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Research paper

The apparent plasticizing effect of polyethylene glycol (PEG) on the crystallinity of spray dried lactose/PEG composites

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Abstract

Aqueous solutions of lactose and polyethylene glycol (PEG) were spray dried in a Büchi Model 191 spray dryer with the aim to investigate the effect of PEG on the crystallinity of the composite. A PEG concentration of 10.7% by weight of solids was studied for PEG 200, 600, 1500, 4000 and 8000. For PEG 200 and 4000 additional concentrations from 1.5–19.3% to 1.5–32.4%, respectively, were investigated. The spray dried composites were analysed with X-ray powder diffraction and modulating differential scanning calorimetry. The crystallinity of lactose in the composites varied from 0% to 60%, dependent on the molecular weight and concentration of PEG. Apparently, lactose crystallinity is promoted by low molecular weight and high concentration of the PEG. PEG did not affect the lactose glass transition temperature. It is suggested that lactose and PEG are solidified separately during spray drying and that partial crystallization of lactose is associated with effects of PEG on the rate of drying.

Keywords: Spray drying; Polyethylene glycol; Lactose; Glass transition temperature; Crystallinity

1. Introduction

Control of the crystallinity of spray dried pharmaceuticals is of major importance. The viscous, glassy amorphous state is generally to prefer when biomolecules are included since these are normally better stabilized in this state [1–3]. Further, dissolution is generally faster from the amorphous state [4,5]. A potential drawback of the amorphous state is that this metastable form will, if not stabilized, spontaneously crystallize over time [6–8]. If uncontrolled crystallization takes place in a dry powder inhalation formulation it can result in agglomeration and caking of the primary particles so that the product becomes non-inhalable [7,9].

Spray drying is often used to produce amorphous composites. The formation of amorphous materials is generally attributed to the rapid drying process leaving very short time for evaporation and formation of the solid phase [10]. However, since crystalline products are obtained in some cases, other factors than the drying time can affect the process. Physico-chemical properties of the processed materials, in particular the glass transition temperature T_g and crystallization temperature T_c, and processing variables, i.e., product temperature, relative humidity of the drying air and drying time during processing, are other determinants. Additives of a high molecular weight, like some polymers with a high T_g, may increase the T_g and/or the stability of the spray dried composite [11]. It is possible that an additive with a low T_g may decrease the T_g and thereby initiate crystallization. If this is the case the additive acts as a plasticizer which promotes crystallization [1,12,13].

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Lactose is typically 100% amorphous after spray drying [14]. Co-spray drying of lactose and PEG 4000 at levels of 1–12% of solids was shown to result in totally crystalline composites [15]. Corrigan et al. [16] co-spray dried similar mixtures of lactose and PEG 4000 and obtained composites containing partly crystalline lactose. When Corrigan et al. [17] co-spray dried PEG 4000 or 20,000 and salbutamol sulphate the concentration of PEG was shown to affect the crystallinity of the final composite while co-spray drying of PEG 4000 and bendroflumethiazide resulted in totally amorphous composites [5].

Chidavaenzi et al. [15] suggested that the presence of PEG gives rise to a prolonged drying time because of the high affinity between PEG and water. By slowing the solidification rate both components are allowed to crystallize. It is possible, however, that the moisture content because of a plasticizing effect promotes crystallization during processing and handling, or that the PEG molecule itself has a direct plasticizing effect. If the PEG has a plasticizing effect this should be revealed by lowering the T_g of the spray dried composite.

PEG of molecular weights 10^2–10^7 have T_g's varying from −98 to −17 °C [18]. Mixtures of PEG and substances with higher T_g's such as lactose ($T_g = 118$ °C) should have T_g's in between these two T_g values provided that the two components are fully miscible. The composite $T_{g(mix)}$ can be estimated by the Gordon–Taylor equation [19,20]:

$$T_{g(mix)} = \frac{w_1 \cdot T_{g1} + k \cdot w_2 \cdot T_{g2}}{w_1 + k \cdot w_2}, \quad (1)$$

where w_1 and w_2 are the mass fractions of materials 1 and 2, respectively, T_{g1} and T_{g2} are the T_g's of materials 1 and 2, respectively, and k is a constant obtained by the Simha–Boyer rule:

$$k \approx \frac{\rho_1 \cdot T_{g1}}{\rho_2 \cdot T_{g2}}, \quad (2)$$

where ρ_1 and ρ_2 are the densities of materials 1 and 2, respectively, and T_{g1} and T_{g2} are the T_g's of materials 1 and 2, respectively. The method assumes that the two materials are miscible and that their free volumes are additive.

The aim of the present study was to investigate the crystallinity promoting effect of PEG on a co-spray dried substance using lactose as a model substance. Lactose/PEG composites were prepared using PEGs of different molecular weights and concentrations. The glass transition, crystallization and melting temperatures of the spray dried composites were determined. An aqueous solution of lactose was spray dried and the product used as a reference to the spray dried PEG/lactose composites.

2. Materials and methods

2.1. Materials

PEGs were obtained from Sigma–Aldrich, USA (PEG 200, PEG 600 and PEG 4000), BASF, Germany (PEG 1500), Merck, Germany (PEG 4000), and Acros Organics, Belgium (PEG 8000). Lactose was obtained from DMV, the Netherlands (Pharmatose 350 Mesh).

2.2. Preparation of feed solutions

Lactose solutions were prepared by dissolving lactose in water of MilliQ quality to a concentration of 10 g per 100 ml water.

Experiments on the effect of the PEG type were performed using feed solutions containing 10 g lactose per 100 ml water and PEG in a concentration of 10.7% by weight of total solids.

The effect of the PEG concentration was investigated in two additional series of experiments with PEG 200 and PEG 4000. The following concentrations of PEG 200 were used: 1.5%, 5.7%, 15.3% and 19.3% by weight of total solids (PEG and lactose). With PEG 4000 the concentrations used were 1.5%, 5.7%, 19.3% and 32.4%.

2.3. Spray drying

All solutions were spray dried in a mini spray dryer Büchi Model 191 (Büchi Labortechnik AG, Switzerland). The spray dryer was equipped with a two-fluid nozzle with an orifice diameter of 0.5 mm. The process variables are given in Table 1.

In the spray dryer the inlet of the drying air is placed beside the atomizer. This arrangement gives rise to a slight heating of the atomizer and the feed. It cannot be excluded that heating of the feed liquid will affect the crystallinity of the spray dried product because the cloud point of aqueous PEG solutions is lowered by the presence of low molecular weight saccharides [21]. In the experiments on the effect of the PEG type, additional experiments were made to evaluate the effect of cooling water: one series with circulating cooling water in the nozzle, and one series without.

All spray drying experiments were made in duplicate. The spray dried materials were collected immediately in closed containers with silica gel and stored at room temperature until analysis.

Table 1
Process conditions recorded during the spray drying experiments

Variable	Value
Feed temperature (°C)	25–29
Feed flow rate (ml/h)	250–300
Nozzle gas flow rate (Nl/h)	550
Aspirator capacity, i.e., drying gas flow rate[a] (%)	100
Inlet gas temperature (°C)	100
Outlet gas temperature (°C)	64–67
Surface temperature of the product collection vessel (°C)	45–47

[a] 100% aspirator capacity corresponds to a drying gas flow of about 45–60 m^3/h.

2.4. Characterization of the spray dried composites

X-ray powder diffraction analysis (XRPD) was performed using a XDS2000 2θ diffractometer (Scintag Inc., USA) with a liquid nitrogen cooled solid-state germanium detector, Cu-Kα radiation (1.5418 Å), 45 kV and 30 mA. The studied angular range was 2–35° (2θ) using a continuous scan of 1°/min and a step size of 0.03°. Two and four millimeter slits were used on the primary side and 0.5 and 0.3 mm slits on the secondary side. Spinning sample holders were used. During analysis, the samples were flushed with dry nitrogen to avoid moisture absorption. The percentage crystallinity of the lactose/PEG samples was determined. To assess the crystal forms of lactose, the collected diffractograms were compared with reference diffractograms for the α-lactose anhydrate, α-lactose monohydrate and β-lactose anhydrate forms.

Modulating differential scanning calorimetry (MDSC) was performed using a DSC 2920 and a DSC Q1000 (TA Instruments, USA). Samples were filled into aluminium pans. The cover was placed loosely and the sample dried in the MDSC under a nitrogen flow for 60 min at 30 °C and then scanned from 10 to 265 °C with a rate of 2.5 °C/min, modulating ±0.25 °C every 40 s. The softwares belonging to the DSC's were used for determination of T_g (midpoint), T_c (midpoint) and T_m (T_{m1}: midpoint and T_{m2}: onset) of the spray dried products.

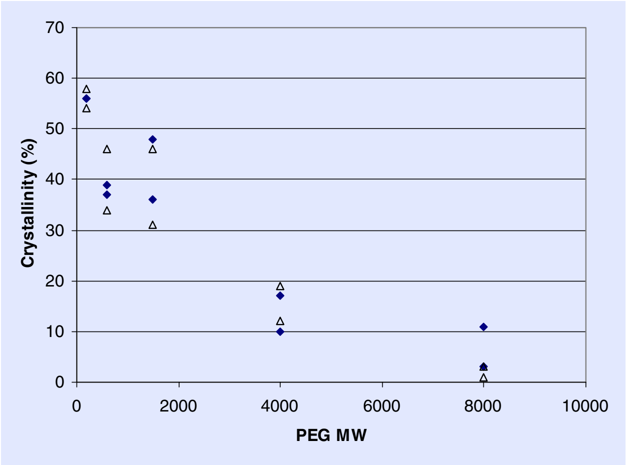

Fig. 1. Effect of the PEG molecular weight on the crystallinity of the spray dried lactose/PEG composites containing 10.7% w/w PEG. Experiments with cooling of nozzle (◆) and experiments without cooling (△).

3. Results

3.1. Spray dried lactose

Spray drying of the 10% lactose feed solution produced an amorphous material, which by MDSC analysis showed a glass transition temperature of 118 °C. This agrees well with data reported in the literature [22]. The crystallization temperature appeared at 174 °C and the melting temperature at 205 °C. The crystallization enthalpy was 101–102 J/g.

3.2. Effect of PEG type

Fig. 1 shows the effect of the molecular weight of PEG on the crystallinity of the co-spray dried lactose/PEG composites containing 10.7% PEG. The highest proportion, 54–58% crystallinity, was obtained using PEG 200 while PEG 8000 resulted in less than 12% crystallinity. In addition, Fig. 1 shows that spray drying with and without circulating cooling water in the nozzle did not affect the crystallinity of the composites.

Table 2 summarises the data obtained by analysis of the composites. XRPD analysis showed that the crystalline part of composites prepared with PEG 4000 and 8000 consisted of β-lactose anhydrate. Composites prepared with PEG 200, 600 and 1500 contained α- and β-lactose anhydrate. Some of the composites prepared with PEG 200 contained α-lactose anhydrate only.

MDSC analysis did not show any glass transition of composites prepared with PEG 200 and 600, while the glass transition temperature of composites containing PEG 1500, PEG 4000 and PEG 8000 was 118 °C, i.e., the same as for spray dried lactose. According to the Gordon–Taylor equation, T_g of the composites should be 81–82 °C.

The melting temperatures of PEG 1500, 4000 and 8000 are 49, 62 and 63 °C, respectively. Table 2 shows that the melting peaks (T_{m1}) are slightly lowered compared to the starting materials. The T_{m2}'s were difficult to determine with good precision due to various shapes of the melting peaks, which may be caused by the different lactose forms in the samples (α-, β- and/or a mixture of them). PEG 200 is liquid at room temperature and the melting point of PEG

Table 2
MDSC analysis of lactose/PEG composites (10.7% w/w PEG) and lactose crystal form determined by XRPD

Composites PEG (MW)	Crystal form	T_g (°C)	T_c (°C)	T_{m1} (°C)	T_{m2} (°C)
200	α-lactose or α and β-lactose	nd	154	nd	220
600	α and β-lactose	nd	175	nd	221
1500	α-lactose or α and β-lactose	118	165	48	215
4000	β-lactose	118	159	59	218
8000	β-lactose	118	155	60	212

Glass transition temperature T_g, crystallization temperature T_c, and melting temperatures T_{m1} and T_{m2} for the two components. nd, not detectable.

600 is 20 °C, which is too low to be detected at the analytical conditions. In PEG's of smaller molecular weight there are less bonds that have to be broken upon melting, and this results in a decreased T_m. The MDSC scans indicated that crystallization of the composites took part at temperatures in the range of 154–175 °C. The crystallization enthalpies were in the range of 1–10 J/g which is significantly lower than that of spray dried lactose (101 J/g).

3.3. Effect of the PEG concentration

Figs. 2 and 3 show the effect of the concentration of PEG 200 and PEG 4000 on the crystallinity of the spray dried composites. They demonstrate that the crystallinity increases as the PEG concentration is increased. Apparently, a plateau is reached at a certain concentration. The plateau level for composites with PEG 200 is around 50–60% crystallinity, and for PEG 4000 around 30–40%. Solutions with 19.3% PEG 200 gave minimal yields since the powder stuck to the walls of the cyclone. Only in one run (out of three) sufficient yield could be captured in the product collection vessel. Higher PEG concentrations were therefore not evaluated. At PEG concentrations just below those required to obtain the plateau value, the crystallinity was more difficult to control (see Figs. 2 and 3).

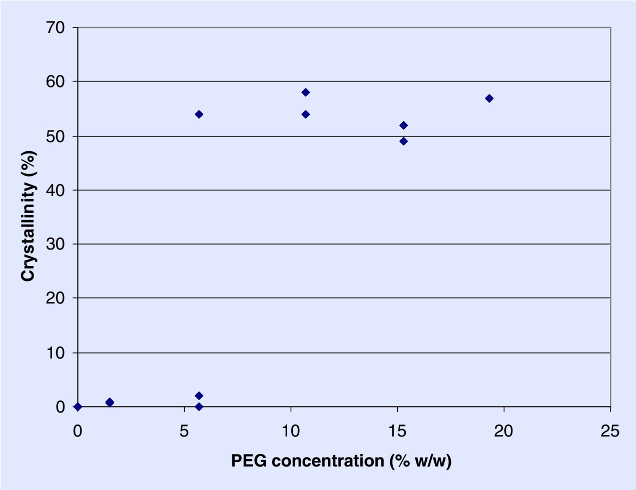

Fig. 2. Effect of the PEG 200 concentration on the crystallinity of spray dried lactose/PEG composites.

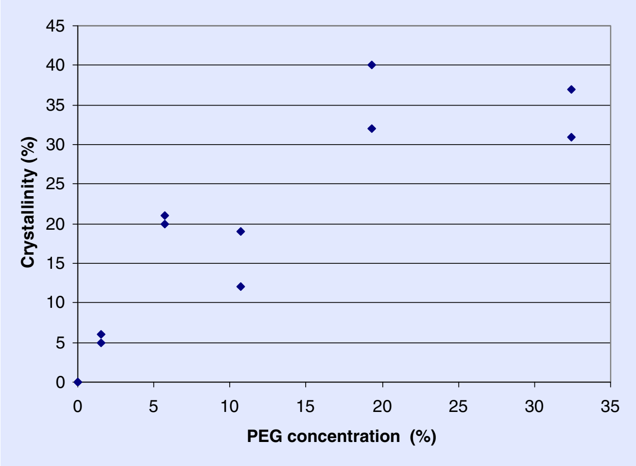

Fig. 3. Effect of the PEG 4000 concentration on the crystallinity of spray dried lactose/PEG composites.

The spray dried composites with PEG 200 contained α-lactose anhydrate or β-lactose anhydrate or a mixture of these forms. With PEG 4000 all composites contained β-lactose anhydrate only.

MDSC analysis of the composites showed that a glass transition could be detected only for the lactose/PEG 200 composite containing 1.5% w/w PEG; T_g was 108 °C. With PEG 4000 the T_g was 118 °C at the low concentration and not detectable at the higher concentrations. T_g calculated by Gordon–Taylor equation is 112 °C at 1.5% w/w PEG 200 or 4000, and further reduced to 57 °C at the 19.3% w/w PEG 200 concentration and 31 °C for the 32.4% w/w PEG 4000 concentration.

The composites containing 1.5% w/w PEG 200 showed crystallization at 132 °C and a crystallization enthalpy of approx. 50 J/g. With 1.5% w/w PEG 4000 showed the crystallization temperature was 120 °C and the crystallization enthalpy was approx. 50 J/g.

In all the PEG/lactose composites melting peaks of lactose with an onset at about 205 °C were observed. With PEG 4000 melting peaks were also observed at 56–60 °C, i.e., at slightly below the temperature for pure PEG 4000, 62 °C; one exception was the 1.5% w/w PEG 4000 composites which did not show any peak of the PEG.

4. Discussion

The results show that the presence of PEG promotes crystallization of lactose when the two components are co-spray dried. Crystallization is favoured by a low molecular weight and a high concentration of PEG. For the partly crystalline composites MDSC analysis showed melting peaks of lactose at approximately the same temperature range as for the spray dried lactose. For PEG a slight lowering of the melting peak of the spray dried product compared to the starting material was seen. This is attributed to crystallization of PEG into folded chains [16].

Apart from the composite prepared with 1.5% PEG 200, a lowering of the glass transition temperature compared to spray dried lactose was not observed. This indicates that only small amounts of the low molecular weight PEG are miscible with lactose. A general plasticizing effect of PEG can be excluded. The melting peak of the crystalline lactose remains almost unaffected of PEG. In the absence of an effect upon the glass transition it is likely that the two components crystallize separately in the composites, although a region of a lactose/PEG mixture may be present.

The formation of β-lactose anhydrate in composites prepared with PEG 4000 and 8000 is in agreement with the findings of Corrigan et al. [16]. Composites prepared with

PEG 200, 600 and 1500 contained anhydrates of α-lactose and/or β-lactose, which is likely to attribute to an effect of the evaporation rate during spray drying. Chidavaenzi et al. [23] found that spray drying of solutions at increased temperatures gave rise to increased contents of β-lactose compared to α-lactose. This effect was attributed to an increased evaporation rate. At temperatures below 93.5 °C, β-lactose is more soluble than α-lactose in water, and above 93.5 °C, the opposite is valid [24]. In the present experiments the outlet gas temperature and, thus, the highest product temperature was about 66 °C. At this temperature the α-lactose form precipitates first at equilibrium. However, due to the short evaporation period equilibration is probably not obtained. β-lactose that is more soluble gets overrepresented. The finding of only the β-lactose form in composites with PEG 4000 and 8000 indicates a higher evaporation rate than with the lower PEG molecular weights because the lower PEG molecular weights bind the water more efficiently. Thus, the α/β lactose ratio seems generally to be an indicator of the evaporation rate during spray drying of lactose.

The effect of PEGs on the lactose crystallization supports the interpretation given by Chidavaenzi et al. [15]. Compared to the higher PEGs, the more hydrophilic PEG 200 prolongs the drying phase during the process. The effect of the PEG concentration can be interpreted in the same manner. There are, however, two observations that do not fully support this interpretation. With an increasing PEG concentration the crystalline proportion of the composites reaches a plateau, which is unexpected if the crystallization should depend only on the prolonged drying phase. Re-crystallization of the amorphous part of the composites is recorded by the MDSC analysis. At PEG concentrations higher than 1.5% the peaks were very small as reflected by the low crystallization enthalpies being approx. 1% of that of spray dried lactose.

It is suggested that lactose and PEG are partly separated during the drying process resulting into composites consisting of three regions: (a) a molecular mixture of lactose and PEG, (b) lactose and (c) PEG. The amount of region (a) increases as the PEG molecular weight decreases; the larger PEG molecules rather separate from the lactose. The relative amount of this region is also affected by the PEG concentration. The influence of the PEG concentration (Figs. 2 and 3) indicates that a critical amount of PEG is needed to start nucleation of lactose crystals and that a limited amount can be mixed on a molecular level with lactose. In the region just below the critical amount of PEG required to obtain a maximum plateau value of crystallinity, it is difficult to control the degree of crystallinity. Additional experiments were performed and confirmed the variation of crystallinity in this region. A similar tendency can be seen in Fig. 3 for PEG 4000 at a concentration of 10.7%.

It is possible that the PEGs lower the T_g of lactose and initiate the crystallization process c.f. the slight decrease of T_g for the composites of lactose/PEG 200. The presence of PEG means binding of water which in itself supports crystallization as does the prolonged drying phase reflected by crystallization of lactose into α- or β-lactose.

The regions (b) and (c) of pure lactose or pure PEG must be present in the composites since the melting peaks of lactose as monitored by MDSC were not affected by the co-spray drying; the melting peak of spray dried PEG was slightly lowered as discussed by Corrigan et al. [16].

The process conditions given in Table 1 indicate a very low relative humidity of the drying air in the drying chamber and cyclone. Accordingly, the MDSC scans did not show any evidence of residual moisture in the composites. Sample storage and analytical conditions were chosen to prevent access of humidity. It is therefore excluded that residual humidity has any importance for the crystalline proportion of the composites. When submitted to gravimetric vapour sorption analysis, humidity initiated re-crystallization of lactose leading to almost 100% crystallinity.

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