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ScienceDirect
International Journal of Pharmaceutics 322 (2006) 22–30
INTERNATIONAL JOURNAL OF PHARMACEUTICS
www.elsevier.com/locate/ijpharm

Physicochemical and in vitro deposition properties of salbutamol sulphate/ipratropium bromide and salbutamol sulphate/excipient spray dried mixtures for use in dry powder inhalers

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Received 20 January 2006; received in revised form 5 April 2006; accepted 9 May 2006
Available online 16 May 2006

Abstract

The physicochemical and aerodynamic properties of spray dried powders of the drug/drug mixture salbutamol sulphate/ipratropium bromide were investigated. The in vitro deposition properties of spray dried salbutamol sulphate and the spray dried drug/excipient mixtures salbutamol sulphate/lactose and salbutamol sulphate/PEG were also determined. Spray drying ipratropium bromide monohydrate resulted in a crystalline material from both aqueous and ethanolic solution. The product spray dried from aqueous solution consisted mainly of ipratropium bromide anhydrous. There was evidence of the presence of another polymorphic form of ipratropium bromide. When spray dried from ethanolic solution the physicochemical characterisation suggested the presence of an ipratropium bromide solvate with some anhydrous ipratropium bromide. Co-spray drying salbutamol sulphate with ipratropium bromide resulted in amorphous composites, regardless of solvent used. Particles were spherical and of a size suitable for inhalation. Twin impinger studies showed an increase in the fine particle fraction (FPF) of spray dried salbutamol sulphate compared to micronised salbutamol sulphate. Co-spray dried salbutamol sulphate:ipratropium bromide 10:1 and 5:1 systems also showed an increase in FPF compared to micronised salbutamol sulphate. Most co-spray dried salbutamol sulphate/excipient systems investigated demonstrated FPFs greater than that of micronised drug alone. The exceptions to this were systems containing PEG 4000 20% or PEG 20,000 40% both of which had FPFs not significantly different from micronised salbutamol sulphate. These two systems were crystalline unlike most of the other spray dried composites examined which were amorphous in nature.

Keywords: Salbutamol sulphate; Ipratropium bromide; Spray drying; Dry powder inhaler; Fine particle fraction

1. Introduction

The move away from pressurised aerosol formulations, due to restriction in chlorofluorocarbon production and use, has led to an increased interest in dry powder inhaler (DPI) formulations as inhalable delivery systems (Dunbar, 2002). Spray drying is a useful technique for producing powders suitable for inhalation. Spray dried powders of sodium cromoglycate, for example (Vidgrén et al., 1989) and salbutamol sulphate (Chawla et al., 1994) have been shown to be of a suitable size for pulmonary delivery (0.5–5 μm aerodynamic diameter).

When formulations consisting of more than one active are to be produced, good mixing is essential to ensure dose uniformity. Spray drying may prove to be a useful method for the production of mixtures of powders for use in dry powder formulations for inhalation since, not only can spray drying result in powders in the inhalation size range with a narrow particle size distribution, but it can result in the production of an intimate mix of components (solid dispersions) (Woolfe et al., 2001). However, the issues of the effect of co-spray drying on the physicochemical properties of the processed materials and the deposition properties of the processed powders must also be addressed.

Typically dry powder inhaler (DPI) formulations consist of a micronised active mixed with an inert diluent or carrier, such as lactose (DPI). The carrier excipients are included to aid flow and dispersiblity of drug particles, which may be highly cohesive when micronised (Timsina et al., 1994). Inclusion of a carrier also overcomes the problem of dose metering if fractions of a milligram of a potent medicament are to be delivered (Ganderton and Jones, 1992). Adequate mixing is essential for

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doi:10.1016/j.ijpharm.2006.05.022

dose uniformity and formulations consisting of a drug and a carrier need to be tested for homogeneity of mixing (Timsina et al., 1994). Co-spray drying drugs with excipients should avoid problems of non-homogeneity of mixing of drug and carriers, while overcoming dose metering problems if small amounts of medicament need to be administered, to facilitate dispersion. While lactose is an obvious excipient of choice, since it is already the most commonly used excipient in DPIs, polyethylene glycols (PEGs) have also been investigated as carriers. Lucas et al. (1998) added micronised PEG 6000 instead of fine particle lactose to mixtures of co-spray dried bovine serum albumin/maltodextrin and coarse lactose and found that PEG 6000 was capable of improving the in vitro deposition of the model therapeutic agent measured using a Rotahaler® attached to a twin stage impinger. PEGs are generally recognised as safe (GRAS) by the U.S. F.D.A.

In the present work we investigate the physicochemical and in vitro deposition properties of spray dried powders of the drug/drug mixture salbutamol sulphate/ipratropium bromide. A pressurised inhalation formulation of this drug combination, using a mixture of the two drugs in a 5:1 salbutamol sulphate/ipratropium bromide ratio is marketed as Combivent™ (Boehringer Ingelheim). However there is little published data on the physicochemical properties of ipratropium bromide and no published data on the effect on physicochemical properties of the drugs of co-spray drying them. We also investigate here the in vitro deposition properties of spray dried salbutamol sulphate and the spray dried drug/excipient mixtures salbutamol sulphate/lactose and salbutamol sulphate/PEG.

2. Methods

2.1. Materials

Salbutamol sulphate and ipratropium bromide were kindly provided by IVAX Pharmaceuticals, Ireland. PEG 4000 was purchased from Riedel de Haën (Germany), PEG 20,000 was purchased from Fluka and lactose monohydrate was purchased from Riedel de Haën (Germany). Salbutamol sulphate and ipratropium bromide monohydrate were supplied as micronised crystalline powders. Physical mixes were prepared using sub 63 μm mesh sieved powders mixed in a Turbula Mixer™ for 5 min.

2.2. Spray drying methodology

Salbutamol sulphate and ipratropium bromide systems were spray dried using a Büchi 190 spray drier. 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. 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.

Ipratropium bromide was spray dried as a 5% (w/v) aqueous solution using an inlet temperature of 150–153 °C, outlet temperature of 102–104 °C, pump rate of 7 and airflow rate of 700 l/h or as a 2.5% (w/v) ethanolic solution (95% ethanol, 5% water) using an inlet temperature of 77–79 °C, outlet temperature of 55–56 °C, pump rate of 6 and airflow rate of 500 l/h.

Salbutamol sulphate/ipratropium bromide systems were co-spray dried from 5% (w/v) aqueous solutions using the following conditions: inlet temperatures of 150–153 °C, outlet temperatures of 99–103 °C, pump rate of 7, airflow rate 650–700 l/h. Salbutamol sulphate/ipratropium bromide systems were also co-spray dried from ethanolic solvents. Salbutamol sulphate:ipratropium bromide 10:1 system was spray dried as a 0.94% (w/v) solution from ethanolic solvent consisting of 84% ethanol and 16% water (inlet temperature 87–94 °C, outlet temperature 60–66 °C). Salbutamol sulphate:ipratropium bromide 5:1 system was spray dried as a 2.5% (w/v) solution from ethanolic solvent consisting of 85% ethanol and 15% water (inlet temperature 95–96 °C, outlet temperature 64–70 °C). Salbutamol sulphate:ipratropium bromide 2:1 system was spray dried as a 0.5% (w/v) solution from ethanolic solvent consisting of 89% ethanol and 11% water (inlet temperature 85–88 °C, outlet temperature 60–64 °C). Pump rates of 6 and airflow rates 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 systems consisting of 5%, 20% and 40% PEG 4000 or PEG 20,000 by weight of total solids were spray dried as 2.5% (w/v) aqueous solutions using a Büchi 191. In the case of the salbutamol sulphate/PEG 4000 systems the spray drying conditions were 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, pump rate setting of 18% and airflow rate of 600 l/h.

Salbutamol sulphate/PEG 20,000 systems were spray dried under 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 20,000 systems, respectively.

2.3. Assessment of physicochemical properties

X-ray powder diffraction measurements (XRD) were made on samples using a Siemens D500 diffractometer 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 taken from 5° to 35° on the two θ scale at a step size of 0.05°/s.

DSC (Mettler Toledo DSC 821e), 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. Samples were run at a heating rate of 10 °C/min under nitrogen purge.

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

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 Pungsten 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.

Fourier transform infrared spectroscopy (FTIR) was carried out using a Perkin-Elmer Paragon 1000 Fourier transform infrared spectrometer. KBr discs were prepared based on 1 mg% sample loading. Discs were prepared by grinding the sample with KBr in an agate mortar and pestle, placing the sample in an evacuable KBr die and applying 8000 kg of pressure, in a Graseby Specac IR press. Two FTIR spectra were obtained for each system.

2.4. Particle size measurement

Particle size was measured by scanning electron microscopy (SEM) (Lee et al., 1996). SEM photographs were taken and imported into Adobe Photoshop version 6.0. The Photoshop measuring tool was used to measure Martin's diameter (Allen, 1990) of 100 particles of each system.

2.5. In vitro aerosol characterisation

In vitro deposition of dry powders for inhalation were determined using a twin impinger (Glaxo Type single stage impactor, Copley Instruments (Nottingham) Ltd.). The instrument complied with specifications for apparatus A of the European Pharmacopoeia (2002) and British Pharmacopoeia (2002). About 60 mg samples of powder were weighed and loaded into size 3 hard gelatin capsules (Chawla et al., 1994), which were individually installed in a Rotahaler device (Glaxo Wellcome Inc., NC). The Rotahaler was attached to the impinger which contained 7 and 30 ml of collecting solvents (deionised water) in stages 1 and 2, respectively. The capsules contents were released by twisting the Rotahaler and the system was vacuumed to produce air streams of 60 l/min for 5 s. The liquids in stages 1 and 2 were collected and diluted as appropriate and measured by UV spectrophotometry or HPLC. Each deposition experiment involved the aerosolisation of one capsule. Fine particle fraction (FPF) was calculated as the amount deposited in the lower stage as a percentage of the emitted dose (amount emitted into upper and lower stages excluding the amount remaining in the device). All systems were analysed in triplicate. Statistical analysis was carried out using Minitab™ statistical software (Version 13.1). In all cases statistical significance was tested for by ANOVA at the 95% confidence interval.

HPLC analysis of the salbutamol sulphate collected from the twin impinger apparatus was performed using a variation of the USP Pharmacopeia (2000) method for HPLC analysis of salbutamol sulphate, as previously described (Corrigan et al., 2004).

In the case of salbutamol sulphate systems (i.e. not co-spray dried), UV measurements (λ 276 nm) were made using a Hewlett Packard 8452A photodiode array UV/vis spectrophotometer using 10 mm quartz cuvettes (Spectrosil), as previously described (Corrigan et al., 2006).

3. Results and discussion

3.1. Salbutamol/ipratropium bromide systems

3.1.1. Ipratropium bromide monohydrate – physicochemical properties

The commercial form of ipratropium bromide was determined to be a crystalline hydrate. Spray drying ipratropium bromide alone from either aqueous solution or ethanolic solution did not result in the production of an amorphous material. Fig. 1 shows the XRD scans of the two spray dried materials and the starting material. The arrows in the XRD scans indicate positions where peaks differ between the three samples.

DSC scans of ipratropium bromide are shown in Fig. 2. The starting material showed a major endotherm with a peak at approximately 237 °C, which was attributed to melting. Two further lower temperature overlapping endotherms between 80 and 120 °C were also visible. TGA analysis of ipratropium bromide monohydrate showed a loss of approximately 4% of total solid mass in the same temperature region as these endotherms. This weight loss is consistent with the loss of a monohydrate

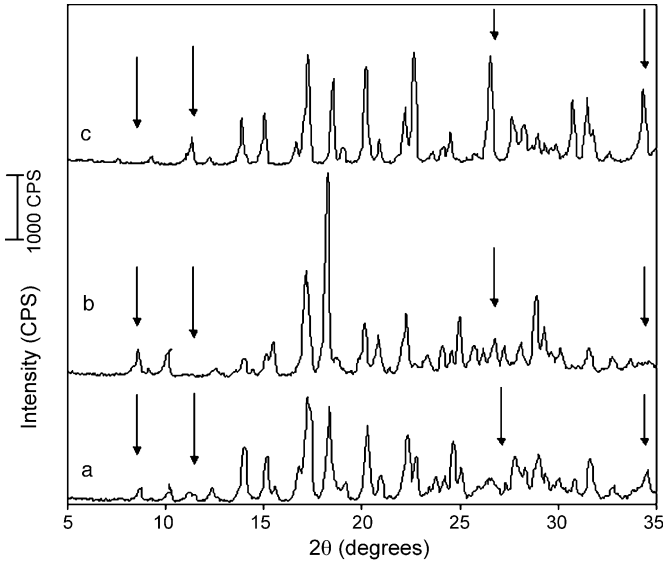

Fig. 1. XRD scans of (a) ipratropium bromide spray dried from ethanolic solution, (b) ipratropium bromide spray dried from aqueous solution and (c) ipratropium bromide monohydrate starting material. The arrows in the XRD scans indicate positions where peaks differ between the three samples.

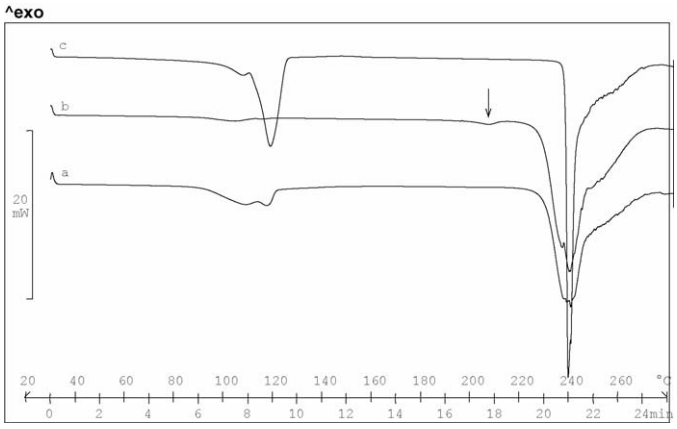

Fig. 2. DSC of (a) ipratropium bromide spray dried from ethanolic solution, (b) ipratropium bromide spray dried from aqueous solution and (c) ipratropium bromide monohydrate starting material. The arrow indicates an endotherm at approximately 208 °C in scan b.

(the loss of one water molecule corresponds to a loss of 4.2% by weight of ipratropium bromide monohydrate when determined on a molecular weight basis).

The DSC of the aqueous spray dried material (Fig. 2, scan b) showed two low temperature endotherms between approximately 85 and 120 °C (at higher magnification), however, TGA did not detect any mass loss associated with these. Another small endothermic peak was visible in the aqueous spray dried material at approximately 208 °C (indicated by the arrow in Fig. 2), just before the larger melting endotherm. This melting endotherm may be indicative of the presence of a polymorphic form of ipratropium bromide. The DSC scan of ipratropium bromide spray dried from ethanolic solution (Fig. 2, scan a) was similar to the DSC scan of the starting material showing two low temperature endothermic peaks as well as the higher melting endotherm. No peak at approximately 208 °C was observed. TGA of the ethanolic spray dried system showed weight loss indicative of loss of solvent of approximately 2.6% indicating that not all the sample was present as the monohydrate. The DSC was also consistent with not all the material being present as the monohydrate. It is likely that some anhydrous ipratropium bromide and/or an ethanol solvate is formed, the small amount present not changing the XRD pattern to a large extent.

FTIR showed similar spectra for ipratropium bromide spray dried from ethanol and ipratropium bromide monohydrate starting material (Fig. 3a). However ipratropium bromide spray dried from aqueous solution showed changes in the OH region (Fig. 3b). Changes in the OH region are indicative of changes in the hydrate form of the drug and were consistent with DSC and TGA experiments which indicated the presence of predominantly the anhydrous form. It should be noted that the drying temperature differed between the aqueous and ethanolic solutions. The inlet temperature used to dry the aqueous solution was approximately 70 °C higher than that used for the ethanolic solution. This may account for apparent differences in the results spray dried products. The DSC scan of the aqueous spray dried system indicated the possibility of the presence of an additional polymorphic form. While some polymorphic forms of drugs show quite large differences by FTIR, the spectra of many polymorphic systems are often found to be only slightly different indicating that the pattern of molecular vibrations is not grossly affected by the differences in crystal structure (Brittain, 1999). FTIR of the aqueous spray dried system did not show peaks, other than in the OH region, which were significantly different from the starting material. EDXA of the spray dried materials showed the presence of bromine consistent with the spray dried materials remaining as the bromide salts.

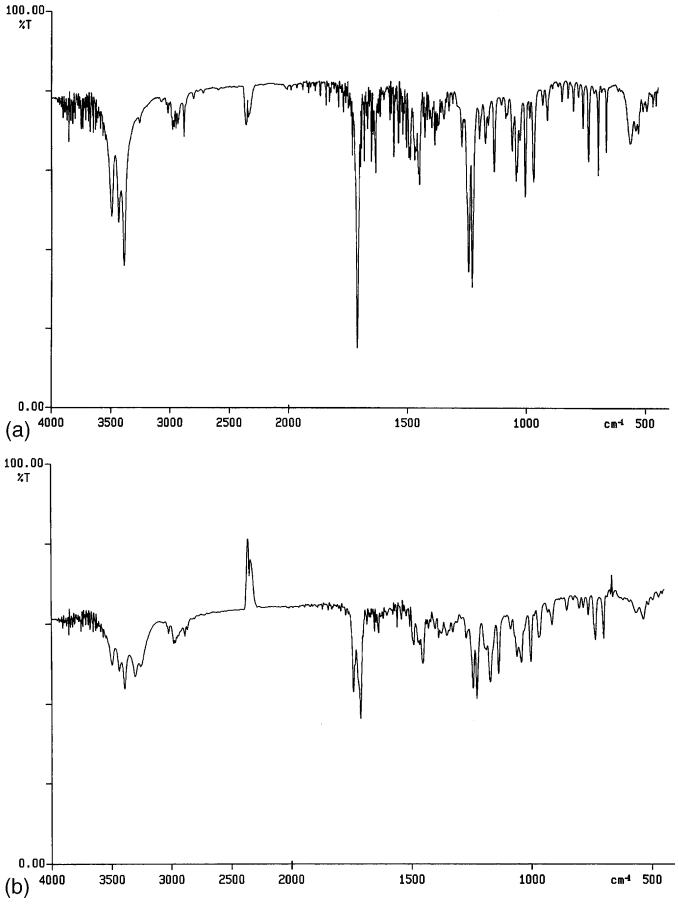

Fig. 3. FTIR scans of (a) ipratropium bromide monohydrate starting material and (b) ipratropium bromide spray dried from aqueous solution.

SEM micrographs of ipratropium bromide spray dried from ethanolic and aqueous solvents and ipratropium bromide monohydrate starting material are shown in Fig. 4. The aqueous spray dried systems showed rough irregular shaped particles with diameters ranging from approximately 5 to 20 μm. Ipratropium bromide spray dried from ethanolic solvent showed larger particles with diameters of the order of 60 μm and larger.

3.1.2. Co-spray dried salbutamol sulphate/ipratropium bromide – physicochemical properties

The amorphous nature of spray dried salbutamol sulphate was previously reported (Corrigan et al., 2004). Salbutamol sulphate:ipratropium bromide 10:1, 5:1 and 2:1 weight ratios were spray dried from aqueous as well as ethanolic solutions. All three weight ratios when spray dried resulted in amorphous powders, regardless of the solvent used in production, as evidenced by the lack of peaks in the XRD scans (Fig. 5a). The systems spray dried from ethanolic solution showed similar amorphous

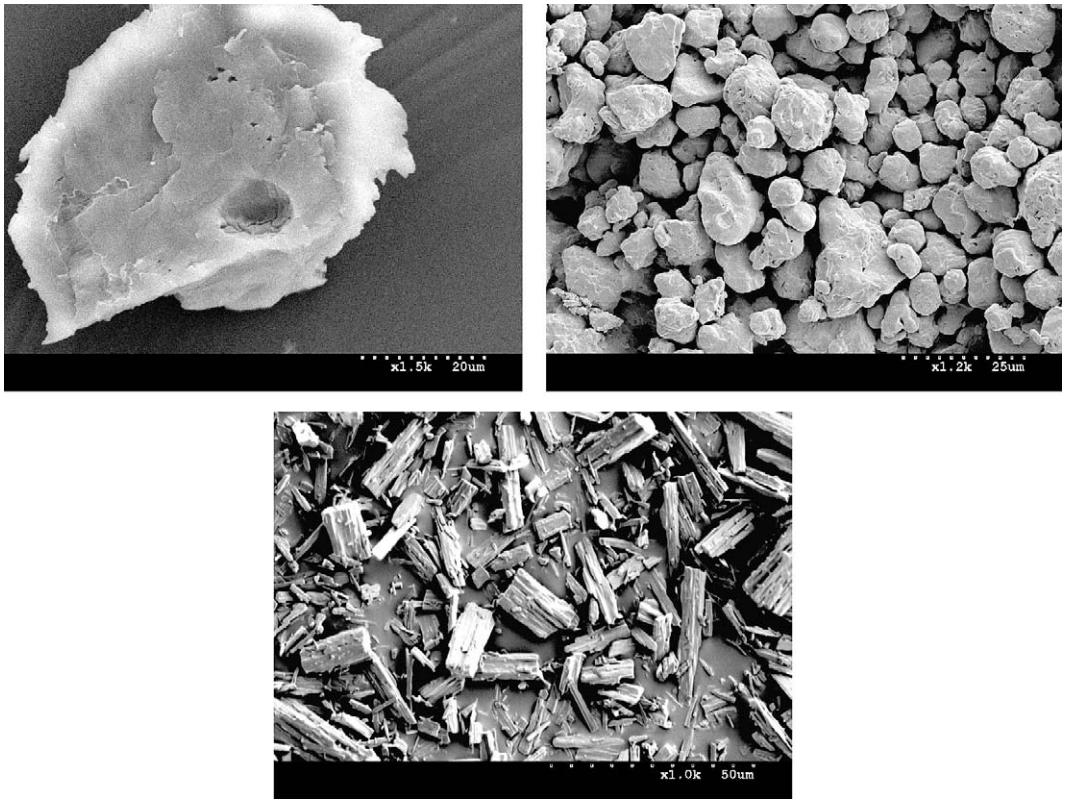

Fig. 4. SEM micrographs of ipratropium bromide spray dried from ethanolic solution (top left), ipratropium bromide spray dried from aqueous solution (top right) and micronised ipratropium bromide (bottom). Scale bars correspond to 20 μm, 25 μm and 50 μm, respectively.

halos to those shown for the aqueous spray dried systems. An XRD scan of a physical mix of crystalline ipratropium bromide monohydrate in amorphous salbutamol sulphate was run to establish whether crystalline ipratropium bromide suspended in amorphous salbutamol sulphate would be detectable by XRD (Fig. 5b). Peaks due to ipratropium bromide were clearly present, even at this low concentration of crystalline material (9%, w/w ipratropium bromide monohydrate). It would appear therefore that ipratropium bromide is present in the non-crystalline state in the co-spray dried system.

DSC scans of salbutamol sulphate:ipratropium bromide systems spray dried from aqueous solution are shown in Fig. 6. DSC scans were similar to those of salbutamol sulphate spray dried alone (Corrigan et al., 2004) except for small endotherms in the 100–120 °C region.

DSC scans for all systems spray dried from ethanolic solvent resembled those for salbutamol sulphate spray dried alone from ethanol (Corrigan et al., 2004). Endothermic peaks prior to approximately 120 °C were not as pronounced as in the equivalent systems spray dried from aqueous solution, otherwise the DSCs were similar.

TGA was consistent with broad endotherms visible by DSC, in the aqueous and ethanolic spray dried systems prior to approximately 100 °C, being due to loss of absorbed solvent. TGA showed weight loss (1–3%) in this region for the spray dried systems, which was not observed for the physical mixes. Amorphous materials are often hygroscopic and this may explain differences in observed mass loss determined by TGA between spray dried composites and physical mixes.

FTIR of the systems spray dried from either solvent showed changes in the OH region and in the 1000–1060 cm^{-1} region compared to equivalent crystalline physical mixes (Fig. 7a and b). The changes in the OH region are consistent with the change in ipratropium bromide from the monohydrate to an anhydrous form. FTIR of all spray dried samples showed no peak at 1031, a peak which was in the FTIR spectrum of physical mix systems, and additional peaks at 1044 and 1003, peaks not evident in the FTIR of the physical mix systems. Changes in the region 1020–1060 cm^{-1} have been described as due to the C–N(H) stretching mode (Brittain, 1999). Differences in bands in the C–N(H) region were apparent for six polymorphic forms of mexiletine hydrochloride (Brittain, 1999). Salbutamol sulphate contains a C–N(H) group and ipratropium bromide contains a nitrogen atom bonded to carbon atoms. Differences observed in the spectra of spray dried salbutamol sulphate:ipratropium bromide systems compared to equivalent physical mixes are likely due to the change in ipratropium bromide from the monohydrate form to an anhydrous amorphous form on spray drying. When solvent molecules are removed from a crystal lattice the new structure is often different enough that the change in molecular vibrations are detectable (Khankari and Grant, 1995).

Fig. 8 presents SEM micrographs of the salbutamol sulphate:ipratropium bromide systems spray dried from aqueous solutions, showing small spherical particles for the three systems. The 10:1 sample showed slightly dimpled particles, with particles ranging in size from 0.2 to 2.6 μm in diameter. The 5:1 system showed particles that were more significantly dimpled with diameters ranging from 0.2 to 4.8 μm and the 2:1 sys-

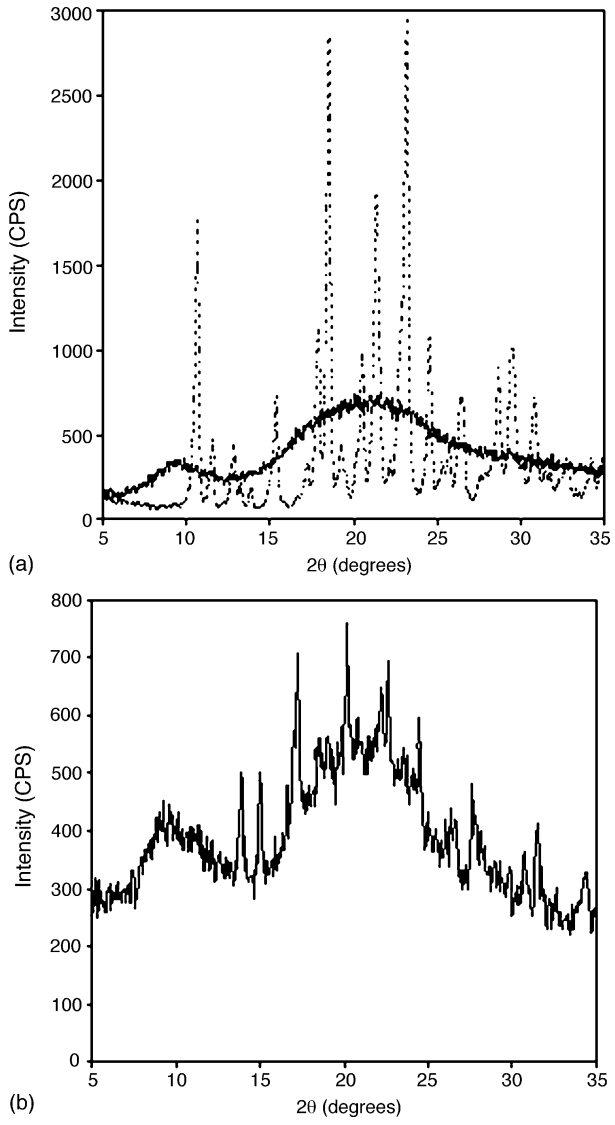

Fig. 5. (a) XRD scans of salbutamol sulphate:ipratropium bromide (SS:IB) 10:1 system spray dried from aqueous solution (continuous line) and crystalline salbutamol sulphate:crystalline ipratropium bromide monohydrate 5:1 physical mix (dashed line); (b) XRD scan of a physical mix of spray dried amorphous salbutamol sulphate:crystalline ipratropium bromide monohydrate 10:1.

tem displayed smooth spherical particles 0.5–5.9 μm in diameter. As the proportion of ipratropium bromide is increased the size of the particles also increases. Average particle sizes were 1.0 ± 0.5 μm, 1.4 ± 1.0 μm and 1.8 ± 1.1 μm for the 10:1, 5:1 and 2:1 systems, respectively. SEM of the salbutamol sulphate:ipratropium bromide systems spray dried from ethanolic solution showed them to be similar in size to those spray dried from aqueous solution. However, under SEM the particles appeared fused.

3.2. In vitro deposition – twin stage impinger experiments

Salbutamol sulphate capsules consisting of micronised salbutamol sulphate, spray dried salbutamol sulphate (spray dried from both solvents) or co-spray dried salbutamol sulphate:ipratropium bromide systems (spray dried from aqueous solution) were analysed by the twin stage impinger (TSI). Results are shown in Table 1. Micronised salbutamol sulphate showed the lowest mean fine particle fraction giving a FPF of 1.5%. Salbutamol sulphate spray dried from aqueous or ethanolic solution gave higher FPFs of 21.7% and 19.6%, respectively.

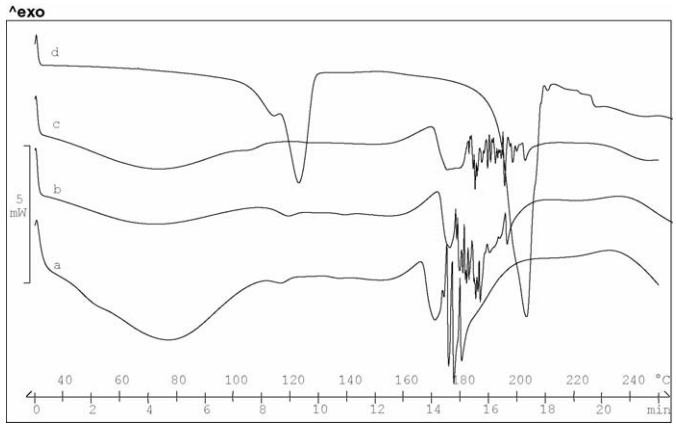

Fig. 6. DSC scans of (a) salbutamol sulphate:ipratropium bromide 10:1 spray dried from aqueous solution, (b) salbutamol sulphate:ipratropium bromide 5:1 spray dried from aqueous solution, (c) salbutamol sulphate:ipratropium bromide 2:1 spray dried from aqueous solution and (d) salbutamol sulphate:ipratropium bromide monohydrate 2:1 physical mix.

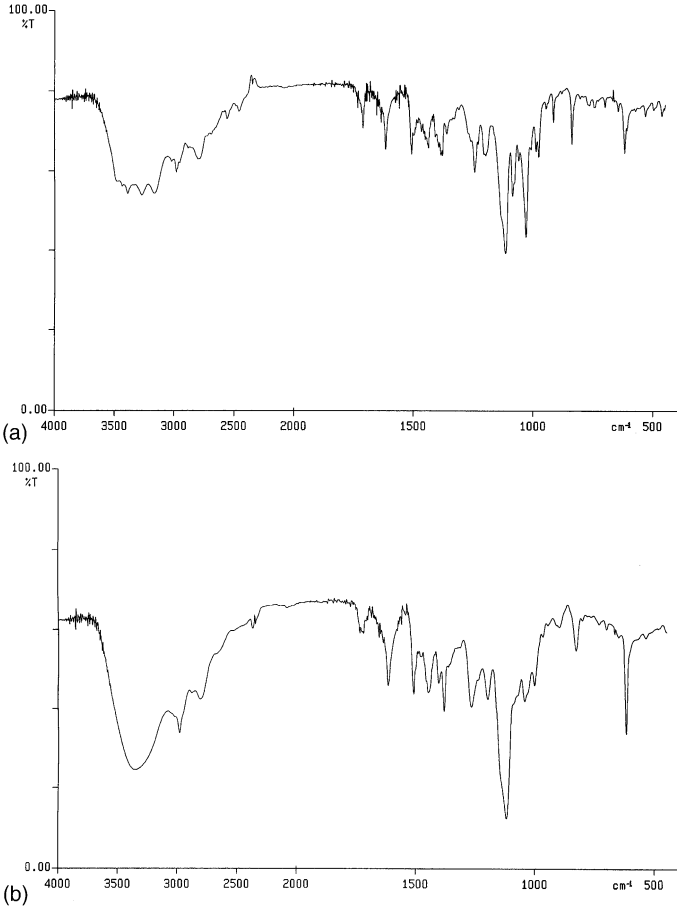

Fig. 7. FTIR scans of (a) salbutamol sulphate/ipratropium bromide monohydrate 5:1 physical mix and (b) co-spray dried salbutamol sulphate/ipratropium bromide 5:1 from aqueous solution.

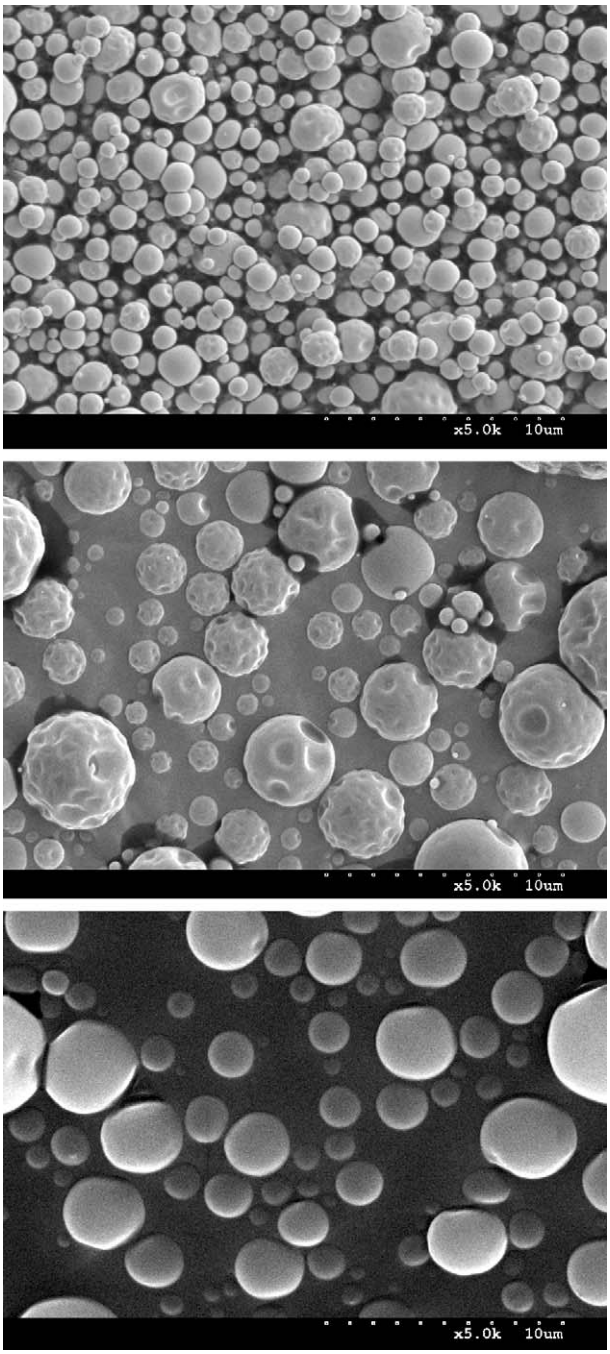

Fig. 8. SEM micrographs of salbutamol sulphate:ipratropium bromide systems 10:1 (top), 5:1 (middle) and 2:1 (bottom) spray dried from aqueous solutions. The scale bar corresponds to 10 μm in all cases.

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 ethanolic solvents, respectively (Corrigan et al., 2004). The surfaces of the particles in both cases were slightly dimpled. The size, shape and surface texture of the particles improves their flowability and deposition relative to the micronised material.

The co-spray dried salbutamol sulphate/ipratropium bromide systems gave higher FPFs than micronised salutamol sulphate but not as high as salbutamol sulphate spray dried alone. The FPFs obtained by the twin impinger experiments were compared by analysis of variance (ANOVA). Although micronised salbutamol sulphate results in the lowest FPF, ANOVA shows that this is however not statistically different (95% confidence interval) from the co-spray dried salbutamol sulphate:ipratropium bromide 2:1 system. The salbutamol sulphate:ipratropium bromide 2:1 system showed larger particles by SEM than the 10:1 or 5:1 spray dried weight ratios (i.e. the 2:1 systems showed particles approximately 1–6 μm in diameter while the 10:1 and 5:1 systems showed approximate diameters of 0.5–3 μm and 0.5–5 μm, respectively) (Fig. 8). Additionally the 10:1 and 5:1 systems consisted of spherical particles with surface dimpling while the 2:1 system consisted of smooth spheres. The 10:1 and 5:1 systems showed statistically higher FPFs than micronised salbutamol sulphate but not as high as salbutamol sulphate systems spray dried alone from either ethanol or water. Chawla et al. (1994) found no significant difference in FPFs between micronised salbutamol sulphate and aqueous spray dried salbutamol sulphate assessed using a Spinhaler® device attached to the TSI. It is well known that the design of the dry powder inhaler device plays a significant role in the deposition pattern of the powder formulation (Timsina et al., 1994) since every type of dry powder inhaler has a specific air flow resistance that limits flow. Therefore the results of Chawla et al. (1994) cannot be directly compared to results using a different inhaler device.

Previously we have spray dried salbutamol sulphate with a range of excipients, i.e. lactose, PEG 4000 and PEG 20,000 (Corrigan et al., 2004). These co-spray dried systems were also analysed by twin stage impinger for comparison. Results for the salbutamol sulphate/chitosan systems were previously reported (Corrigan et al., 2006). The FPFs for these systems and for the remaining co-spray dried salbutamol sulphate/excipient systems are shown in Table 2. An ANOVA was performed to compare the FPFs of all co-spray dried systems.

Salbutamol sulphate/lactose systems spray dried as 10% (w/v) solutions gave significantly higher FPFs than micronised salbutamol sulphate but not as high as salbutamol sulphate/chitosan systems, which showed FPFs between 28 and 36% (Corrigan et al., 2006). The salbutamol sulphate/lactose 20% system spray dried as a 2.5% (w/v) solution gave significantly higher FPFs than the other salbutamol sulphate/lactose systems spray dried as 10% (w/v) solutions. This was consistent with the smaller particle sizes produced on spray drying using the lower feed concentration (Corrigan et al., 2004). 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 (Corrigan et al., 2004). The 20% system spray dried as a 2.5% (w/v) solution gave FPFs comparable to most of the salbutamol sulphate/chitosan systems (Corrigan et al., 2006).

The spray dried PEG-containing systems did not appear significantly different from each other when analysed with all the other systems in the ANOVA. ANOVA uses a standard deviation determined from the pooling of the standard deviations of all the samples and assumes that all the systems have equal variance.

Table 1
Mean fine particle fractions (FPF) and standard deviations of salbutamol sulphate (SS) from capsules containing salbutamol sulphate raw material, spray dried salbutamol sulphate and co-spray dried salbutamol sulphate/ipratroprium bromide composites obtained using the twin impinger

System	XRD amorphous (A) or crystalline (C)	Mean FPF % ($n = 3$)	Standard deviation ($n = 3$)
Micronised salbutamol sulphate	C	1.54	0.29
Spray dried SS (from aqueous solution)	A	21.68	2.35
Spray dried SS (from ethanolic solution 95%)	A	19.63	5.14
Spray dried SS/ipratropium bromide 10:1 (from aqueous solution)	A	9.07	2.56
Spray dried SS/ipratropium bromide 5:1 (from aqueous solution)	A	11.77	1.47
Spray dried SS/ipratropium bromide 2:1 (from aqueous solution)	A	5.24	1.77

The amorphous/crystalline nature of the systems is also indicated.

Table 2
Mean fine particle fractions (FPF) and standard deviations of salbutamol sulphate (SS) from capsules of co-spray dried salbutamol sulphate/excipient composites obtained using the twin impinger

System	XRD amorphous (A) or crystalline (C)	Mean FPF % ($n = 3$)	Standard deviation ($n = 3$)
Spray dried SS/lactose 5%	A	11.17	3.40
Spray dried SS/lactose 20% as 10% (w/v) feed solution	A	13.54	1.33
Spray dried SS/lactose 20% as 2.5% (w/v) feed solution	A	25.69	4.13
Spray dried SS/lactose 40%	A	13.14	1.43
Spray dried SS/PEG 4000 5%	A	8.25	1.41
Spray dried SS/PEG 4000 20%	C	0.93	0.12
Spray dried SS/PEG 4000 40%	C	4.55	0.18
Spray dried SS/PEG 20,000 5%	A	4.80	0.15
Spray dried SS/PEG 20,000 20%	A	7.35	2.07
Spray dried SS/PEG 20,000 40%	C	1.95	0.30

The amorphous/crystalline nature of the systems is also indicated.

Considering the differences between the various systems with respect to composition, production parameters, etc., we compared each salbutamol sulphate/excipient group to micronised salbutamol sulphate by separate ANOVAs so that real differences are not masked by the overall pooled standard deviation. The results of an ANOVA comparing salbutamol sulphate/PEG 4000 5%, 20% and 40% and micronised salbutamol sulphate showed that the fine particle fraction for PEG 4000 20% system, which had the lowest FPF, was not statistically different to micronised salbutamol sulphate. It was not surprising that the PEG 4000 20% system had a significantly lower FPF than the 5% or 40% systems since it consisted of fused agglomerates while SEM micrographs showed the PEG 4000 5% system to have particles with diameters of 4–10 μm and the PEG 4000 40% system to include 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 (Corrigan et al., 2004). The physical properties of the spray dried powders appear to be highly dependent (in a non-linear manner) on the formulation composition. It was previously determined that the PEG 4000 20% system was the only one of the three composites studied that was found to contain some crystalline salbutamol sulphate (Corrigan et al., 2004). The presence of the crystalline phase may be responsible for the altered physical appearance of the recovered solid.

The salbutamol sulphate/PEG 4000 5% system showed the highest FPF, being statistically higher than micronised salbutamol sulphate or the 20% and 40% systems. The 40% system gave a significantly higher FPF than micronised salbutamol sulphate or the 20% system but not as high as the 5% system.

The results of an ANOVA comparing salbutamol sulphate/PEG 20,000 5%, 20% and 40% and micronised salbutamol sulphate showed that the PEG 20,000 40% system gave FPFs that were not statistically different from micronised salbutamol sulphate. This was not unexpected since the 40% system showed particles as large as 10 μm in diameter unlike the 5% and 20% systems in which all particles were less than 8 μm in diameter (Corrigan et al., 2004). The 5% and 20% systems showed higher FPFs than micronised salbutamol sulphate, these two systems not being statistically different from each other with respect to fine particle fraction.

4. Conclusions

Crystalline ipratropium bromide raw material is a hydrate. Spray drying ipratropium bromide from aqueous solvent resulted in a crystalline material. Physicochemical characterisation by DSC, TGA and FTIR identified that mainly anhydrous ipratropium bromide is produced on spray drying ipratropium bromide from aqueous solvent with some evidence of another polymorphic form of ipratropium bromide being present. Spray drying ipratropium bromide from ethanolic solvent resulted in a crystalline material with an XRD pattern different from that of the material spray dried from aqueous solvent and more

similar to the ipratropium bromide starting material. Physicochemical characterisation suggested the presence of anhydrous ipratropium bromide and/or a solvate.

Co-spray drying salbutamol sulphate with ipratropium bromide resulted in X-ray amorphous composites for the three weight ratios studied of 10:1, 5:1 and 2:1 salbutamol sulphate:ipratropium bromide monohydrate in spite of the fact that ipratropium bromide spray dried alone is crystalline.

The particle morphology and size of salbutamol sulphate/ipratropium bromide or salbutamol sulphate/excipient spray dried systems varied depending on the systems spray dried and the spray drying parameters used. Spray drying proved a successful method of producing microspherical particles which, for many of the systems, deposited in the lower region of the twin stage impinger indicating that they were in the respirable range.

It has been shown that the surface morphology of a carrier can affect the respirable fraction of a drug (Kawashima et al., 1998; Zeng et al., 2000), due to different strengths of adhesion between the drug and the carrier. Zeng et al. (2000) found that increasing either the surface smoothness or the elongation ratio of lactose crystals increased the fine particle fraction of salbutamol sulphate from dry powder inhalers.

The adhesion of particles is a surface phenomenon and therefore the morphology of the surface will have a significant effect on the adhesion of particles (Ganderton and Jones, 1992). Amorphous materials behave in a different manner to crystalline materials and this influences interactions including the powders cohesiveness and adhesion between the powder and other phases (Briggner et al., 1994). Of the spray dried systems investigated, the ones with the lowest fine particle fraction were those which were not X-ray amorphous (salbutamol sulphate/PEG 4000 20%, salbutamol sulphate/PEG 4000 40%, salbutamol sulphate/PEG 20,000 40% (Corrigan et al., 2004)).

In the case of salbutamol sulphate/ipratropium bromide spray dried materials; twin stage impinger results of the different weight ratios gave fine particle fractions which were not statistically different despite differences in particle morphology/surface topography. Of the three weight ratios of salbutamol sulphate:ipratropium bromide studied, two of the systems, the 10:1 and 5:1 systems, showed spherical shaped particles with indentations. The 2:1 system showed predominantly smooth spherical particles. It is apparent that factors other than morphology, such as particle size and density will also affect the results of FPF measurements.

Manipulation of the spray drying conditions can lead to the alteration of particle sizes of the resultant powders and hence the amount of powder that deposits in the lower impinger can be modified. Spray drying is a useful method of obtaining composite microspherical particles in the inhalable range.

Acknowledgements

Financial support for much of the work contained in this paper was provided by IVAX Pharmaceuticals U.K. Limited and is gratefully acknowledged.

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