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International Journal of Pharmaceutics 273 (2004) 171–182
international journal of pharmaceutics
www.elsevier.com/locate/ijpharm

Predicting the physical state of spray dried composites: salbutamol sulphate/lactose and salbutamol sulphate/polyethylene glycol co-spray dried systems

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Received 12 August 2003; received in revised form 16 December 2003; accepted 6 January 2004

Abstract

The effect of spray drying salbutamol sulphate, salbutamol sulphate/lactose and salbutamol sulphate/polyethylene glycol (PEG) solutions was investigated. Co-spray drying salbutamol sulphate with lactose, which is amorphous when spray dried alone, resulted in amorphous composites. Co-spray drying salbutamol sulphate with PEG 4000 and PEG 20,000, which do not form amorphous systems when spray dried alone, resulted in systems of varying crystallinity, the crystallinity depending on the weight ratio of polymer to drug.

Examination of the physical properties of these salbutamol sulphate co-spray dried systems and those of bendroflumethiazide/PEG and lactose/PEG composites suggested that the formation and physical stability of amorphous composites prepared by spray drying is dependant on whether the glass transition temperature, T_g, of one of the two components is high enough to result in a T_g of the composite sufficiently high that the Kauzmann temperature of the mix is greater than the temperature of storage. The modified Gordon–Taylor equation proved to be useful in predicting the likelihood that a two-component composite will be amorphous on spray drying. Furthermore, the Gordon–Taylor equation was also useful in predicting the likely physical stability of amorphous two component composites and predicted that even polymers with apparently low T_gs, such as PEGs, may be stabilised in an amorphous composite by a suitable additive having a sufficiently high T_g.

Keywords: Spray dried composites; Salbutamol sulphate; Physical stability prediction; Gordon–Taylor equation

1. Introduction

Salbutamol is widely used in inhaler products. Dry powder inhaler formulations generally consist of micronised drug and inert coarse carrier particles. The excipients are included to aid flow and dispersibility of drug particles, which may be highly cohesive when micronised (Timsina et al., 1994). Inclusion of a carrier excipient also overcomes the problem of dose metering if fractions of a milligram of a potent medicament are to be delivered (Ganderton and Jones, 1992). Spray drying is known for its ability to produce fine microspherical powders with good flow properties and therefore should prove a useful method of production for inhalation products, especially for the production of powders for dry powder inhalers. Since co-spray drying for inhalation delivery appears to have advantages, in terms of powder particle size and flowability, as well as uniformity of the mix, the model drug salbutamol sulphate was co-spray dried with

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doi:10.1016/j.ijpharm.2004.01.005

various proportions of lactose and polyethylene glycols (PEGs) and their solid state properties evaluated.

In this paper, we also examine the predicted glass transition temperatures and Kauzmann temperatures of salbutamol sulphate co-spray dried systems together with those of previously co-spray dried systems such as lactose/PEG (Corrigan et al., 2002) and bendroflumethiazide/PEG systems (Corrigan et al., 2003). Compatible blends of amorphous materials exhibit a single glass transition (T_g) intermediate between the T_g values of the individual components (Hancock and Zografi, 1994). The higher the T_g is relative to the actual storage temperature the more stable the system will be. The Kauzmann temperature is generally accepted as the temperature below which translational and rotational motions cease on pharmaceutically relevant time scales (Hancock et al., 1995). Metastable amorphous materials are expected to be physically stable when stored at a temperature less than or equal to their Kauzmann temperature (Hancock et al., 1995; Zhou et al., 2002).

2. Experimental

2.1. Materials

Salbutamol sulphate was kindly provided by IVAX Pharmaceuticals, Ireland, PEG 4000 was purchased from Riedel de Haën (Germany) and PEG 20,000 was purchased from Fluka. Physical mixes were prepared using sub 125 μm mesh sieved powders mixed in a Turbula Mixer™ for 5 min (at 42 rpm).

All spray dried systems were analysed by DSC and XRD within 1 h of production.

2.2. Spray drying methodology

Salbutamol sulphate was spray dried as a 10% w/v aqueous solution and as a 0.6% w/v solution from ethanolic solvent consisting of 75% ethanol and 25% water. A Büchi 190 spray drier was used. When spray drying the aqueous solution, an inlet air temperature of 150–152 °C, an outlet temperature of 75–78 °C, pump setting 7, and an airflow rate of 650 l/h were used. When spray drying the ethanolic solution an inlet air temperature of 100–102 °C, an outlet temperature of 60–64 °C, a pump rate setting of 6%, and an airflow rate of 500 l/h were used.

Salbutamol sulphate/lactose systems, consisting of 5, 20 and 40% lactose by weight of total solids, were spray dried as 10% w/v aqueous solutions using a Büchi 191 spray drier with an inlet air temperature of 150 °C, an outlet air temperature of 103–105 °C, a pump rate setting of 10% and airflow rate of 600 l/h. The 20% lactose system was also spray dried at a feed concentration of 2.5% w/v from an aqueous solution under the same conditions except that the outlet temperature range was 98–103 °C.

Salbutamol sulphate/PEG 4000 systems consisting of 5, 20 and 40% PEG 4000 by weight of total solids were spray dried as 2.5% w/v aqueous solutions using a Büchi 191 with an inlet air temperature of 150 °C, outlet temperatures of 91–97, 92–97 and 95–98 °C for the 5, 20 and 40% PEG 4000 systems, respectively, a pump rate setting of 18% and airflow rate of 600 l/h.

Salbutamol sulphate/PEG 20,000 systems consisting of 5, 20 and 40% PEG 20,000 by weight of total solids were spray dried as 2.5% w/v aqueous solutions using a Büchi 191 and the same conditions as for the PEG 4000 systems, except that the outlet temperatures were 100–105, 90 and 96–100 °C, for the 5, 20 and 40% PEG 4000 systems, respectively.

2.3. Assessment of physicochemical properties

X-ray powder diffraction measurements (XRD) were made on samples using a Siemens D500 Diffractometer as previously described (Corrigan et al., 2002).

Differential scanning calorimetry (DSC) was performed using a Mettler Toledo DSC 821^e as previously described (Corrigan et al., 2002).

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

Energy Dispersive X-Ray Analysis (EDXA) was carried out using Princeton Gamma Tech Imix-PTS EDX analysis on the Hitachi S-3500N variable pressure SEM with a 10 mm^2 UTW detector. For qualitative EDXA, powder samples were utilised and an area mapped for the presence of the atom being analysed.

HPLC analysis of salbutamol sulphate was performed using a variation of the USP Pharmacopeia (USP Pharmacopeia, 2000) method for HPLC analysis of salbutamol sulphate, with sodium-1-heptanesulfonic acid used in the preparation of the mobile

phase instead of sodium-1-hexane-sulfonic acid. A C18 column (Techopak 10 C18, Labquip) attached to a Shimadzu LC-10 AT VP liquid chromatograph with a Shimadzu SCL-10A system controller, a Shimadzu SPD-10A VP UV-Vis detector, a Shimadzu DGU-14 degasser and a SIL-10AD VP autoinjector was used and the system was operated at a flow rate of 1 ml/min. Samples were analysed using Shimadzu Class VP software (version 6.10).

True density measurements were performed by helium pycnometry using a calibrated AccuPyc 1330 instrument (Micromeritics, USA). Prior to analysis, the samples were dried overnight to a constant weight in a vacuum oven at 50 °C with a vacuum pressure of 600 mbar. The mass of each sample was accurately determined using a MT5 microbalance (Mettler Toledo, Switzerland). Each sample was analysed in duplicate.

3. Results and discussion

3.1. Salbutamol sulphate

Salbutamol sulphate spray dried from water resulted in an amorphous product evidenced by the halo shown by XRD. The production of amorphous salbutamol sulphate on spray drying from aqueous solution was previously reported by Chawla et al. (1994). Spray drying of salbutamol sulphate from ethanolic solution (75%) also yielded a similar amorphous product. The starting material showed an endothermic peak by DSC at a temperature at approximately 200 °C, consistent with the findings of Ward and Schultz (1995) and recently ascribed to decomposition (Larhrib et al., 2003).

The lack of visible exotherms, together with the lower and broader melting endotherms, obtained by DSC of spray dried salbutamol sulphate, is consistent with the material remaining amorphous on heating. HPLC indicated that both spray dried salbutamol sulphates were not altered chemically by the process. EDXA detected sulphur atoms in the spray dried material consistent with the spray dried material remaining as the sulphate salt form. Chawla et al. (1994) spray dried salbutamol sulphate from aqueous solution and compared the infrared spectra to that of their starting material. They also concluded that spray drying did not appear to alter salbutamol sulphate chemically.

SEM micrographs of the spray dried material showed small spherical particles with diameters ranging from approximately 1 to 7 μm and approximately 1 to 3 μm for particles produced from the aqueous and ethanolics solvents, respectively. The surfaces of the particles in both cases were slightly dimpled.

3.2. Salbutamol sulphate/lactose systems

The salbutamol sulphate/lactose 5, 20 and 40% systems were all amorphous, as shown by XRD analysis (Fig. 1). The 20% systems showed similar XRD and DSC scans regardless of the feed concentration at which they were spray dried. The XRD scans of the various spray dried systems show diffuse halos. In contrast a physical mix of salbutamol sulphate/lactose 20% showed peaks attributable to both crystalline components (Fig. 1).

The DSC scans of spray dried salbutamol sulphate/lactose composites and a DSC scan of a physical mix of salbutamol sulphate/lactose 20% is shown in Fig. 2. The DSC scans of the spray dried systems did not show exothermic events indicative of recrystallisation of amorphous material. The spray dried systems did show degradation of salbutamol sulphate on heating, which was not evident in the physical mixes. The DSC scans of the spray dried salbutamol sulphate/lactose systems appeared very similar to the scans of salbutamol sulphate spray dried alone. The spray dried salbutamol sulphate/lactose systems showed broad endotherms prior to 100 °C consistent with loss of absorbed moisture. Two very small endotherms at approximately 120 and 140 °C and a broad melting peak starting at approximately 165 °C, with jagged peaks indicating degradation, were also observed. The lactose used in the physical mix was lactose monohydrate, therefore the endotherm visible in the DSC scan of the physical mix at approximately 150 °C is consistent with the dehydration of the monohydrate. The melting endotherm of spray dried lactose alone by DSC has an onset temperature at 217 °C (Corrigan et al., 2002). In the co-spray dried salbutamol sulphate/lactose systems no distinct peak was observed at this temperature. The melting of lactose may have shifted to a lower temperature and be obscured by the salbutamol sulphate related endotherm. In the case of the physical mix of salbutamol sulphate/lactose, the broad endotherm at approximately

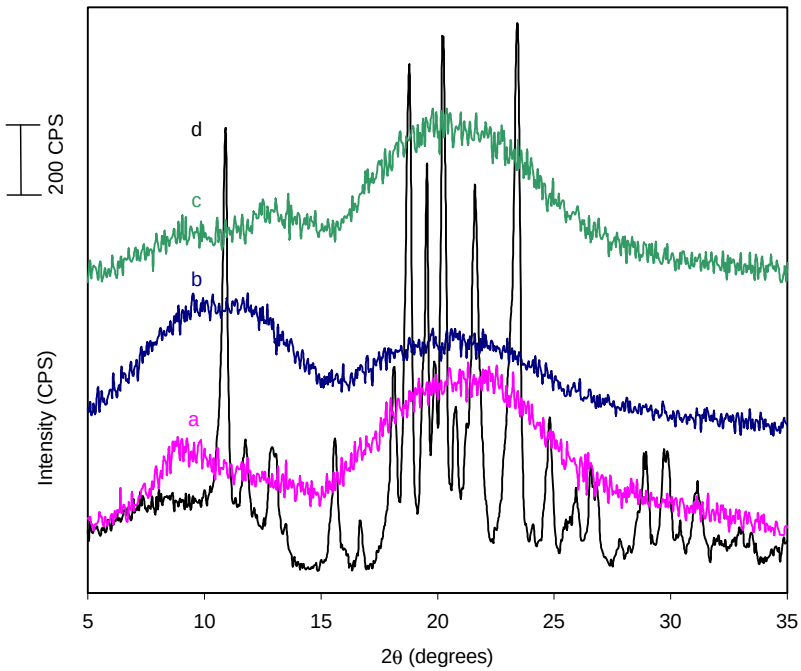

Fig. 1. XRD scans of (a) spray dried salbutamol sulphate/lactose 5%; (b) spray dried salbutamol sulphate/lactose 20%; (c) spray dried salbutamol sulphate/lactose 40%; and (d) physical mix of salbutamol sulphate/lactose 20%.

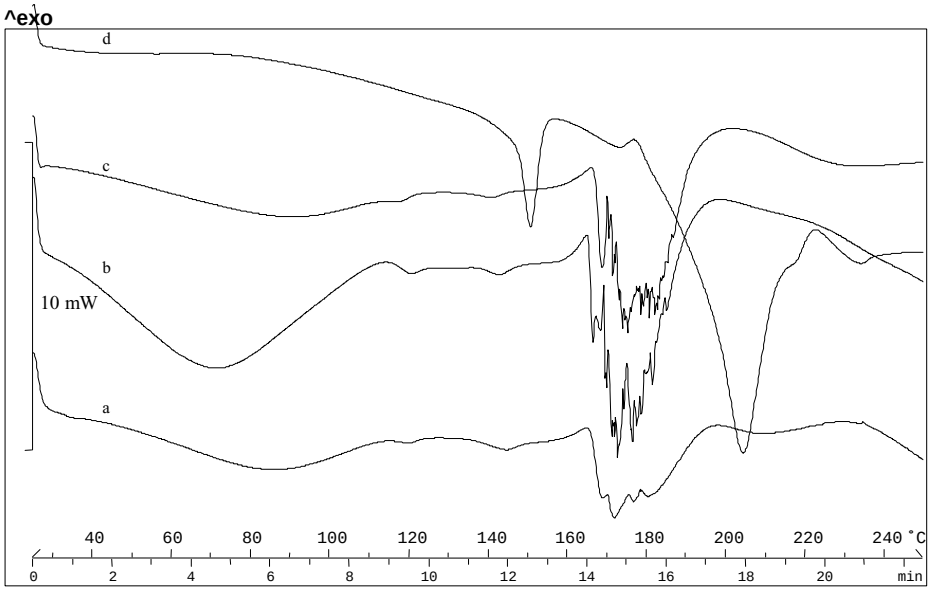

Fig. 2. DSC scans of (a) spray dried salbutamol sulphate/lactose 5%; (b) spray dried salbutamol sulphate/lactose 20%; (c) spray dried salbutamol sulphate/lactose 40%; and (d) physical mix of salbutamol sulphate/lactose monohydrate 20%.

200 °C is likely to be due to the degradation of salbutamol sulphate (Larhrib et al., 2003).

Spray drying salbutamol sulphate/lactose solutions produced a powder, however microscopic examination indicated that the spherical particles produced appeared to absorb moisture and merge together within a matter of seconds. The particles of the salbutamol sulphate/lactose 5% system were approximately 1–15 μm in diameter. Particles of the 20% system spray dried as a 10% w/v solution were approximately 1–20 μm in diameter. Salbutamol sulphate/lactose 20% spray dried at the lower feed concentration of 2.5% w/v resulted in particles with a narrower size distribution, particles being approximately 2–10 μm in diameter. The salbutamol sulphate/lactose 40% system resulted in particles 5–15 μm in diameter. (However, these particles had already started to merge by the time they were gold coated, therefore their true size is expected to be smaller.) Lactose spray dried alone from water (as a 10% w/v solution) produced smooth spherical particles approximately 1–4 μm in diameter. The particle size range for the co-spray dried systems appeared to be broader and larger particles were found than when the individual components were spray dried alone. The inlet–outlet temperature difference was much larger for salbutamol sulphate spray dried from water than for the salbutamol sulphate/lactose co-spray dried systems, however a similar temperature difference, to that used for the mixed systems, was employed for lactose spray dried alone (Corrigan et al., 2002). A higher airflow was used in spray drying salbutamol sulphate than was used for the salbutamol sulphate/lactose systems. The difference in airflow may be responsible for the particle size differences observed (Masters, 1985).

3.3. Salbutamol sulphate/PEG 4000 systems

Fig. 3 shows the XRD scans of spray dried salbutamol sulphate/PEG 4000 composites (containing 5, 20 and 40% PEG 4000 by weight of total solid). No intensity peaks indicative of crystallinity were apparent by XRD for the 5% system. The 20 and 40% PEG 4000 systems did show some peaks indicative of the presence of some crystalline PEG, however these peaks were of low intensity compared to physical mixes, indicating reduction in crystallinity of PEG 4000 during processing.

Previous studies on lactose/PEG 4000 composites, spray dried from water, showed the PEG crystallinity to be reduced on spray drying, the extent being dependent on the concentration of PEG 4000 in the system (Corrigan et al., 2002). PEG was shown to be amorphous when spray dried with lactose at a concentration of 10% PEG, while at other concentrations (5, 20 and 30% PEG 4000), there was evidence of reduced PEG crystallinity.

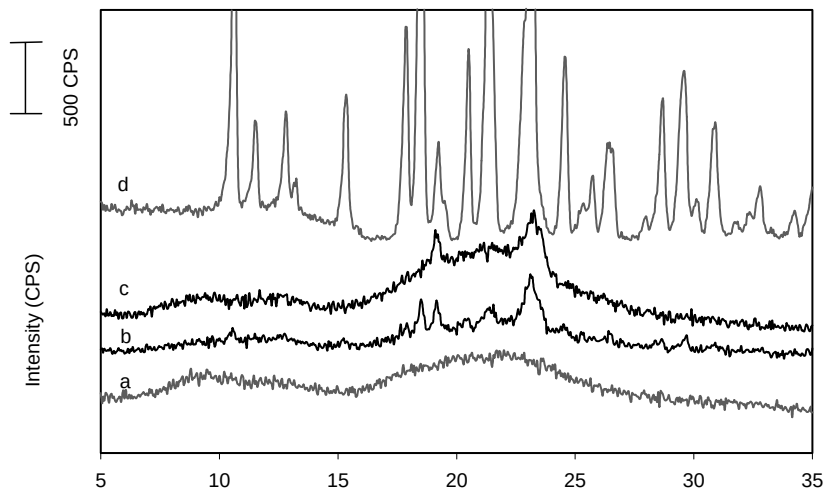

Fig. 3. XRD scans of (a) spray dried salbutamol sulphate/PEG 4000 5%; (b) spray dried salbutamol sulphate/PEG 4000 20%; (c) spray dried salbutamol sulphate/PEG 4000 40%; and (d) physical mix of salbutamol sulphate/PEG 4000 5%.

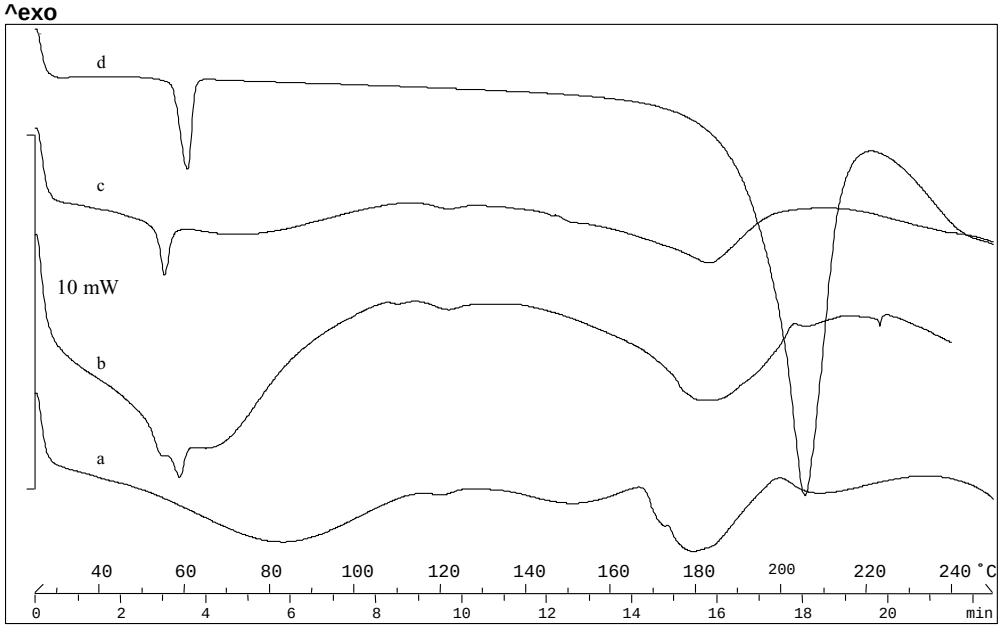

Fig. 4. DSC scans of (a) spray dried salbutamol sulphate/PEG 4000 5%; (b) spray dried salbutamol sulphate/PEG 4000 20%; (c) spray dried salbutamol sulphate/PEG 4000 40%; and (d) physical mix of salbutamol sulphate/PEG 4000 5%.

The salbutamol sulphate/PEG 4000 20% system appeared to contain some crystalline salbutamol sulphate unlike the 40% system, which showed only the two peaks at approximately 19 and 23° 2θ attributable to crystalline PEG 4000.

No melting endotherm for PEG 4000 was visible in the DSC scan of the spray dried 5% system, however a melting endotherm for PEG 4000 can be seen for the 5% physical mix (Fig. 4). This indicates that DSC can detect the presence of crystalline PEG 4000 at this level and therefore implies that less than 5% crystalline PEG is present in the spray dried system. The 20% PEG 4000 system showed two melting endotherms for PEG 4000 which could represent melting of some once folded PEG (metastable) as well as melting of the extended chain form of PEG (Chatham, 1985; Kambe, 1980; Corrigan et al., 2002). The 40% PEG 4000 system showed a PEG melting peak, which occurred at a slightly lower temperature than in the equivalent physical mix (possibly due to the presence of the once folded metastable form). The magnitude of the PEG endotherm in the 40% system was less than for the 5% physical mix implying less than 5% crystalline PEG is present. No recrystallisation exotherms are visible by DSC for any of the spray dried systems and the melting endotherms of salbutamol sulphate are broader and reduced in onset temperature compared to the physical mixes.

SEM micrographs showed spherical salbutamol sulphate/PEG 4000 5% particles with diameters of 4–10 μm. The salbutamol sulphate/PEG 4000 20% system appeared to consist of fused aggregates of spheres (Fig. 5a). Large fused aggregates had diameters of approximately 25–30 μm. Individual spheres were approximately 2–6 μm in diameter. The salbutamol sulphate/PEG 4000 40% SEM micrographs showed spherical structures of approximately 70 μm in diameter, consisting of many tiny particles as well as separate spherical individual particles approximately 1–5 μm in diameter (Fig. 5b).

3.4. Salbutamol sulphate/PEG 20,000 systems

Fig. 6 shows the XRD scans of the spray dried salbutamol sulphate/PEG 20,000 systems. The 5 and 20% systems were completely amorphous by XRD with respect to salbutamol sulphate and polymer. The 40% PEG 20,000 system showed peaks indicative of crys-

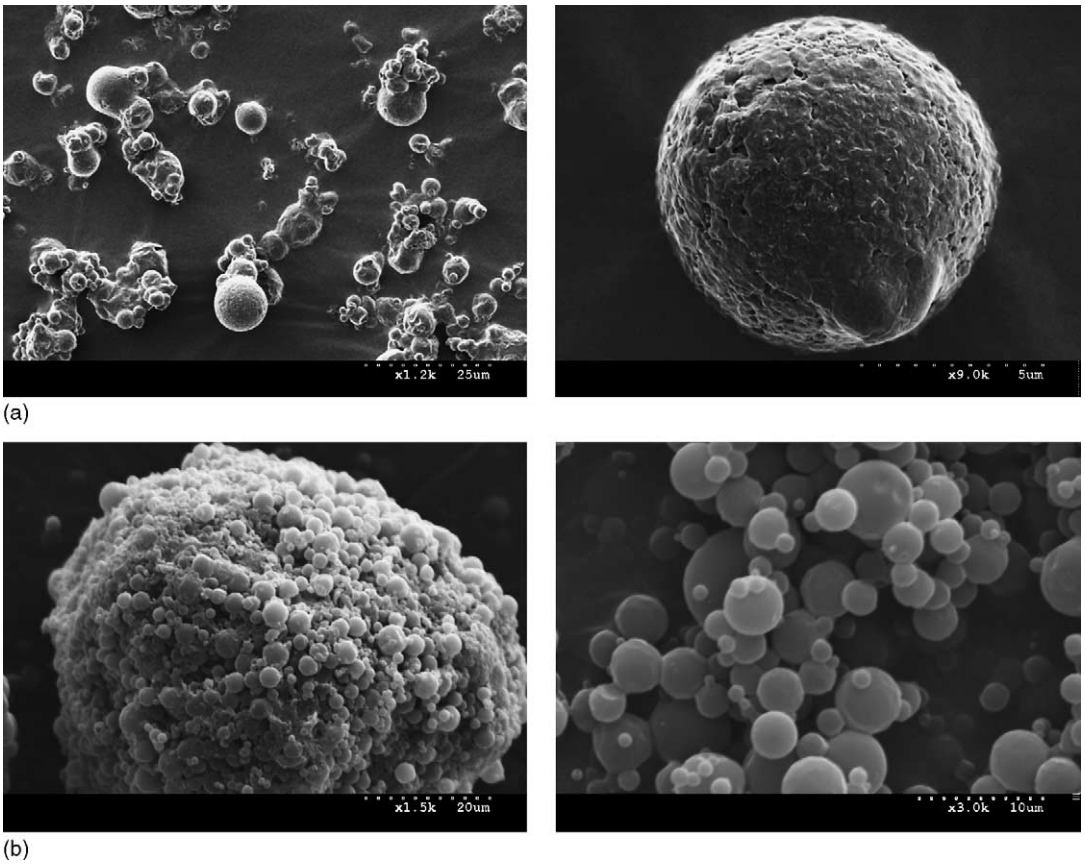

Fig. 5. (a) SEM micrographs of spray dried salbutamol sulphate/PEG 4000 20%. (b) SEM micrographs of spray dried salbutamol sulphate/PEG 4000 40%.

talline PEG 20,000. These peaks were smaller in magnitude than the equivalent physical mix. No peaks were present for crystalline salbutamol sulphate in the 40% system indicating that it is either amorphous or present as a molecular dispersion within the PEG 20,000.

Fig. 7 shows the DSC scans of the various spray dried salbutamol sulphate/PEG 20,000 systems. Neither the 5% nor the 20% system shows an endotherm indicative of melting of crystalline PEG. The 40% PEG 20,000 system does show a melting endotherm in the PEG region but this is much reduced in enthalpy compared to the 40% PEG 20,000 physical mix, being less than half the magnitude of the PEG melting endotherm of the 20% PEG physical mix shown in Fig. 7 (scan d). The spray dried PEG 20,000 20% system showed a distinct exotherm by DSC indicating recrystallisation of amorphous salbutamol sulphate prior to the salbutamol sulphate endotherm (indicated by the arrow in Fig. 7 (scan b)). This salbutamol sulphate/PEG 20,000 20% system was the only co-spray dried system containing salbutamol sulphate to show a visible recrystallisation exotherm during heating by DSC. The 5 and 40% systems do not show obvious exotherms. Salbutamol sulphate systems spray dried alone did not show recrystallisation exotherms by DSC, nor did other salbutamol sulphate co-spray dried systems. The endotherm for salbutamol sulphate in the 20% PEG 20,000 system is likely due to the presence of some recrystallised salbutamol sulphate as opposed to melting of an amorphous form. This endotherm is quite broad when compared to a physical mix implying that the salbutamol sulphate is perhaps not as crystalline as that in the physical mix. The fact that other salbutamol sulphate spray dried systems

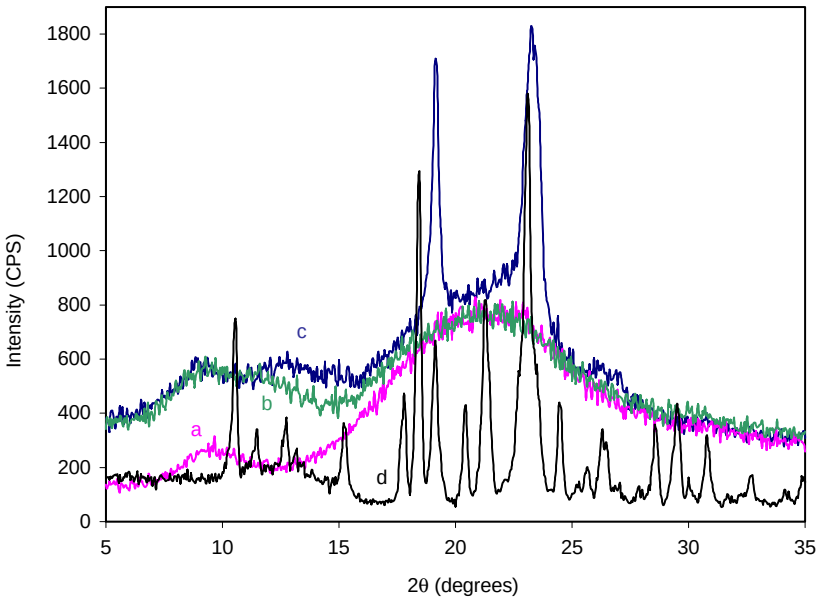

Fig. 6. XRD scans of (a) spray dried salbutamol sulphate/PEG 20,000 5%; (b) spray dried salbutamol sulphate/PEG 20,000 20%; (c) spray dried salbutamol sulphate/PEG 20,000 40%; and (d) physical mix of salbutamol sulphate/PEG 20,000 20%.

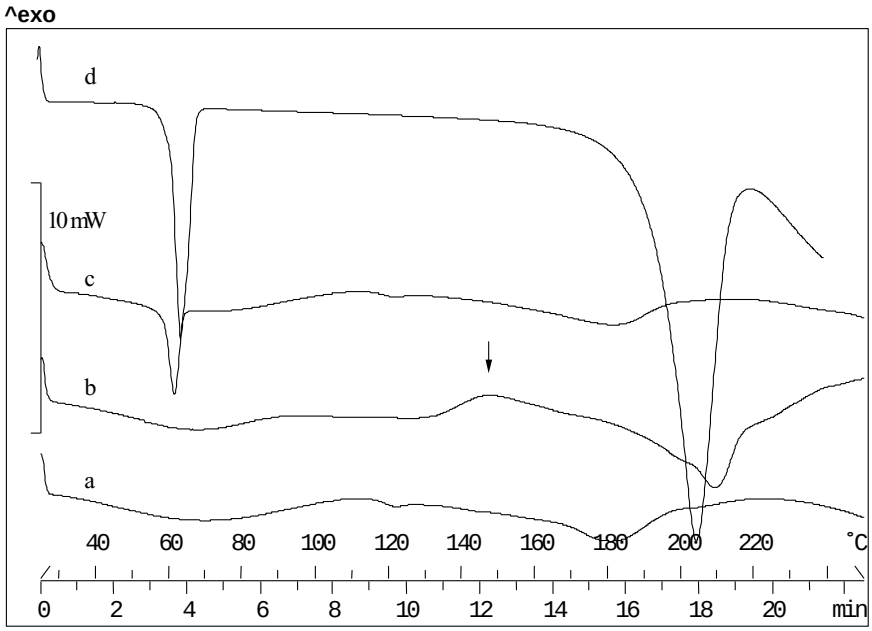

Fig. 7. DSC scans of (a) spray dried salbutamol sulphate/PEG 20,000 5%; (b) spray dried salbutamol sulphate/PEG 20,000 20%; (c) spray dried salbutamol sulphate/PEG 20,000 40%; and (d) physical mix of salbutamol sulphate/PEG 20,000 20%. The arrow indicates the exothermic peak.

show broad lower temperature endotherms which are not preceded by a clear exothermic event implies that the salbutamol sulphate is present as a glass which does not recrystallise on heating. The 20% PEG 20,000 system, therefore, is consistent with the presence of amorphous salbutamol sulphate rather than a solid solution of salbutamol sulphate in PEG 20,000. Chiou and Niazi (1971) investigated solid dispersions of sulfathiazole and urea prepared by the melt method. XRD analysis of the solid dispersion systems showed no peaks indicative of sulfathiazole indicating that it may be present either as a solid solution or as an amorphous phase. Differential thermal analysis of the solid dispersion showed an exotherm followed by a melting endotherm, the melting endotherm occurring at a lower melting temperature than in equivalent physical mixes. On storage the melting endotherm gradually increased in onset melting temperature and weak diffraction lines attributable to sulfathiazole appeared by XRD. They concluded that sulfathiazole was likely to have been present as an amorphous phase rather than as a molecular dispersion based on the fact that sulfathiazole alone shows a tendency to super-cool to a glassy state and because of the presence of a DSC exotherm, a lower onset melting endotherm and the appearance of peaks by XRD following storage.

SEM micrographs of spray dried salbutamol sulphate/PEG 20,000 systems are shown in Fig. 8. The 5 and 40% PEG 20,000 consisted of smooth spherical particles with numerous indentations. The 20% system showed particles that were spherical but with fibrous surfaces. The 5 and 20% PEG 20,000 particles were approximately 2–8 μm in diameter. The 40% PEG 20,000 system consisted of particles with diameters from approximately 2 to 10 μm.

3.5. Glass transition temperatures and physical state and stability of spray dried composite materials

The physical form of the composites, i.e. crystalline or amorphous, obtained on spray drying either salbutamol sulphate, lactose (Corrigan et al., 2002) or bendroflumethiazide (BFMT) (Corrigan et al., 2003) with increasing PEG content is summarised in Table 1. Of the three drugs, bendroflumethiazide has the least tendency to crystallise in the presence of increasing amounts of PEG. When spray dried as a single component lactose, bendroflumethiazide and salbutamol

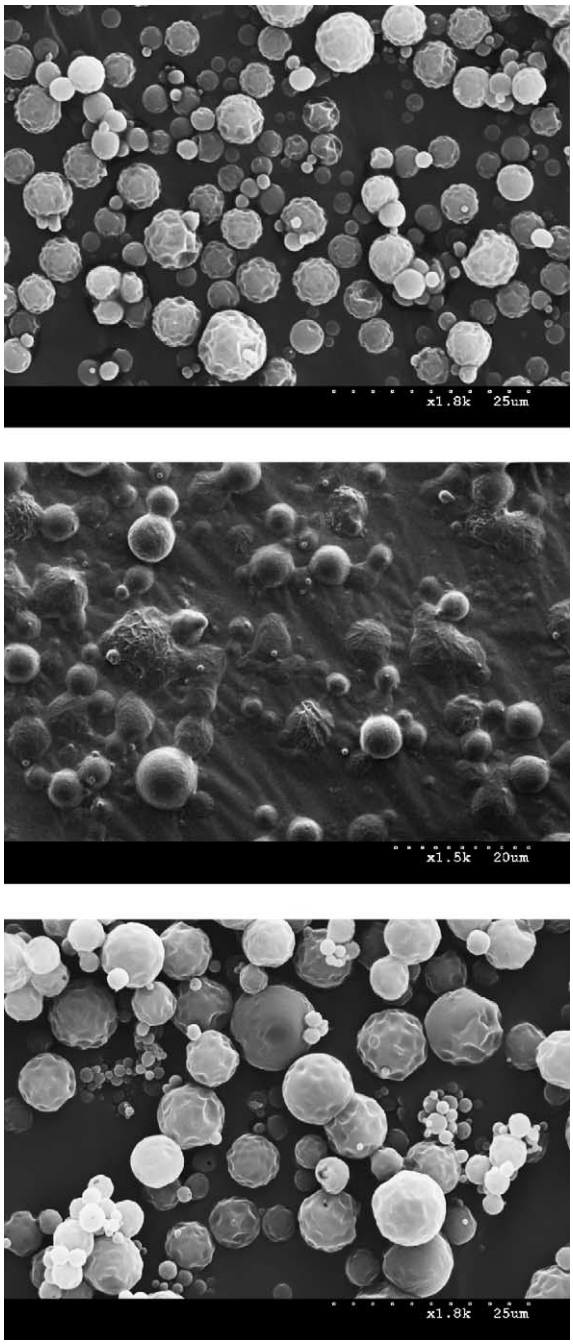

Fig. 8. SEM micrographs of spray dried salbutamol sulphate/PEG 20,000 5% (top), 20% (middle) and 40% (bottom).

Table 1
Crystallinity of PEG 4000 in BFMT/PEG 4000, salbutamol sulphate/PEG 4000 and lactose/PEG 4000 systems

System	PEG 4000 by weight of total solids				
	5%	10%	20%	30%	40%
BFMT/PEG	–	am	am	am	–
Lactose/PEG	am[a]	am	c	c	–
Salbutamol sulphate/PEG	am	–	c	–	c

am: amorphous, c: peaks indicative of crystallinity.
[a] Crystallinity suggested by XRD but not by DSC.

sulphate are amorphous with T_g above room temperature (Table 2), while PEGs are semicrystalline materials and exhibit a T_g which depends on the molecular weight of the sample (Craig, 1995). In the molecular weight range of 10^2–10^7 the T_g varies from approximately −98 to −17 °C depending on molecular weight (Craig, 1995). The very low T_gs of PEGs indicate that at room temperature, following spray drying, the materials are likely to be crystalline. Previously when Corrigan et al. (1984) spray dried a range of thiazide diuretics they found that the larger molecular weight compounds formed amorphous phases more readily than the lower molecular weight thiazides. Amorphous systems produced from the higher molecular weight thiazides were more physically stable than amorphous systems produced from the lower molecular weight thiazides. The PEGs do not contain large side groups and this might explain why they are less likely to form amorphous systems on spray drying. Bodmeier and Chen (1988) described linear macromolecular polymers without bulky side groups, such as polylactic acid, as having strong and extensive intermolecular bonding coupled with adhering stiffness of the polymeric chains leading to strong chain interactions. They used these facts to explain the difficult disruption of a liquid filament into individual particles resulting in fibrous spray dried material.

Compatible blends of amorphous materials exhibit a single T_g that is intermediate between the T_g values of the individual components (Hancock and Zografi, 1994). The low T_gs of PEGs indicate that these materials are likely to act as plasticisers and this has been shown previously for systems containing 10, 20 and 30% PEG (with either lactose (Corrigan et al., 2002)) or BFMT (Corrigan et al., 2003). Considering the glass transition behaviour of amorphous solids in terms of polymer free volume theory, the glass transition of a mix of two components ($T_{g\,mix}$) can be determined by Eq. (1) (Gordon and Taylor, 1952):

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

where $K = \rho_1(\Delta_{\alpha 2})/\rho_2(\Delta_{\alpha 1})$, Δ_α is the thermal expansivity of T_g, w is the weight faction and ρ is the true density of the material. Numbers 1 and 2 are indicative of the two different components.

Hancock and Zografi (1994) describe that since $(\Delta_\alpha)T_g$ is approximately constant, K can be calculated from the densities (ρ_1 and ρ_2) of the two components using Eq. (2).

$$K = \frac{\rho_1 T_{g1}}{\rho_2 T_{g2}} \quad (2)$$

$T_{g\,mix}$ was calculated for salbutamol sulphate/PEG 4000 systems containing 10, 20 and 30% PEG 4000,

Table 2
The estimated glass transition temperature of a mix of two components systems ($T_{g\,mix}$ (°C)) determined from Eq. (1) using the K value obtained from Eq. (2), and estimated Kauzmann temperatures (°C) calculated as $T_g - 50$ K. T_g of pure drug components are also shown

PEG content in mix (%)	BFMT/PEG 4000		Lactose/PEG 4000		Salbutamol sulphate/ PEG 4000	
	$T_{g\,mix}$ (°C)	Kauzmann temperature (°C)	$T_{g\,mix}$ (°C)	Kauzmann temperature (°C)	$T_{g\,mix}$ (°C)	Kauzmann temperature (°C)
0	120.0	70.0	104.0[a]	54.0	64.0[b]	14.0
10	88.3	38.3	76.8	26.8	48.5	−1.5
20	62.7	12.7	54.6	4.6	34.5	−15.5
30	41.8	−8.3	35.8	−14.2	21.9	−28.1

[a] Elamin et al. (1995).
[b] Ward and Schultz (1995).

and also for the BFMT/PEG 4000 and lactose/PEG 4000 reported previously (Corrigan et al., 2002, 2003). True densities were taken as 1.5 g/cm^3 for lactose, 1.18 g/cm^3 for PEG 4000 (Handbook of Pharmaceutical Excipients, 1994) and were measured as 1.27 g/cm^3 for salbutamol sulphate and 1.54 g/cm^3 for BFMT. For PEG 4000 a T_g of −41 °C was estimated from $T_g = 0.7T_m$ (Hancock and Zografi, 1994; Brittain, 1999).

Table 2 shows the $T_{g\,mix}$ data calculated for BFMT/PEG 4000, lactose/PEG 4000 and salbutamol sulphate/PEG 4000 mixed systems. The $T_{g\,mix}$ values for the BFMT/PEG 4000 systems were in good agreement with the values obtained experimentally using modulated DSC (Corrigan et al., 2003). Experimentally obtained values were 83, 69 and 45 °C for the 10, 20 and 30% PEG/BFMT systems, respectively.

The data suggests that amorphous BFMT/PEG systems are more likely to form and be physically more stable at room temperature than lactose/PEG systems, which in turn should be more physically stable than salbutamol sulphate/PEG systems with respect to ease of recrystallisation. This trend was reasonably consistent with the crystallinity of PEG found in these systems as shown in Table 1. The higher the T_g is above the actual storage temperature, the more stable the system will be. Metastable amorphous materials are expected to be physically stable when stored at a temperature less than or equal to their Kauzmann temperature. The Kauzmann temperature of a material is generally ∼50 K below the T_g of the material (Hancock et al., 1995; Zhou et al., 2002). Table 2 shows the estimated Kauzmann temperatures of the mixed PEG 4000 systems (based on $T_g - 50$ K) (Hancock et al., 1995; Zhou et al., 2002).

The Kauzmann temperature estimates in Table 2 indicate that at room temperature the salbutamol sulphate/PEG 4000 systems and the lactose/PEG 4000 20 and 30% systems will not be stable. The lactose/PEG 4000 10% should be stable. Analysis of this system showed it to be the most X-ray amorphous of all the lactose/PEG 4000 systems (Corrigan et al., 2002). The BFMT/PEG 4000 10% should also be stable at room temperature since it has a Kauzmann temperature of 38 °C. The 20 and 30% PEG/BFMT systems have Kauzmann temperatures below room temperature and therefore are likely to be unstable. These systems had not, however, recrystallised by the time they were initially analysed (Corrigan et al., 2003).

Table 3
The $T_{g\,mix}$ (°C) determined from Eq. (1) using the K value obtained from Eq. (2), and estimated Kauzmann temperatures (°C) calculated as $T_g - 50$ K, for salbutamol sulphate/lactose systems

System	$T_{g\,mix}$ (°C)	Kauzmann temperature (°C)
Salbutamol sulphate/lactose 5%	65.5	15.5
Salbutamol sulphate/lactose 20%	70.4	20.4
Salbutamol sulphate/lactose 40%	77.4	27.4

The $T_{g\,mix}$ values and the Kauzmann temperatures were also calculated for salbutamol sulphate/lactose mixed systems and are shown in Table 3. The T_g values used in the calculations were the experimentally derived T_gs shown in Table 2. The $T_{g\,mix}$ and Kauzmann temperature values increase as the lactose content increases. The salbutamol sulphate/lactose spray dried systems were all amorphous when analysed by XRD which is consistent with the high $T_{g\,mix}$ and Kauzmann temperature values calculated for these systems.

Zhou et al. (2002) produced amorphous forms of several model compounds and determined their Kauzmann temperatures experimentally. Results were generally in agreement with the $T_g - 50$ K values of the compounds. Zhou et al. (2002) described that one of their model amorphous systems, ritonavir, showed excellent physical stability above its Kauzmann temperature. This indicated that although the Kauzmann temperature is a useful parameter, knowledge of the Kauzmann temperature alone is not adequate to understand the physical stability of an amorphous system. Zhou et al. (2002) stated that configurational entropy and molecular mobility values as a function of temperature need to be assessed in addition to T_g and Kauzmann temperatures. They concluded from their work that compounds with high T_gs, high configurational entropy barriers, high Kauzmann temperatures and low molecular mobilities are expected to show the greatest stability. The measurement of molecular mobility is beyond the scope of this paper.

4. Conclusions

Co-spray drying salbutamol sulphate with lactose, which is amorphous when spray dried alone, resulted

in amorphous composites. Co-spray drying salbutamol sulphate with PEG 4000 and PEG 20,000, which do not form amorphous systems when spray dried alone, resulted in systems of varying crystallinity, the crystallinity depending on the weight ratio of polymer to drug.

Feed concentration was an important factor in determining particle size of the resultant spray dried powders. Thus, decreasing the feed concentration from 10 to 2.5% w/v resulted in the production of smaller diameter particles with a narrower size distribution.

Depending on the percentage of excipient, differing particle morphologies were found including homogeneous spherical particles, fused particles, large spherical aggregates consisting of many smaller spheres, particles with a smooth surface having indentations and particles with a fibrous surface.

The formation and physical stability of amorphous composites formed by spray drying was found to depend on whether the T_g of one of the components is high enough to result in a $T_{g\,mix}$ sufficiently high that the Kauzmann temperature of the mix is greater than the temperature of storage. The Gordon–Taylor equation was useful in predicting the likelihood that a two component composite will be amorphous on spray drying. Furthermore, the Gordon–Taylor equation appears to be useful in predicting the likely physical stability of amorphous two component composites and predicted that even polymers with apparently low T_gs, such as PEGs, may be stabilised in an amorphous composite by a suitable drug/additive with a sufficiently high T_g.

Acknowledgements

The authors would like to thank Neal Leddy, Colin Reid and David John of the Electron Microscope Unit, Trinity College, for their help and expertise and also Lidia Tajber for valuable discussion of the work.

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