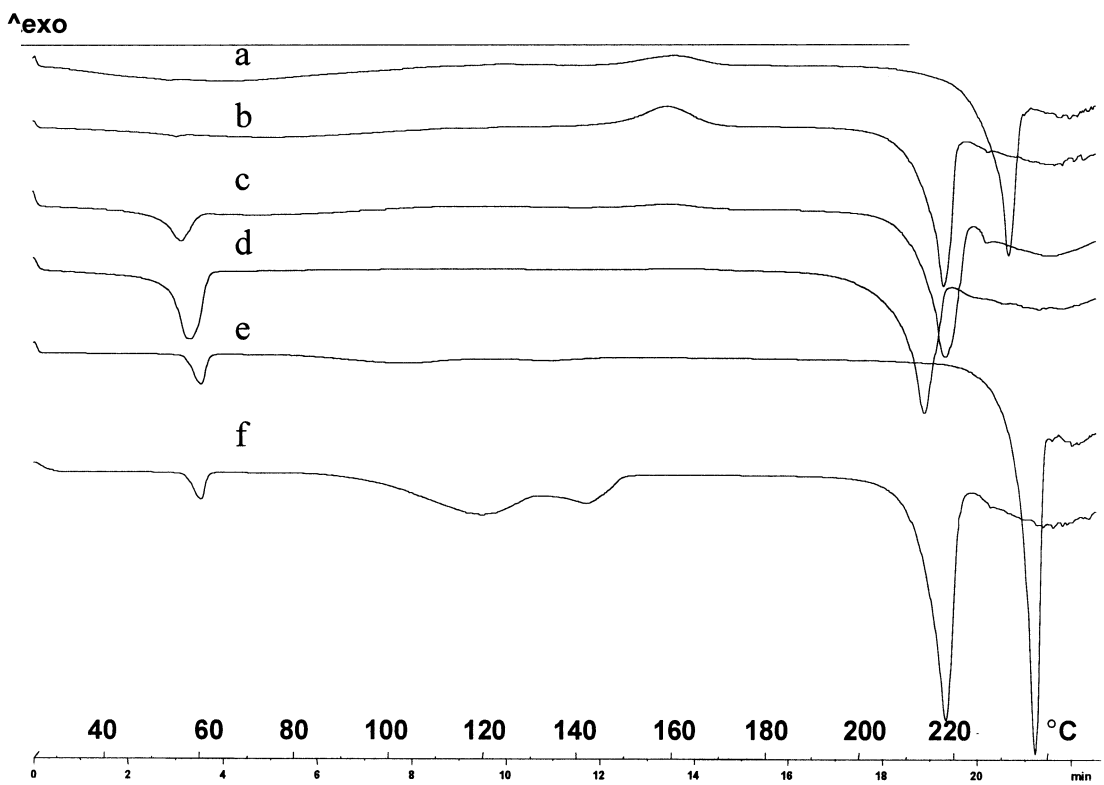

Fig. 5. DSC of spray dried lactose/PEG (5, 10, 20, 30% PEG) and physical mix of lactose anhydrous/PEG 5% and lactose monohydrate/PEG 5%. (a) Spray dried lactose/PEG 4000 (5%); (b) spray lactose/PEG 4000 (10%); (c) spray lactose/PEG 4000 (20%); (d) spray lactose/PEG 4000 (30%); (e) physical mix anhydrous lactose/PEG 4000 (5%); (f) physical mix lactose monohydrate/PEG 4000 (5%).

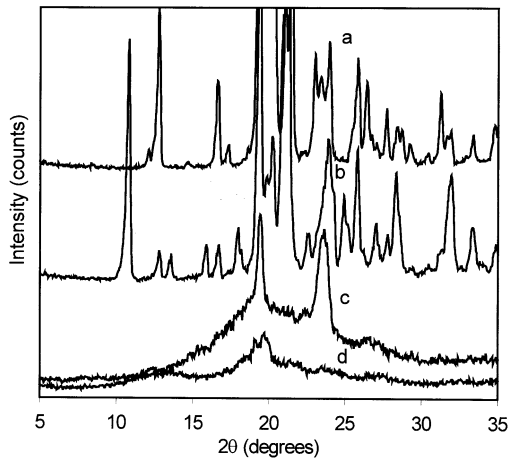

Fig. 6. XRD of lactose/PEG 4000 (10%) (a) physical mix lactose monohydrate/PEG 10%; (b) physical mix lactose anhydrous/PEG 10%; (c) physical mix amorphous lactose/PEG 10%; (d) spray dried lactose/PEG 10%.

lactose, and a slight reduction in PEG crystallinity, when compared with physical mix samples. An exotherm indicative of recrystallisation of amorphous lactose was measurable by DSC at higher resolution.

In summary, immediately following spray drying, all spray dried systems showed some amorphous lactose. The crystallinity of PEG is much reduced as indicated by the comparative sizes of the melting endotherms (Fig. 5). Lactose monohydrate was not present in any system, evidenced by the absence of dehydration endotherms in the DSC scans and lack of appropriate XRD peaks, for example the characteristic peak at 16.4. TGA experiments also confirmed the absence of the monohydrate. The physical mix of lactose monohydrate/PEG 5% showed an unusual dehydration endotherm, having two endothermic peaks. The form of lactose initially present in the spray-dried systems was dependent on the percentage of PEG in the composite. When 5% PEG was incorporated β-lactose was the only form of crystalline lactose present. When the PEG content is increased to 10% and above, the crystalline form of lactose when present is that of α-anhydrous lactose. PEG 4000 appears to be amorphous when present as 10% of the composite. While DSC scans show no detectable melting endotherm for the 5% PEG system, some crystalline PEG is suggested by XRD. Decreased PEG crystallinity was evident when solutions containing 20 and 30% PEG were spray dried.

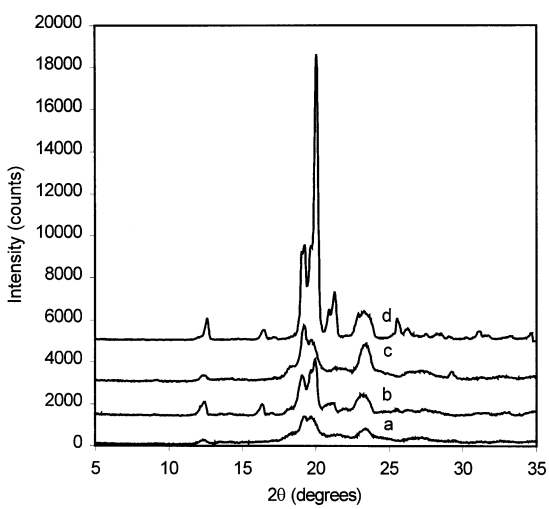

Fig. 7. XRD of spray dried lactose/PEG 4000 (a) spray dried lactose/PEG 4000 (20%); (b) spray dried lactose/PEG 4000 (20%) after storage for 10 days at 4 °C 75% RH; (c) spray dried lactose/PEG 30%; (d) physical mix of lactose monohydrate and PEG (20%).

SEM of lactose-PEG spray-dried composites showed that spherical particles were produced. The scanning electron micrograph of spray dried lactose/PEG 10% shows similar morphology to that found by Chidavaenzi et al. (2001). The approximate particle size of the spray dried lactose/PEG systems was 2–5 μm in diameter.

3.3. Effect of storage

3.3.1. Lactose/PEG 4000 (5%)

The physical instability of these high energy lactose/PEG composites was evident from the XRD data in Fig. 4, which showed recrystallisation of PEG in the 5% PEG system when stored at 4 °C 34% RH for 16 days. Fig. 8 shows DSC scans of spray dried lactose/PEG 5% stored under a range of temperature and RH conditions. Some recrystallisation of PEG had occurred after 5 days when stored at 4 °C 34% RH (probably the once folded PEG chain form). The exotherm due to crystallisation of amorphous lactose was also ab-

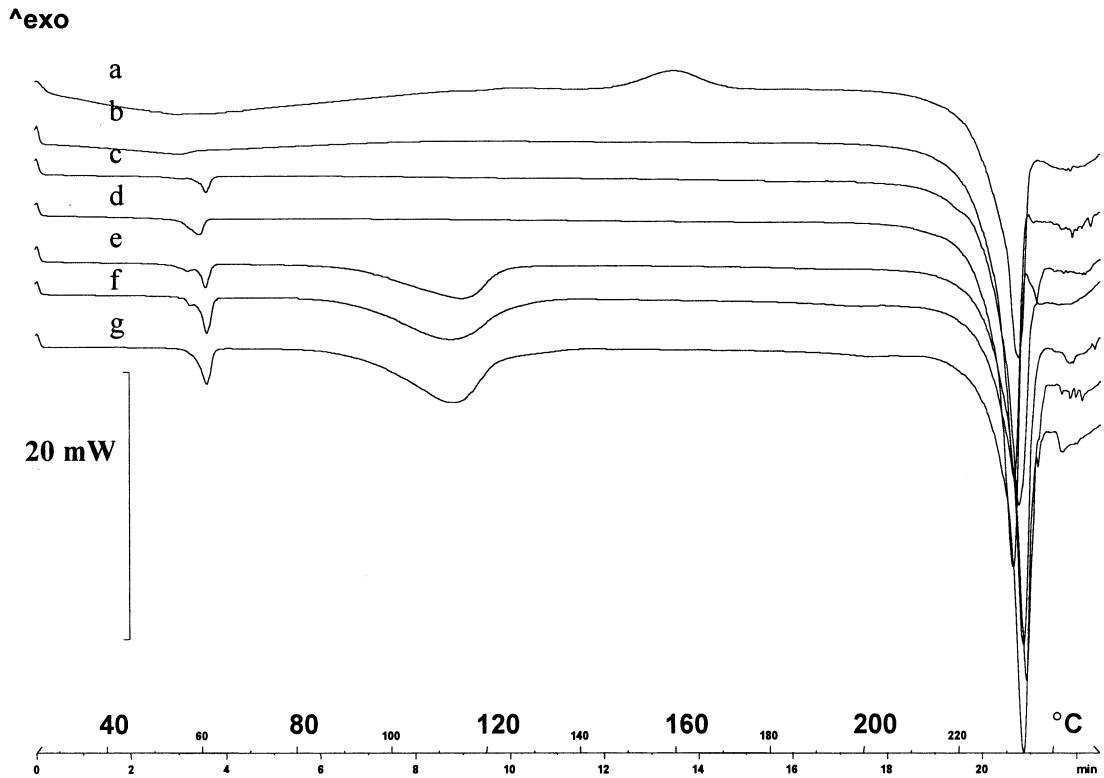

Fig. 8. DSC scans of lactose/PEG 5% following storage. (a) Spray dried lactose/PEG 5%; (b) spray dried lactose/PEG 5% stored at 4 °C 34% RH for 5 days; (c) spray dried lactose/PEG 5% stored at 45 °C 31% RH for 1 day; (d) spray dried lactose/PEG 5% stored at 30 °C 32% RH for 5 days; (e) spray dried lactose/PEG 5% stored at 30 °C 75% RH for 1 day; (f) spray dried lactose/PEG 5% stored at 30 °C 75% RH for 5 days; (g) spray dried lactose/PEG 5% stored at 30 °C 75% RH for 16 days.

sent. Lactose remained as the β form for the 10-month duration of storage under these conditions, as evidenced by peaks at 10.5 by XRD and the melting temperature by DSC. DSC and XRD data (Figs. 8 and 9) indicated that storage at the higher temperature and RH of 30 °C and 75% RH, resulted in conversion of lactose to a mixture of α-lactose monohydrate and β-lactose by 24 h, followed by conversion to α-lactose monohydrate alone. This behaviour is consistent with findings of Briggner et al. (1994) for lactose spray dried alone. PEG recrystallises and apparently transforms to the more stable extended chain form on storage at higher temperatures and humidity as can be seen from the DSC data in Fig. 8. The characteristic PEG double endotherms are clearly present after 5 days storage at 30 °C and 75% RH (Fig. 8e and f). Recrystallisation to some once folded chain PEG that melts at lower temperatures is observed and on further storage a single endotherm representative of melting of the more stable extended chain conformation is evident after 16 days (Fig. 8g).

3.3.2. Lactose/PEG 4000 (10%)

Fig. 10 shows DSC scans obtained on storage of spray dried lactose/PEG (10%) at 45 °C 75% RH. Recrystallisation of PEG occurred, firstly (after 6 h at 45 °C 75% RH) to the once folded form and then to a mixture of once folded and extended chain form (by 22 h). By 46 h, at 45 °C and 75% RH, the presence of some α-lactose monohydrate is observable by DSC (Fig. 10, scan d) and also XRD.

3.3.3. Lactose/PEG 4000 (20%)

The DSC scans of spray dried lactose/PEG (20%) are shown in Fig. 11. Initially PEG onset melting temperature was lower than that seen on storage and in physical mixes. This could be due to the lowered crystallinity and/or some PEG being present in the metastable once folded form. Following storage for 1 year at 4 °C 34% RH the PEG appears to remain in the once folded form. At 4 °C 34% RH no increase in lactose crystallinity was observed on storage. By week 15 a low temperature endotherm is observed in the 45 °C 31% RH sample, implying collapse of amorphous lactose, consistent with findings of Buckton et al. (1998) for lactose present alone. However, by 1 year this collapsed lactose does not appear to have recrystallised. Any crystalline lactose present remains as the anhydrous α form. Storage at low humidity but higher temperatures results in recrystallisation of PEG to the extended form, the rate depending on the temperature.

Fig. 11 also shows DSC of spray dried, stored spray dried (45 °C 75% RH) and physical mixtures of lactose/PEG (20%). Storage at high humidity resulted in conversion to α-lactose monohydrate as evidenced by the dehydration

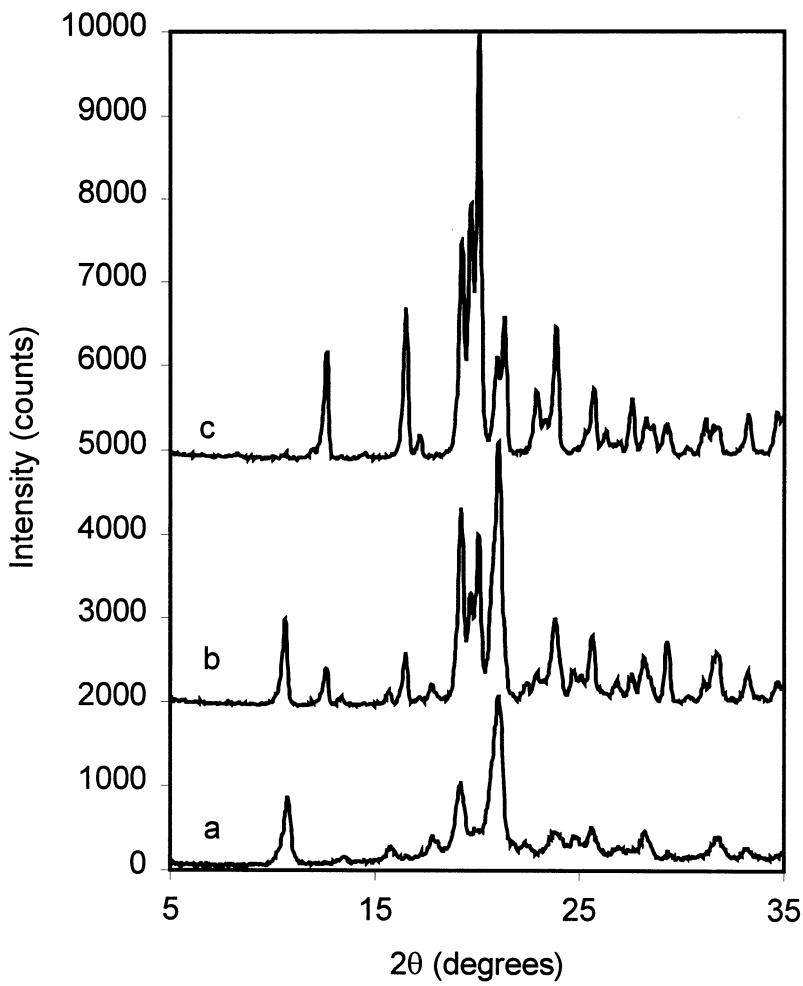

Fig. 9. Effect of storage conditions on the XRD pattern of spray dried lactose/PEG 5%. (a) Spray dried lactose/PEG 5%; (b) spray dried lactose/PEG 5% stored for 1 day at 30 °C 75% RH; (c) spray dried lactose/PEG 5% stored for 7 weeks at 30 °C 75% RH.

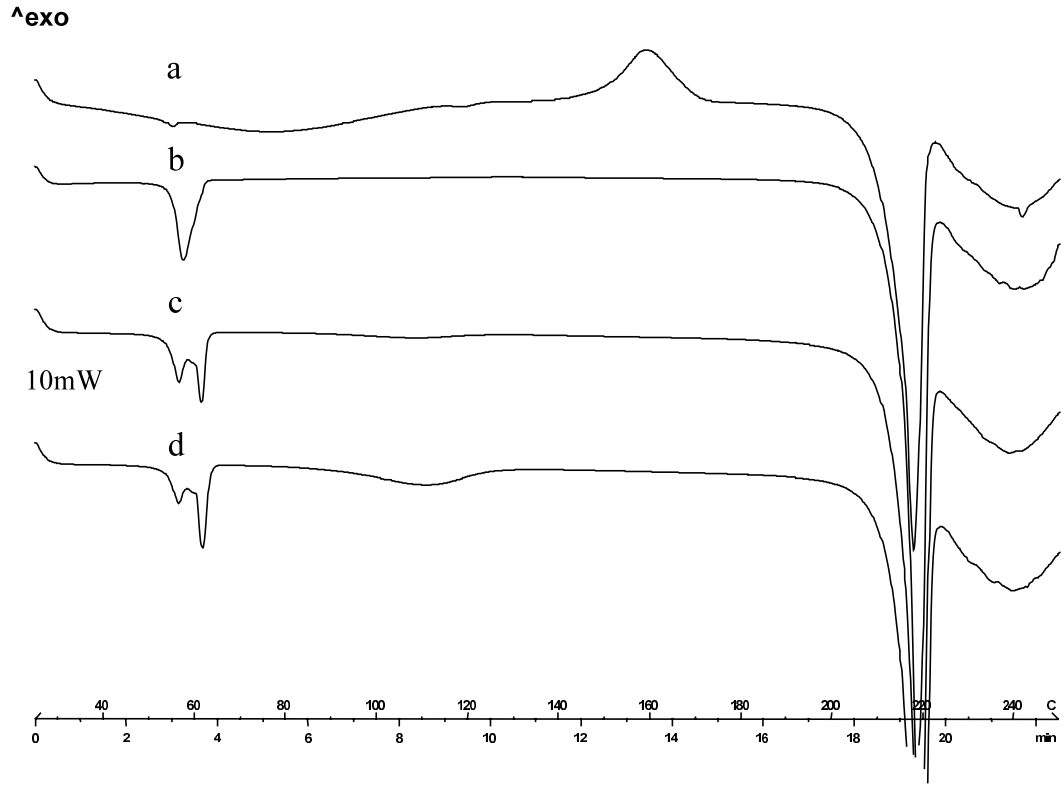

Fig. 10. DSC of spray dried lactose/PEG 4000 (10%) stored at 45 °C 75% RH showing beginning of conversion of PEG to more stable extended form by 22 h. (a) Spray dried lactose/PEG 4000 (10%) prior to storage; (b) spray dried lactose/PEG 4000 (10%) after 6 h storage at 45 °C 75% RH; (c) spray dried lactose/PEG 4000 (10%) after 22 h storage at 45 °C 75% RH; (d) spray dried lactose/PEG4000 (10%) after 46 h storage at 45 °C 75% RH.

endotherm. Conversion to α-lactose monohydrate occurred by 3 days storage even when stored at 4 °C. When stored at 4 °C 75% RH for 1 year a shoulder on the left of the PEG 4000 melting peak was observed indicating some PEG was still present in the once folded conformation. When the samples stored at 30 and 45 °C were analysed after storage for 3 days PEG melting was seen to be that of the extended chain form only. XRD of lactose/PEG 4000 over time (Fig. 7, scan b) shows an increase in the intensity of PEG peaks which is consistent with the increase in heats of fusion found by DSC indicating recrystallisation of PEG.

Jouppila et al. (1997) have shown that the transformation of amorphous lactose in freeze-dried skim milk, at relative humidities of 66.2% and greater, can be quantified using the Avrami equation and XRD peak intensity at 19, 20 and 22° as a measure of the extent of transformation. This equation may be written as

$$I = I^{\max}[1 - e^{-(K(t - t_0))^n}] \quad (1)$$

where I is the peak intensity at time t, t_0 is an induction time, $I^{\max}$ the peak intensity at time infinity, K the crystallisation rate constant, and n is the Avrami exponent which depends on the nucleation mechanism and the number of dimensions in which growth is occurring. Similarly Schmitt et al. (1999) used an equation of this form, having the value of 3 for n on the assumption of three-dimensional growth; to quantify spray dried lactose recrystallisation at a relative humidity of 57.5%, using gravimetry data. Thus in the absence of an induction time and expressing crystallinity as fraction or percent, Eq. (1) may be simplified to:

$$\theta = 1 - e^{-(Kt)^3} \quad (2)$$

where θ is the fraction or percentage crystallinity. From the storage data obtained at 75% RH and 45 °C, it is evident, from the growth in XRD peak intensities of the lactose/PEG composites, that the amorphous lactose converts to crystalline lactose monohydrate. Since PEG shows strong broad XRD peaks at 19.2 and 23.3°, the peak considered to best represent lactose monohydrate recrystallisation was that at 16.4° (Buma and Wiegers, 1967). Percent crystallinity, based on this peak for the spray dried lactose/PEG 10% composite, the most amorphous sample, is plotted in Fig. 12. Also included in Fig. 12 is the fitted line obtained using Eq. (2). The data gave a reasonably good fit with $K = 0.239$ per day (± 0.0127), $R^2 = 0.986$. The crystallisation of monohydrate is also evident from the DSC data in that it resulted in an increase in the endothermic peak at approximately 140 °C on the DSC scan. Thus ΔH for the dehydration endotherm could also be used to monitor the rate of recrystallisation of the monohydrate. This data is also shown in Fig. 12 for the 10% PEG system. A better fit to Eq. (2) was obtained giving a K estimate of 0.222 ± 0.006 ($R^2 = 0.997$), close to that obtained by XRD. Similar analysis of the ΔH of dehydration by DSC for pure lactose, lactose/PEG 5% and lactose/PEG 20% spray dried systems gave K values of 0.369 (± 0.026), 0.207 (± 0.033) and 0.565 (± 0.143), respectively. This limited data suggests that the presence of PEG at low concentrations (when it is mainly amorphous) may retard crystallisation of lactose. At higher PEG concentrations lactose recrystallisation may be accelerated.

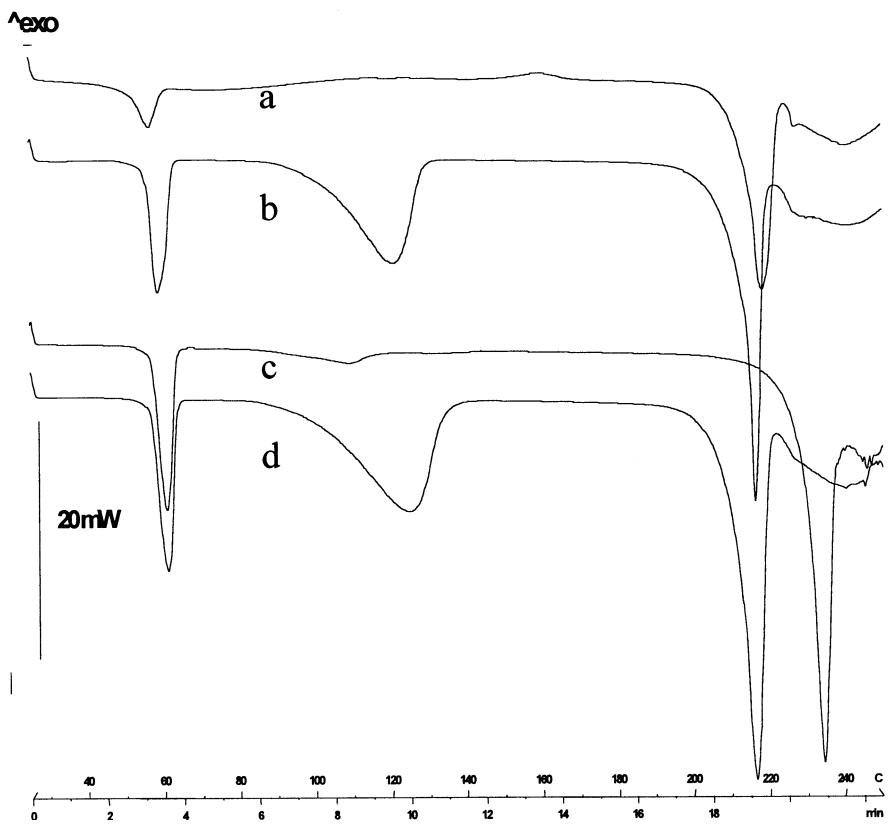

Fig. 11. DSC of lactose/PEG 20% (a) spray dried lactose/PEG (20%) prior to storage; (b) spray dried lactose/PEG 4000 (20%) stored for 3 days at 45 °C 75% RH; (c) physical mix of anhydrous lactose/PEG 4000 (20%); (d) physical mix of lactose monohydrate/PEG 4000 (20%).

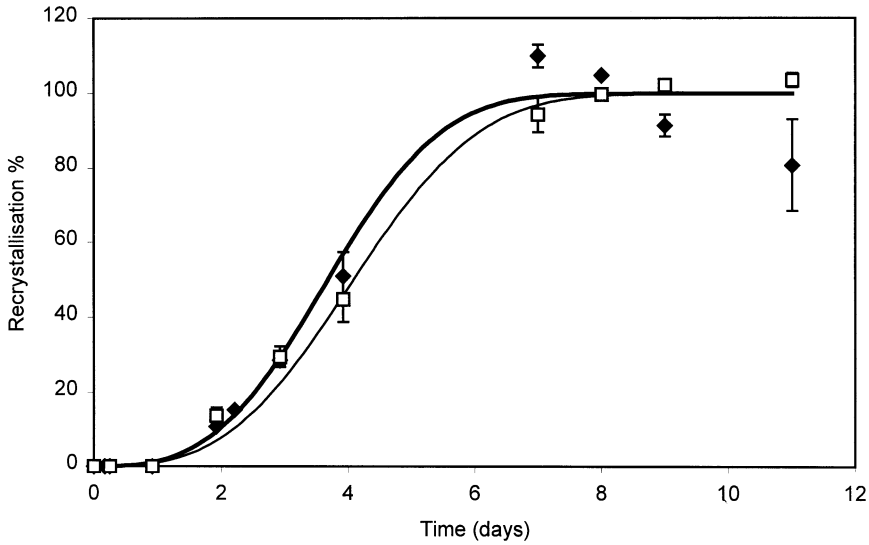

Fig. 12. Rate of recrystallisation of α-lactose monohydrate from spray dried lactose/PEG (10%). (◆) XRD; (□) DSC; (▬) fitted XRD; (—) fitted DSC.

4. Conclusions

The crystallinity of co-spray dried lactose/PEG 4000 composites varies depending on percentage of PEG present. All co-spray dried systems analysed contained amorphous lactose together with varying amounts of crystalline lactose. The crystalline lactose is initially present as β-lactose (i.e. in the lactose/PEG (5%) system), or as anhydrous α-lactose (i.e. in the lactose/PEG 4000 10, 20, 30% systems). The lactose/PEG 4000 (10%) system was initially the most amorphous of the spray dried composites prepared. Chidavaenzi et al. found crystalline β-lactose present when 12% PEG was spray dried with lactose but not when 1, 2, 4% PEG was present. We found β-lactose present when 5% PEG was spray dried with lactose but found it to be absent for 10, 20, 30% PEG systems. Chidavaenzi et al. found some crystalline α-lactose monohydrate present in all their spray dried lactose/PEG systems. None of the systems spray dried in the current work showed the initial presence of α-lactose monohydrate. On storage at low humidity, XRD and DSC data showed no conversion to lactose monohydrate, the initial amorphous lactose recrystallising to α-anhydrous lactose, or in the case of lactose/PEG 5% only β-lactose was observed. Storage of the spray dried lactose/PEG composites at high humidity results in conversion to α-lactose monohydrate, consistent with the findings of Briggner et al. (1994) for recrystallisation of spray dried lactose alone.

The crystallinity of PEG 4000 depended on its concentration in the composites. When spray dried alone it remained crystalline with 10–15% reduction in peak intensities. DSC shows a slight reduction in melting temperature, which could be due to the presence of some once folded chains or as a result of the slight reduction in crystallinity. PEG is known to be unstable when exposed to prolonged heating (Chatham, 1985). Spray drying of PEG did not result in polymer chain breakdown or in discoloration, which is typical of over exposure to heat. PEG was shown to be amorphous when spray dried with lactose at a concentration of 10% PEG. For all other concentrations of PEG studied, some crystalline PEG was likely present on spray drying but a non-crystalline form was also present as evidenced by the increase in PEG crystallinity, detected by both XRD and DSC, on storage. PEG appears to recrystallise as the extended chain form when stored at temperatures and humidity higher than 4 °C 34% RH.

DSC data suggested that initially the once folded form recrystallises on storage followed by recyrstallisation/conversion to the more stable extended chain conformation. Chidavaenzi et al. found that PEG spray dried with lactose was present in the extended chain conformation consistent with our results of spray dried lactose/PEG following storage.

The apparent lower crystallinity of the lactose/PEG systems prepared in the current work compared with those of Chidavaenzi et al. may be related to the differing spray drying conditions employed, namely feed concentration and airflow rate. Due to the rapid recrystallisation of some of these systems the timing of first analysis is critical to the interpretation of the results obtained.

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