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Spray drying of budesonide, formoterol fumarate and their composites—I. Physicochemical characterisation

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ABSTRACT

The objective of this work was to examine the physicochemical properties of spray dried budesonide, formoterol fumarate and their mixtures at two different weight ratios: 100:6 and 400:6 of budesonide and formoterol fumarate, respectively. A comparison of the thermal properties, crystalline/amorphous nature and particle size of the starting micronised as well as processed materials was carried out. The micronised drugs on their own and the physical mixtures were crystalline in contrast to the spray dried counterparts which were shown to be amorphous. The glass transition temperatures (T_gs) of the processed actives were determined and appeared at 89.5 and 88 °C for budesonide and formoterol fumarate, respectively. As for the spray dried composites, an indication of miscibility and/or interactions between the components was indicated by differential scanning calorimetry and infrared analysis. The spray drying in all cases resulted in smooth, spherical microparticles of sizes suitable for inhalation.

1. Introduction

Spray drying is a technique that has a wide range of applications in pharmaceutical production (Broadhead et al., 1992). This process has been used extensively as a potential alternative to milling for the production of fine particles suitable for inhalation and it has been recognised that spray dried particles can be produced in sizes suitable for pulmonary delivery. For instance, Vidgren et al. (1987) manufactured spherical particles of disodium cromoglycate that were mainly in the range of 1–5 μm and had favourable *in vitro* deposition properties, indicating suitability for delivery by oral inhalation. Salbutamol sulphate has also been demonstrated to form spherical microparticles upon spray drying with sizes implying usability as inhalable powders (Chawla et al., 1994). Recently, Corrigan et al. (2006) demonstrated that indeed, spray dried salbutamol sulphate gave around 13 times better fine particle fraction (FPF) than micronised drug in *in vitro* twin impinger studies. In the same study, co-spray dried salbutamol sulphate/ipratropium bromide 10:1 and 5:1 (w/w) systems showed an increase in FPF compared to micronised salbutamol sulphate. Spray drying can also be employed to prepare porous particles for metered dose inhaler formulations (Dellamary et al., 2000) and to process proteins for use in dry powder inhalers (Ståhl et al., 2002; White et al., 2005). Exubera®, the first inhalable insulin product marketed in Europe and the US, was a spray dried formulation of insulin with stabilising excipients.

A phase change often occurs during the spray drying process and it may lead to the production of amorphous substances (Corrigan et al., 1984). Examples of substances employed in inhalation therapies exhibiting the phenomenon of polymorphism are crystalline disodium cromoglycate and salbutamol sulphate. These drugs can easily be converted into amorphous phases (Vidgren et al., 1987; Chawla et al., 1994). Although it is known that amorphous materials exhibit enhanced solubility and dissolution properties (Corrigan and Holohan, 1984), they are potentially unstable on storage and may switch back into their crystalline counterparts. This may be an issue especially when the glass transition temperature of a compound is relatively close to that of the storage temperature; therefore, knowledge of physicochemical properties, particularly the thermal characteristics, is necessary for the prediction and understanding of the performance of the final formulation.

This work has focused on characterisation of possible changes in the solid-state properties upon processing of two pharmaceutical actives: budesonide and formoterol fumarate as well as their blends. Examples of physical processing of budesonide can be found in the literature and for instance Steckel et al. (1997) have reported that budesonide may be treated by supercritical fluid processing but no changes in crystallinity were observed. Spray drying of the drug has also been reported by Tarara et al. (2004), but in this

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case lipid-coated PulmoSpheres™ budesonide microcrystals were produced from emulsion-based stock.

Physicochemical properties of commercially available formoterol fumarate have been well characterised by Jarring et al. (2006), but no data have so far been published about spray drying this drug alone. Spray drying was employed in the production of hollow porous particles called PulmoSpheres™, but the content of formoterol fumarate in the final powder was very low, 1.8% (w/w) (Dellamary et al., 2000). Other constituents used in this work were lactose monohydrate and calcium chloride as well as perfluorooctyl ethane as the blowing agent. Only scanning electron microscopy (SEM), TEM and density analyses were carried out, therefore the full physicochemical characterisation was lacking.

The purpose of the present study was to characterise and compare the physicochemical and micromeritic properties of budesonide and formoterol fumarate dihydrate as well as their mixtures before and after spray drying. Also, the potential suitability of the spray dried powders for use in DPIs is of interest. For the mixtures, the following weight ratios: 100:6 and 400:6 (budesonide to formoterol fumarate dihydrate) were chosen to cover the therapeutic range of the marketed combination inhaler, Symbicort®, which is available at 100:6, 200:6 and 400:12 μg ratios of budesonide to formoterol fumarate dihydrate, respectively.

2. Materials and methods

2.1. Materials

Micronised budesonide and formoterol fumarate dihydrate were kindly donated by IVAX Pharmaceuticals (Waterford, Ireland). Ethanol was obtained from Cooley Distillery (Ireland). Methanol and acetonitrile were HPLC grade and purchased from Lab-Scan. Deionised and HPLC water were produced by a Purite Prestige Analyst HP water purification system. Potassium bromide (KBr) for infrared experiments was purchased from Spectrosol, thoroughly dried before use and stored in a desiccator over silica gel prior preparation of KBr discs.

2.2. Preparation of the systems

The systems were spray dried as solutions using a Büchi 191 Mini Spray Dryer (Büchi Laboratoriums-Technik AG, Flawil, Switzerland) fitted with a standard 0.7 mm two-fluid nozzle. The atomising air pressure at which the spray dryer operated was set to 5 bar.

Budesonide was spray dried as a 1% (w/v) solution containing 95% (v/v) ethanol and 5% (v/v) deionised water under the following processing conditions—inlet temperature: 77–78 °C, peristaltic pump setting: 15%, airflow rate: 600 Nl/h and aspirator setting: 85%. The outlet temperature recorded was 56–57 °C. Formoterol fumarate dihydrate was processed from 0.2% (w/v) ethanolic solution made of 98% (v/v) ethanol and 2% (v/v) deionised water. The inlet temperature used was 78–79 °C, peristaltic pump setting: 30%, airflow rate: 500 Nl/h and aspirator setting: 80%. The resulting outlet temperature was 50–52 °C.

The budesonide/formoterol fumarate dihydrate 100:6 and 400:6 weight ratio systems were spray dried from ethanolic solution based on 95% (v/v) ethanol and 5% (v/v) deionised water using the following process parameters—inlet temperature: 78–79 °C, peristaltic pump: 30%, airflow rate: 600 Nl/h and aspirator setting: 100%. These parameters resulted in the outlet temperature of 52–56 °C. The concentration of the 400:6 solution was 2.5% (w/v). The concentration of the 100:6 solution was 1.75% (w/v) and was limited by the solubility of formoterol fumarate.

For comparison purposes, the equivalent physical mixtures of budesonide and formoterol fumarate dihydrate in the ratio of 100:6 and 400:6 were prepared. Stoppered vial (10 ml), containing accurately weighed quantities of micronised substances "as supplied" was placed in a Turbula mixer (Glen Greston Ltd., Middx, UK) and mixing was carried out for 15 min at 42 revolutions per min.

2.3. Thermal analysis

Differential scanning calorimetry (DSC) experiments were conducted using a Mettler Toledo DSC 821^e with a refrigerated cooling system (LabPlant RP-100). Nitrogen was used as the purge gas. Hermetically sealed 40 μl aluminium pans with three vent holes were used throughout the study and sample weights varied between 4 and 10 mg. Thermogravimetric analysis (TGA) was performed using a Mettler TG 50 module linked to a Mettler MT5 balance in the furnace under nitrogen purge. Sample weights between 5 and 12 mg were used and placed into open aluminium pans. A heating rate of 10 °C/min was implemented in all DSC and TGA measurements. Analysis was carried out and monitored by Mettler Toledo STAR^e software (version 6.10) with a Windows NT operating system.

2.4. X-ray diffraction (XRD) analysis

Powder XRD analysis was conducted using nickel filtered Cu Kα (λ = 1.54056) monochromatic radiation on a Siemens D500 Diffractometer with a DACO MP wide-range goniometer. The anode X-ray tube was operated at 40 kV and 30 mA. Measurements were taken from 5° to 35° on the 2θ scale at a step size of 0.05°/s. Low background silicon mounts (Bruker AXS, UK) were used to support the sample during measurements.

2.5. Infrared analysis (FTIR)

Infrared spectra were recorded on a Nicolet Magna IR 560 E.S.P. spectrophotometer equipped with MCT/A detector, working under Omnic software version 4.1. A spectral range of 650–4000 cm^{-1}, resolution 2 cm^{-1} and accumulation of 64 scans were used in order to obtain good quality spectra. A KBr disc method was used with 1% (w/w) sample loading.

2.6. Visualisation of particles

SEM analysis was performed using a Hitachi S-3500N variable pressure scanning electron microscope. Samples were glued onto aluminium stubs and sputter coated with gold prior to analysis.

2.7. Particle sizing

Measurements of particle size distributions of budesonide and formoterol fumarate dihydrate before and after spray drying were obtained using a laser diffraction particle sizer Mastersizer 2000 (Malvern Instruments, UK). Particles were dispersed using a Scirocco dry feeder instrument with 3 bar pressure unless stated otherwise. An obscuration rate of 0.5–6% was obtained under a vibration rate of 50–70%. The sizes quoted are average values of two measurements.

3. Results and discussion

3.1. Budesonide

Budesonide was supplied as a micronised powder. The DSC analysis of the powder confirmed the crystalline nature of the starting material as only one endotherm peaking at 263.5 °C was observed.

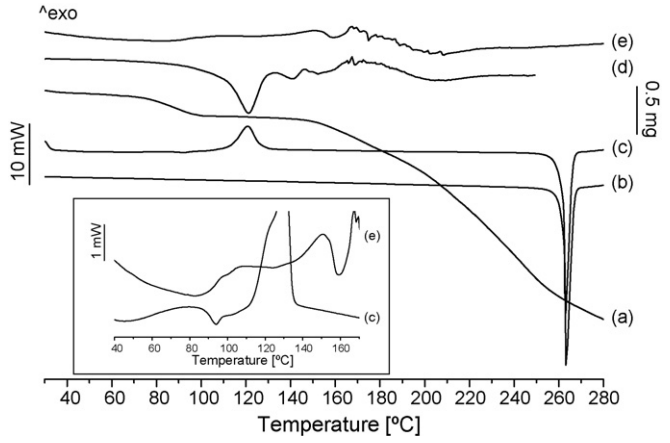

Fig. 1. Thermal analysis: (a) TGA of crystalline formoterol fumarate, (b) DSC of crystalline budesonide, (c) DSC of spray dried budesonide, (d) DSC of crystalline formoterol fumarate and (e) DSC of spray dried formoterol fumarate. Magnified are the glass transition temperature of budesonide and the recrystallisation peak of the spray dried formoterol fumarate. The scale on the right-hand side applies to curve a and the scale on the left-hand side applies to curves b–e.

The onset was at 262 °C, which is in a good agreement with the observation of Velaga et al. (2002) who stated that the melting point of crystalline budesonide is 258.7 °C. The DSC thermogram of the micronised budesonide powder is presented in Fig. 1b. The X-ray diffractogram of micronised budesonide analysed is shown in Fig. 2a and was typical of a crystalline material. The peak positions and their relative intensities were consistent with the XRD spectrum presented by Pham and Wiedmann (2001).

Spray dried budesonide was amorphous as shown by DSC (Fig. 1c) and XRD (Fig. 2c). A recrystallisation exotherm was seen in the DSC thermogram, with a peak at ~130 °C and this was followed by a melting endotherm with a peak at ~262 °C. The exotherm was preceded by a glass transition with the midpoint at ~89.5 °C (the transition is presented at a higher magnification in Fig. 1). The presence of the glass transition at approximately 90 °C is in good agreement with the theoretical estimated temperature of 102 °C, obtained by calculating 0.7 times the melting temperature in Kelvin (Brittain, 1999). TGA showed approximately a 1% weight loss between 25 and 100 °C. XRD showed a pattern typical of amorphous material with no distinct peaks but a diffuse halo as depicted in Fig. 2c.

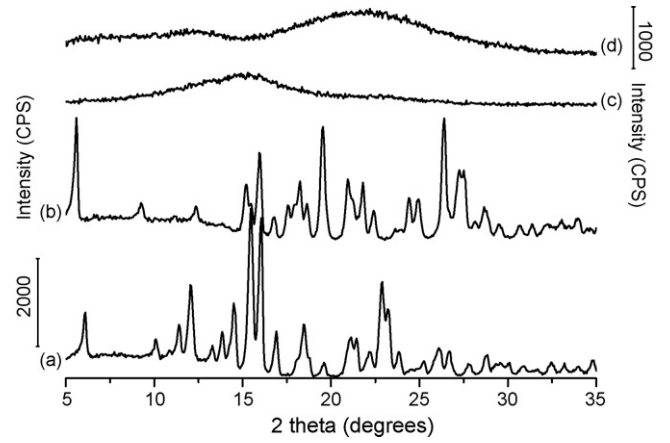

Fig. 2. X-ray diffraction patterns of (a) crystalline budesonide, (b) crystalline formoterol fumarate dihydrate, (c) spray dried budesonide and (d) spray dried formoterol fumarate. The scale on the left-hand side applies to curves a and b and the scale on the right-hand side applies to curves c and d.

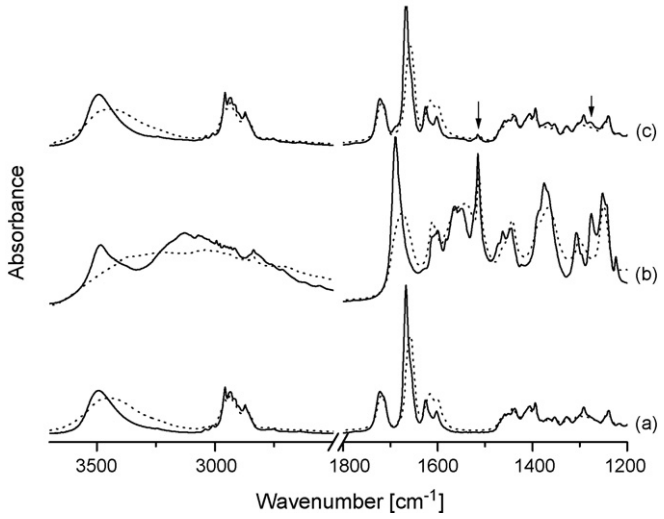

Fig. 3. FTIR spectra of (a) crystalline budesonide (solid line) and spray dried budesonide (dotted line), (b) crystalline formoterol fumarate dihydrate (solid line) and spray dried formoterol fumarate (dotted line) and (c) the physical mixture of budesonide and formoterol fumarate dihydrate 100:6 (solid line) and spray dried mixture (dotted line). The arrows indicate the bands of formoterol fumarate dihydrate.

The FTIR spectrum of budesonide showed carbonyl stretching bands at 1723 and 1667 cm^{-1} (Fig. 3a). The first carbonyl stretch peak at 1723 cm^{-1} was assigned as belonging to the non-conjugated acetyl C=O vibrations and the second peak at 1667 cm^{-1} to the conjugated dihydrobenzenoquinone C=O consistent with the findings of Tarara et al. (2004). Spray drying resulted in a material demonstrating a similar spectrum, but the peaks were more diffuse as a result of loosing the crystal lattice ordering. Moreover, a shift in the conjugated C=O stretching band from 1667 cm^{-1} (the crystalline form) to ~1658 cm^{-1} (the amorphous form) was observed, suggesting a possible change in the environment of the conjugated C=O group of budesonide. Also the OH bands appearing as a broad peak located in the 3300–3700 cm^{-1} region changed shape with broadening of the peak and a shift in the peak maximum from 3491 to 3448 cm^{-1} as a result of spray drying.

Budesonide supplied as a micronised material was composed of rough, irregular in shape particles typical of milled crystalline material (Fig. 4a) with a median particle size of 1.4 μm. The spray dried batch was composed of slightly larger and spherical particles with smooth surfaces as presented in Fig. 4b. The median particle size of this powder was determined to be 2.7 μm. The particle size distributions in both cases were monomodal.

3.2. Formoterol fumarate

Formoterol fumarate dihydrate raw material, when subjected to a DSC analysis, gave three endothermic peaks, as shown in Fig. 1d. The first peak, which was also the largest, appeared at ~122 °C and this was followed by the second endotherm with an onset at ~130 °C. The last endotherm was the smallest and began at ~147 °C. Above ~150 °C a thermal decomposition of the material was seen in the form of a jagged baseline. By TGA (Fig. 1a), a 5.4% mass loss in one step occurred in the 25–120 °C range, out of which 4.3% can be associated with the release of crystalline water, since the weight of two water molecules expressed as a percentage of total weight of formoterol fumarate dihydrate is 4.3%. The remaining 1.1% probably accounts for some surface moisture. On the basis of the above observations, the peak at ~122 °C was ascribed to dehydration. The weight loss which occurred beyond 155 °C is consistent with thermal decomposition seen by DSC.

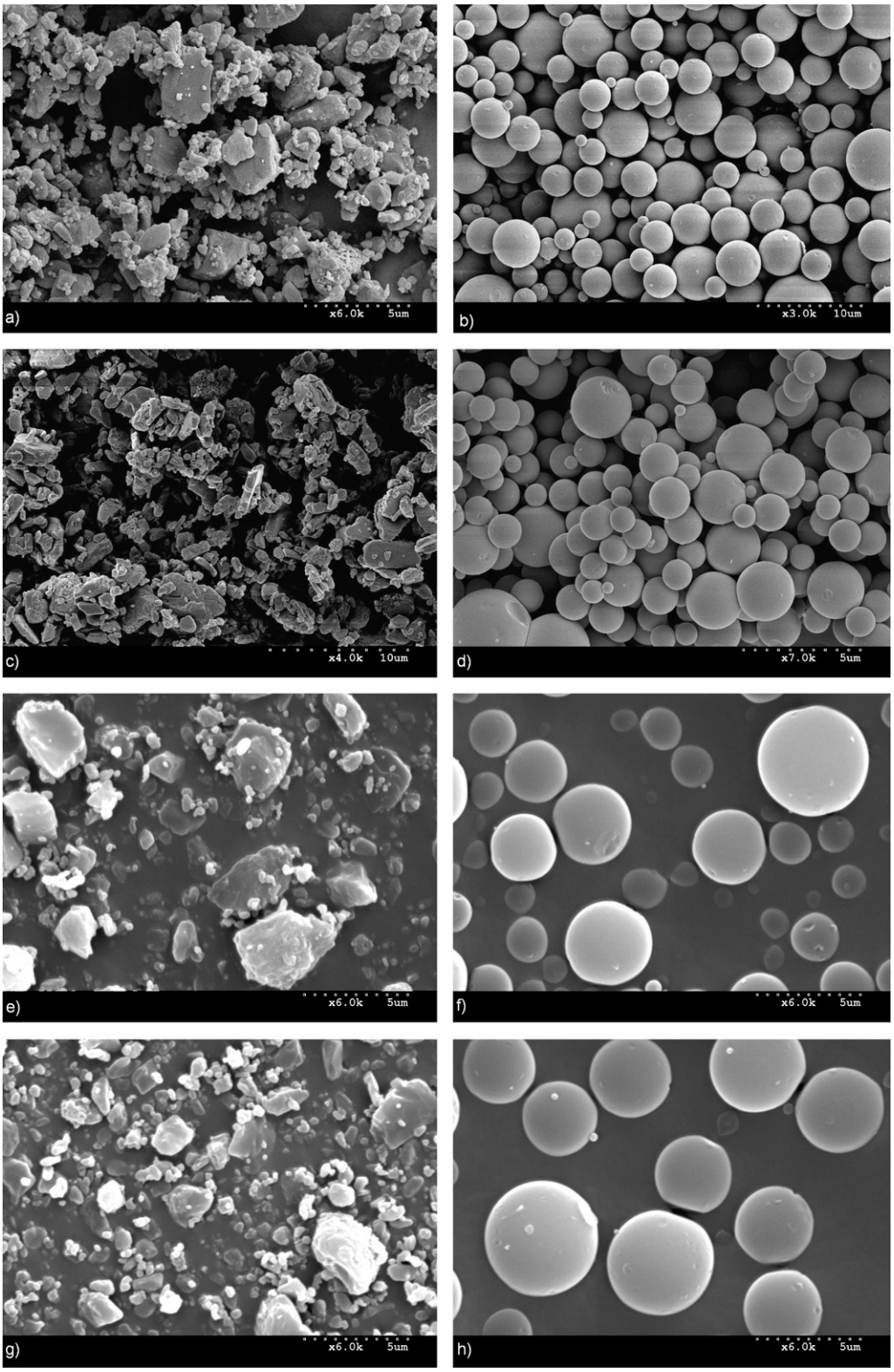

Fig. 4. SEM micrographs of (a) micronised budesonide, (b) spray dried budesonide, (c) micronised formoterol fumarate, (d) spray dried formoterol fumarate, (e) physical mixture of budesonide/formoterol fumarate dihydrate 100:6, (f) the corresponding 100:6 spray dried system, (g) physical mixture of budesonide/formoterol fumarate dihydrate 400:6 and (h) the corresponding 400:6 spray dried system. Note the different magnifications of the presented micrographs.

Jarring et al. (2006) in their investigations on formoterol fumarate crystal forms quoted the melting point by DSC of the dihydrate form to appear at 125 °C but no DSC curve of this form has been published making a direct comparison of the thermograms impossible. One of the anhydrous forms of the drug presented in Jarring et al.'s paper, prepared by drying the dihydrate in a stream of dry nitrogen and referred to as "anhydrate A", melted at 127 °C. The endotherm at ~130 °C detected in this work could be due to

an overlap of the dehydration and melting peaks therefore giving the appearance that the melting occurs at a slightly higher temperature. The other anhydrate polymorphs of formoterol fumarate addressed by Jarring et al. (2006) as "anhydrate B" and obtained from 99.5% (v/v) ethanol had a melting point of 150 °C, consistent with the onset temperature of melting of the third endothermic peak found in the DSC experiments.

The starting powdered material of formoterol fumarate was crystalline as seen in Fig. 2b with a well-defined peak pattern corresponding to that of dihydrate and recorded by Apperley et al. (2003) and Jarring et al. (2006), which collectively with the DSC analysis confirms that this material is a dihydrate.

Spray drying of formoterol fumarate resulted in an amorphous form of the drug as shown by a diffuse "halo" in the XRD pattern observed in Fig. 2d. A thermal event, which could be interpreted as an exotherm with a peak at ~106 °C and possibly recrystallisation of the amorphous phase, was seen in the DSC of the spray dried formoterol sample (Fig. 1e). This was followed by a melting endotherm with an onset at ~154 °C (both of the peaks were visible at a higher magnification as presented in Fig. 1). It has been noted that the temperature of the melting endotherm is slightly shifted upwards on the temperature scale when compared to the crystalline form. The exotherm was preceded by and overlapped with a broad endotherm which could be due to solvent liberation and indeed, thermogravimetry demonstrated ~3% weight loss for the spray dried material occurring from 25 to 100 °C, likely associated with some solvent traces remaining after processing. As the material was confirmed by the X-ray analysis to be amorphous, an attempt was made to expose the glass transition event that may have been overlapped by the broad endotherm of solvent evaporation. This was carried out by DSC and the sample was first subjected to a heating up to 90 °C, the temperature at which the recrystallisation exotherm began. It was then cooled down to 25 °C and reheated. Upon the second heating it was observed that the solvent liberation endothermic event had disappeared and a T_g of formoterol fumarate at ~88 °C was detected.

FTIR scans of spray dried and crystalline formoterol fumarate were alike with the peaks being more distinct and sharper for the latter sample as seen in Fig. 3b. Processing led to disappearance or shift of the band at 3484 cm^{-1}. It has been reported that the water molecules in formoterol fumarate dihydrate form two bridges via H-bonding between the formoterol moiety and the fumarate ion (Jarring et al., 2006) and according to the literature data (Socrates, 2001), the OH stretch vibration of water hydrogen bonded to other molecules appears at 3500 cm^{-1}. It is thus reasonable that the peak at 3484 cm^{-1} is assigned to the stretch vibration of the crystalline water molecules in the hydrate. A similar phenomenon was reported by Akao et al. (2001) for crystalline trehalose dihydrate. The disappearance of this peak indicates the lack of crystalline water in the spray dried sample. A second change in the FTIR spectra of the drug was a shift of the C=O stretching band, also called the amide I group (Socrates, 2001), of the formamide group from 1690 cm^{-1} for the crystal to 1675 cm^{-1} for the amorphous counterpart. This may be a sign of a restructuring of hydrogen bonds between the drug molecules as the carbonyl stretching band tends to change its position when involved in hydrogen bonding (Socrates, 2001).

Small spheres with smooth surfaces, typical of spray dried amorphous material were observed by SEM in contrast to irregular and rough particles of the unprocessed sample of formoterol fumarate (Fig. 4c and d). The shape of the particles was the main difference between these batches, as the median particle size was very similar, being 2.0 and 1.9 μm for the raw particulate material and spray dried sample of formoterol fumarate, respectively. The smaller particles of spray dried formoterol fumarate in relation to those of spray dried budesonide may be a result of a lower feed concentration of formoterol (0.2%, w/v) in comparison to the concentration of the budesonide solution (1%, w/v). A similar trend was observed previously for spray dried salbutamol sulphate composites (Corrigan et al., 2006).

3.3. Budesonide/formoterol fumarate physical mixtures and spray dried composite materials

The DSC trace of the physical mixture prepared from budesonide and formoterol fumarate dihydrate in the ratio of 100:6 (Fig. 5a) resembled the overlaid DSC curves of the individual drugs. Three endothermic peaks at ~102 °C, ~140 °C (visible at a higher magnification as seen in Fig. 5) and ~245 °C were detected and ascribed to dehydration and melting of formoterol fumarate dihydrate and melting of budesonide, respectively.

The endotherms of formoterol were shifted towards lower temperatures, especially evident for the 400:6 mix (Fig. 5b). This is consistent with some degree of interaction and/or miscibility between the two components. The melting peak of budesonide was broadened and asymmetric, most likely due to the presence of the thermal decomposition products of formoterol fumarate dihydrate.

TGA of the 100:6 physical mix showed weight loss occurring after 175 °C corresponding to a loss of approximately 2.2%. No such loss was detected for either of the 400:6 systems. This loss, probably due to degradation of formoterol fumarate, was not detected in the 400:6 systems possibly due to the very low amount of formoterol fumarate dihydrate present.

The physical blends were crystalline by XRD, as expected. The peaks of both substances, as seen in Fig. 6a, were evident in the 100:6 mix despite the low level of formoterol present in the mixture, but no peaks indicative of formoterol fumarate could be detected in the 400:6 physical mixture (Fig. 6b) due to the low concentrations of formoterol fumarate present.

Formoterol fumarate dihydrate/budesonide mixtures, regardless of the ratio in which they were mixed, on spray drying resulted in amorphous systems as shown by diffuse halos in the XRD. The curves c and d in Fig. 6 illustrate typical diffractograms of the composites.

A recrystallisation exotherm was evident in the DSC (presented in Fig. 5c) of the budesonide/formoterol fumarate 100:6 co-spray dried system with an onset at 119 °C, this was followed

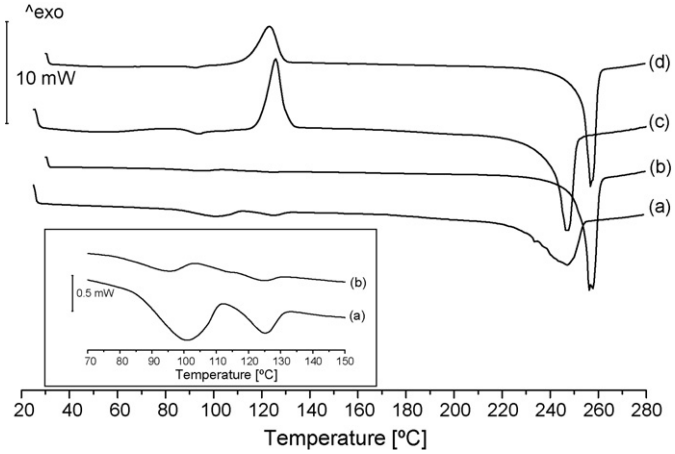

Fig. 5. DSC analysis of (a) physical mixture of budesonide/formoterol fumarate dihydrate 100:6, (b) physical mixture of budesonide/formoterol fumarate dihydrate 400:6, (c) budesonide/formoterol fumarate 100:6 spray dried mixture and (d) budesonide/formoterol fumarate 400:6 spray dried mixture. Magnified are endothermic peaks of formoterol fumarate in the both of the physical mixtures.

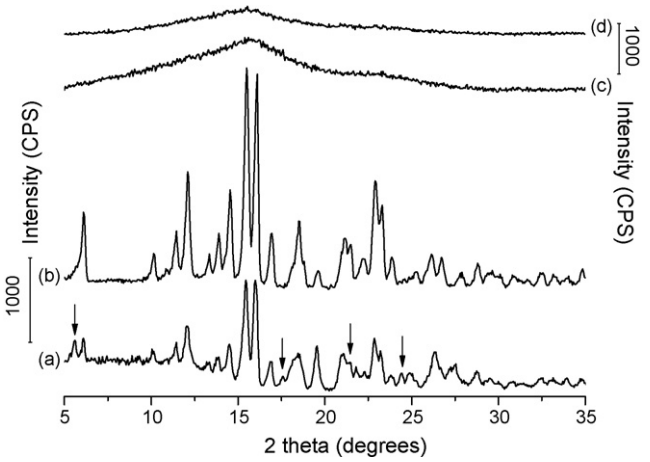

Fig. 6. X-ray diffraction patterns of (a) physical mixture of budesonide/formoterol fumarate dihydrate 100:6, (b) physical mixture of budesonide/formoterol fumarate dihydrate 400:6, (c) budesonide/formoterol fumarate 100:6 spray dried mixture and (d) budesonide/formoterol fumarate 400:6 spray dried mixture. The arrows indicate the peaks of formoterol fumarate. The scale on the left-hand side applies to curves a and b and the scale on the right-hand side applies to curves c and d.

by a melting endotherm which had a peak at 242 °C. Furthermore, there appeared to be a relaxation endotherm associated with the glass transition (seen at a similar temperature as for spray dried budesonide alone) with a midpoint at 90.2 °C. The 400:6 co-spray dried system (Fig. 5d) showed a glass transition, at approximately 89.7 °C. A recrystallisation exotherm was observed beginning at 114 °C, followed by melting at 253 °C. The higher temperature recrystallisation exotherm and the higher glass transition temperature observed in the 100:6 system compared to the 400:6 system and spray dried budesonide alone, implies that the higher amount of formoterol fumarate present in this system may act as an antiplasticiser, i.e. an additive which raises the glass transition temperature of a substance (Hancock and Zografi, 1994), thereby increasing the stability of the amorphous system.

Furthermore, the T_gs of both drugs and of the composite systems suggest good physical stability on storage at room temperature, since amorphous materials are presumed to be physically stable when kept at a temperatures less than or equal to their Kauzmann temperatures (T_Ks), where $T_K = T_g - 50$ K (Hancock and Zografi, 1997). Another advantage in terms of stability is the hydrophobic nature of budesonide, allowing for a limited moisture sorption. Indeed, when the spray dried budesonide, formoterol fumarate and the co-spray dried mix 100:6 were examined after around 4 years of storage at 4 °C in a vacuum desiccator, they were still completely X-ray amorphous. Also FTIR spectra were typical of the disordered forms.

Infrared scans of the freshly prepared physical mixture and spray dried samples of the 100:6 ratio resembled those of budesonide and two arrows in Fig. 3c point at bands of formoterol fumarate. Minor differences in some of the peak positions in the FTIR spectra of the mechanical mix and processed samples as well as the spray dried blend and spray dried budesonide were discerned, especially broadening of the band in the 3200–3600 cm^{-1} region was seen. Also, this band of the spray dried mix showed a shift towards lower wavenumbers on comparison with a spectrum of spray dried budesonide.

The spray dried composite materials consisted of smooth, spherical particles in contrast to rough and irregularly shaped particles of the mechanical mixes. The SEM micrographs comparing the mechanical mixtures and spray dried particles are presented in Fig. 4. The co-spray dried particles were approximately 1–5.5 μm in diameter by SEM and about the same size as those of spray dried budesonide.

4. Conclusions

Spray drying of budesonide, formoterol fumarate and budesonide/formoterol fumarate systems resulted in the production of microspherical particles. Spray dried materials made of particles with sizes between 1 and 7 μm have proven to be superior than micronised powders in *in vitro* twin impinger studies (Corrigan et al., 2006). Therefore, the actives spray dried in this work, both on their own or as the mixtures have potential for use as inhalable powders. Furthermore, the particle size distribution appeared narrower by SEM for the spray dried systems when compared to the physical mixes, with fewer particles in the less than 0.5 μm size range (particles which would be too light to deposit in the lungs and would be exhaled).

All spray dried systems appeared amorphous by X-ray diffraction studies. An exothermic peak, indicative of recrystallisation, was observed in the DSC scan of all spray dried materials, confirming the disordered nature of the systems. Altering the crystalline state of the drugs may increase their rather poor aqueous solubilities, which may also improve their pulmonary absorption.

The high glass transition temperatures of these amorphous samples suggest a good physical stability, which was confirmed on storage. This may be even further augmented by the possibility of specific interactions arising between these two drug substances and a phenomenon whereby interactions between a polymer and a drug resulted in increased T_gs of formed blends has been reported previously (Tajber et al., 2005).

The effect of changing spray drying parameters on the properties of the resulting powders and an assessment of the *in vitro* deposition properties of the spray dried powders, to determine their suitability for oral inhalation will be described in Part II of this paper.

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