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Particle formation of budesonide from alcohol-modified subcritical water solutions

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ABSTRACT

Recently, subcritical water (SBCW: water that has been heated to a temperature between 100 °C and 200 °C at pressures of up to 70 bar) has been used to dissolve several hydrophobic pharmaceutical compounds (Carr et al., 2010a). Furthermore, a number of active pharmaceutical ingredients (APIs) have been rapidly precipitated from SBCW solutions (Carr et al., 2010b,c). It is possible to alter the precipitate morphology by altering the processing variables; including the SBCW-API solution injection temperature and adding impurities (such as pharmaceutical excipients, e.g. lactose) to the precipitation chamber.

The work presented in this article demonstrates that the morphology of pharmaceutical particles can be tuned by adding organic solvents (ethanol and methanol) to the SBCW-API solutions. Particle morphology has also been tuned by adding different pharmaceutical excipients (polyethylene glycol 400 and lactose) to the precipitation chamber. Different morphologies of pharmaceutical particles were produced, ranging from nanospheres of 60 nm diameter to 5 μm plate particles. Budesonide was used as the model API in this study. Two experimental products were spray dried to form dry powder products. The aerodynamic particle size of the powder was established by running the powder through an Andersen Cascade Impactor. It has been shown that the drug particles produced from the SBCW micronization process, when coupled with a spray drying process, are suitable for delivery to the lungs.

1. Introduction

Budesonide is a glucocorticoid steroid with a high topical to systemic activity ratio that is typically used to treat asthma and rhinitis (Budavari, 1996). For the treatment of asthma, the drug is delivered into the lungs via inhalation. Budesonide is often delivered in combination with formoterol fumarate; a bronchodilator (Banerjee et al., 2001). Other compounds can be added as excipients to drug formulations to facilitate the absorption of API into the body. Pharmaceutical excipients can include compounds such as lactose (Dudognon et al., 2006), polyethylene glycol (PEG) (Steckel and Wehle, 2004), dextrose and potassium sorbate (Nilsson and Santesson, 2001).

In order for a drug to be delivered efficiently into the lungs, the maximum particle size needs to be below 5 μm (Huang and Wang, 2006). The restrictions on the particle size are related to the relative tortuosity of the lung chambers – where, if a particle is too large the particle will not be able to penetrate to the lower lung absorption sites (Vozone and Marques, 2002). Conversely, if the particle is too small, the particle will be expelled by other areas of the lungs (Fu et al., 2002). Thus, stringent control over the particle size distribution needs to be achieved.

Micronization of budesonide has been achieved using a number of methods, which include traditional milling and precipitation techniques (Dudognon et al., 2006). Micronization of budesonide via supercritical antisolvent (precipitation) techniques requires the use of methylene chloride or acetone as a solvent (with CO_2 as the antisolvent) (Lobo et al., 2005; Martin et al., 2002). These solvents are toxic and can be difficult to remove from the drug matrix post-micronization, particularly in the low levels required for pharmaceutical application (Lakatos, 2008). While it is possible to remove residual solvents to the level required by industry using supercritical techniques, often high volumes of CO_2 are required.

A recently introduced alternative to supercritical fluid micronization techniques is the SBCW micronization technique (Carr et al., 2010b). The use of SBCW as a solvent to micronize budesonide has an advantage over these methods, as SBCW (even with small amounts of alcohol modifiers) is non-toxic and does not require rigorous solvent removal steps, even if present in non-trace levels in the drug matrix. The technique typically involves the heating of water to up to 200 °C to dissolve a hydrophobic drug. The hydrophobic drug is soluble in SBCW because the dielectric constant (a measure of polarity) of water is lowered at elevated temperatures. By rapidly cooling the solution, the polarity of water

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is increased, which induces supersaturation in the solution, leading to rapid precipitation of API in water.

For some compounds, such as budesonide, the solubility in water is low, even in SBCW at 200 °C. The purpose of using organic solvents is to increase the solubility of budesonide in SBCW, and thus increase the yield of the precipitation process. It is possible to increase the solubility of budesonide in SBCW tenfold by adding up to 20% (v/v) ethanol (Carr et al., 2010a). Both ethanol and methanol were used in this study to decrease the dielectric constant of water.

It is possible that the addition of these solvents to the SBCW-API solution may add a degree of tunability to the precipitate morphology. It has been shown in supercritical fluid (SCF) systems that a change in solvent can lead to a change in precipitate morphology (Subramaniam et al., 1997; Yeo and Kiran, 2005). While the mechanisms governing particle formation in SCF systems may be different to that for SBCW particle formation, it is likely that the presence of organic solvents in the experiments conducted in this work may affect the precipitation of drug particles.

It has been shown previously that the presence of an excipient in the precipitation chamber can affect the morphology of the precipitate (Carr et al., 2010c). The effect of two commonly used pharmaceutical excipients, lactose and polyethylene glycol 400 (PEG400), on the morphology of the precipitated model API particles was investigated. The materials were selected based on the common usage of both materials as pharmaceutical excipients. Both lactose and PEG400 were selected because they are commonly used carriers for naproxen and budesonide (Steckel and Wehle, 2004; Nilsson and Santesson, 2001; Nokhodchi et al., 2007; Naikwade and Bajaj, 2009; Kinnarinen et al., 2003). The excipients were added to PC in proportions similar to those found in common API formulations for lung delivery.

In order to demonstrate the particles produced from the SBCW-micronization process have the potential to be delivered into the lungs, the suspension needed to be dried. A model suspension of API in water was spray dried. Spray drying was selected because it is a continuous drying process, which may be considered for a continuous SBCW micronization process for producing dry powders in the future. The spray dried powder was then subjected to inhalable drug delivery testing via a Cascade Impactor to simulate aerodynamic performance of the particles in the human lungs.

2. Materials

Budesonide (≥99% purity) and polyethylene glycol 400 (PEG, molecular weight: 380–420 amu [atomic mass units]) were purchased from Sigma–Aldrich. Anhydrous lactose (pharmacopoeia calibration standard) was obtained from Fluka. 99.8% ethanol and reagent grade acetone (for washing) were purchased from Univar. HPLC grade methanol was purchased from Burdick and Jackson. This methanol was also used for UV quantification of budesonide from the Andersen Cascade Impactor plates. De-ionized water was used for all experiments.

3. Method

The method of dissolution of APIs in SBCW and the method of precipitation of APIs from SBCW solutions have been presented previously (Carr et al., 2010b,c, 2009). The solubility of budesonide in SBCW and SBCW–alcohol mixtures between 100 °C and 200 °C has already been published (Carr et al., 2010a). The same method as used by Carr et al. was used (Carr et al., 2010a). A schematic of the experimental apparatus is shown in Fig. 1. The fittings and tubing were of stainless steel (type 316). A Druck pressure transducer and indicator were fitted and a Shimadzu GC-8A chromatography oven was used as the heating unit.

3.1. Dissolution of API in SBCW/SBCW–organic solvent mixtures

Four mixtures of organic solvents with water were made at concentrations of 0%, 10% (v/v) and 20% (v/v) ethanol and 10% (v/v) methanol. The pump P1 was filled with the water/alcohol mixture. For each run, the SV was loaded with an excess solute (typically double the mass of budesonide present in a saturated solution at 200 °C. The solubility vessel (SV) had an internal volume of 6.4 mL. The vessel was then filled with the water/alcohol mixtures from the syringe pump P1. The "line end" was left open during the filling period, and once water/alcohol solution dripped out, it was sealed off with a stainless steel cap. The water overflow ensured that air was purged from the system.

The operating pressure was set to 70 bar via the syringe pump, thus ensuring that water was in the liquid state throughout the experiment. The system was brought to the selected temperature using the GC oven with pressure from thermal expansion relieved through V4.

Once the set temperature was reached, the system was left to equilibrate for 10 min while being internally stirred by an oscillating magnetic bar. The internal magnet was guided by an external iron ring magnet driven by an electric motor. The external ring magnet oscillated at 72 strokes per minute.

After 10 min of mixing, the magnetic stirrer was stopped and the nitrogen supply, preset to 72 bar, was allowed to contact the solution by opening V3. The high pressure nitrogen was used to maintain a constant vessel pressure, thereby preventing the vaporization of SBCW inside the apparatus during product collection.

3.2. Particle formation

Valve (V3, when opened) permitted the flow of SBCW solution from the SV to a collection vessel where precipitation occurred. The line to the precipitation vessel was 1/16″ OD stainless steel tubing. The line was located inside the oven to minimize temperature changes prior to the particle formation vessel. A nozzle with an ID of 1 mm was used to deliver the SBCW solution into the particle formation vessel for all experiments. The nozzle was a standard Swagelok 1/16″ tube. The flow from the SV to the precipitation vessel was controlled by V3 (Fig. 1).

The collection vessel (PC) was filled with 60 mL of water at room temperature and a backpressure of 20 bar was applied to ensure that the water remained in the liquid state throughout the experiment. Backpressure was monitored using a Druck pressure transducer.

A weighed amount of budesonide was loaded into the SV. The system was filled with water and pressure and temperature were equilibrated as described for solubility measurements. The system was then stirred for 10 min and subsequently contacted with nitrogen at 72 bar. The valve V3 was then cracked open 1/4 turn to allow the solution to flow to the PC vessel. The flow was stopped once the first nitrogen bubble was seen. The pressure of the sight gauge was continuously monitored to ensure a constant backpressure was maintained. As the volume of the collection chamber was much larger than the volume of injected solution, the pressure of PC remained at 20 bar throughout the experiment.

The content of the PC vessel was collected using a plastic syringe and transferred to a glass collection vial. The API was separated from the water suspension by vacuum filtration through a 0.45 μm HV hydrophilic Millipore membrane filter. The vacuum was provided by an Adixen Pascal 2000SD vacuum pump.

3.3. Particle formation in the presence of excipients

Lactose is a commonly used carrier/excipient for the delivery of budesonide into the lungs (Naikwade and Bajaj, 2009). The thera-

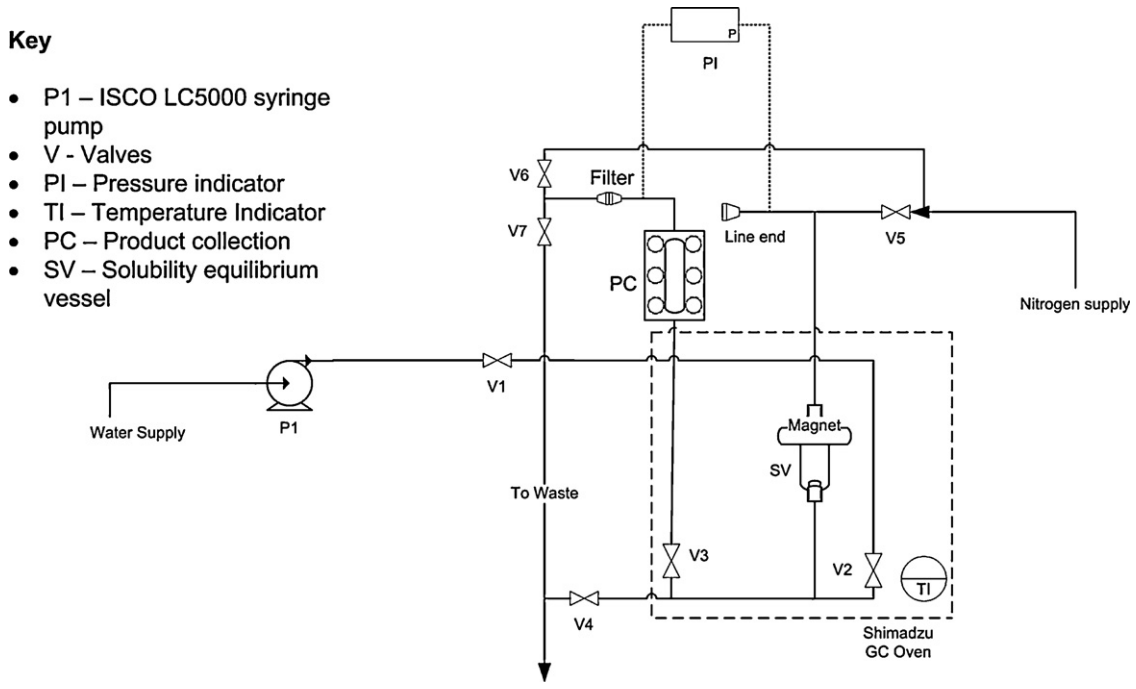

Fig. 1. Subcritical water particle formation apparatus.

peutic ratios have been described in the literature as 1:15 and 1:30 (w/w) ratios of budesonide API to lactose (Kinnarinen et al., 2003). Thus, for each temperature, a mass of lactose was added to the 60 mL water in PC, where the mass of lactose added was 15 or 30 times the mass of budesonide injected into PC at each temperature (based on the solubility data reported in Carr et al., 2010a).

PEG has been used as an excipient for the pulmonary delivery of budesonide into the lungs (Steckel and Wehle, 2004; Naikwade and Bajaj, 2009). The effect of PEG as a modifier for particle formation in the PC was investigated on the morphology of budesonide. PEG was added to budesonide at 4:1 and 8:1 (w/w) ratios (PEG:budesonide), as they are common ratios used in budesonide formulations (Nilsson and Santesson, 2001). A mass of PEG was added to the water in PC in these ratios.

3.4. Spray drying of suspensions of budesonide in water

A spray dryer was used to dry lactose solutions and budesonide suspensions in lactose solutions. A Buchi 290 spray dryer was used. The spray nozzle had an ID of 1/16″. The inlet temperature was set to 170 °C. The compressed air flow was set to 40 on the instrument gauge. The flowrate of the liquid solutions/suspensions was delivered at 15% pump rate (gauge reading). The aspirator was set to 100% (gauge reading). Before injecting the test solutions to the drying chamber, water was injected for 25 min, which was the time required to stabilize the outlet temperature of the drying chamber. The outlet temperature for all experiments, which differed for each solution, was recorded for all spray dried samples.

Experimental conditions were kept constant between samples, as the purpose of the spray dryer was to produce a powder post-SBCW processing and not to optimize the spray drying process.

3.5. Measurement of the aerodynamic performance of the particles

A model 8301 Anderson Cascade Impactor was used to measure the aerodynamic particle sizes of spray dried budesonide and lactose suspensions/solutions. A basic schematic of the Cascade Impactor is shown in Fig. 2. The experiments were run with 8 stages (stages 0–7) at 28.3 L/min (Kinnarinen et al., 2003). Each stage corresponded to an aerodynamic particle size, and a corresponding stage in the human respiratory system. In order to properly simulate a standard breath (4 L of air per breath), a flowtime of 8.5 s was used. All of the powders tested in the Cascade Impactor were sealed within a gelatin capsule (capsule size 3GS, purchased from Capsugel). An Aerolizer dry powder inhaler was used to break the pill and subject the contents to a flow of air. A Copley vacuum pump and TPK solenoid control valve were used to control the vac-

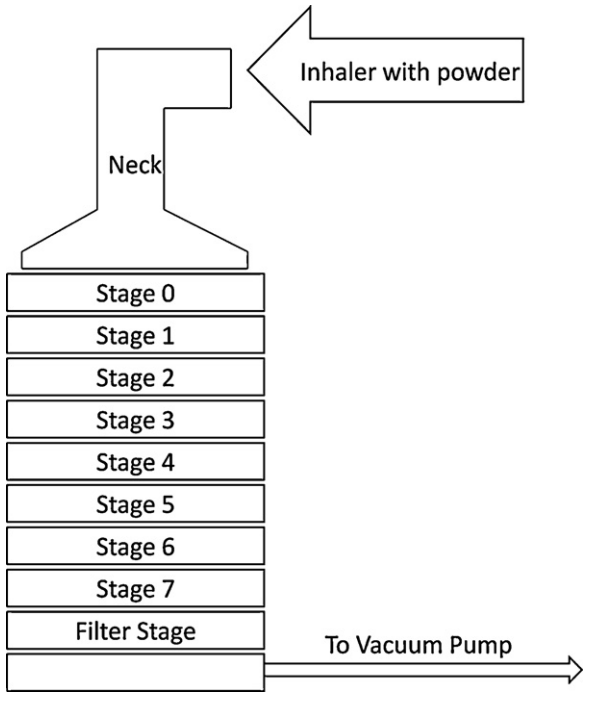

Fig. 2. Standard setup of the Andersen Cascade Impactor.

Table 1
Budesonide particle formation conditions and summary of results.

Experiment number	Temperature (°C)	Ethanol fraction (%, v/v)	Methanol fraction (%, v/v)	Solubility (mg/mL)	Average number particle diameter (SEM, nm)	X_{10} (nm)	X_{50} (nm)	X_{90} (nm)	Morphology (shape)
B1	200	0	0	2.35	200	60	100	200	Spheres
B2	130	20	0	2.22	730	300	630	1290	Spherical particles and plates
B3	150	20	0	6.72	778	530	930	1630	Spherical particles and plates
B4	160	0	10	2.15	50.1	24.0	50	100.0	Rounded particles

uum flowrate (measured with a Copley flowmeter) and inhalation pressure for all experiments (Scientific, 2006).

In order to establish the mass of the powders at each stage, the plate at each stage was weighed pre- and post-experiment. The mass of material at each stage was converted into a mass fraction. When budesonide was deposited on the plates, the masses were also measured using UV spectrometry. Each plate was put in a glass Petri dish. Methanol (4 mL) was added to the dish to dissolve the budesonide. The plates were washed in the methanol and then removed. The methanol–budesonide solution from the Petri dish was then transferred by pipette into a 10 mL grade-A volumetric flask. The volume was made up to 10 mL in the volumetric flask and the concentration of budesonide in the API-methanol solution was determined through UV spectrometry using the Beer–Lambert law.

In order to measure the concentrations of lactose and budesonide in a spray dried formulation, both the mass difference method and the UV method were used. Methanol is a poor solvent for lactose, and a good solvent for budesonide (Budavari, 1996). Thus UV spectrometry could be carried out accurately for the methanol–budesonide solutions, as lactose was not present in the methanol. The proportion by mass of lactose in the formulation was determined by subtracting the difference of the weighed plates with the deposited budesonide and lactose on them and the UV results for budesonide.

In order to compare the micronized budesonide/spray dried lactose product to an unprocessed product, a blend of the raw budesonide and lactose was prepared. Budesonide and lactose were blended in a 1:4 budesonide:lactose mass ratio. The budesonide and lactose were combined using a mortar and pestle.

3.6. Dynamic laser scattering and electron microscopy methods

A Brookhaven dynamic light scattering (DLS) instrument was used to determine the particle size distributions of budesonide in water. Suspensions were collected directly from the PC and injected into the cuvettes for analysis. Results are reported as the X_{10}, X_{50}, and X_{90} number diameter (corresponding to the diameter of particles at the 10th percentile, 50th percentile and 90th percentile respectively).

A Hitachi S900 scanning electron microscope (SEM) was used to image the product. The API powder was dispersed onto double sided carbon tape and then placed on a sample holder. Samples were chromium coated. An average particle diameter was calculated (number diameter) from the SEM images by measuring the sizes of 100 particles in an SEM image and taking an average of the measured diameters.

3.7. X-ray diffraction method

The X-ray diffraction (XRD) machine used was a Philips multipurpose X-ray diffraction system (MPD). The budesonide powder was placed on a polished iron sample holder. The beam angle was varied from 6° to 60° with a 0.0206 2θ step size. The X-ray generator was set at 45 kV and 40 mA. The diffraction patterns of the processed materials were analysed and compared to the diffraction patterns of the raw material to evaluate changes in the crystal structure. The mass of powder loaded into the XRD plates was 0.12 g for each sample.

3.8. Differential scanning calorimetry method

A TA Instruments differential scanning calorimeter (DSC) 2010 was used. Dried powder samples (5–10 mg) were loaded into aluminum pans and sealed. The samples were cooled to −50 °C and the temperature was ramped at 10 °C/min to 300 °C in a nitrogen atmosphere.

3.9. Thermogravimetric analysis method

The purpose of the thermogravimetric analysis (TGA) was to evaluate the mass of residual solvent in the samples post-micronization. A TA Instruments Thermogravimetric Analyzer was used. Dried budesonide (1–5 mg) on a platinum pan. The temperature was ramped at 10 °C/min up to 120 °C, and then run isothermally at 120 °C for 60 min in a nitrogen atmosphere.

4. Results

4.1. Budesonide dissolved in SBCW and SBCW–alcohol mixtures

Experimental conditions used to micronize budesonide are shown in Table 1. The budesonide precipitated from subcritical water solutions, in the absence of organic solvents, crystallized into rounded particles with a number average diameter of 300 nm, as shown in Fig. 3(b). The particles that precipitated from SBCW–ethanol solutions tended to be larger than the budesonide precipitated from pure SBCW, as shown in Fig. 3(c and d). The particles precipitated from ethanol modified SBCW solutions tended to crystallize as plate crystals. When methanol was used as a co-solvent, small spherical particles with a diameter of 50 nm were precipitated.

Similar spherical and rounded particles of budesonide have been formed from a Solution Enhanced Dispersion of Supercritical fluids (SEDS) process (Schiavone et al., 2004). The particle size distributions of the spheres produced in the subcritical water system were comparable to the distributions of products from the SEDS process (Fig. 4).

In the absence of excipients, a change in SBCW–budesonide injection temperature did not affect the budesonide precipitate morphology over the tested temperature range. While the X_{50} number diameter of budesonide precipitated from a 130 °C with 20% ethanol–SBCW solution was 630 nm and that of budesonide precipitated from a 150 °C with 20% ethanol–SBCW solution was 930 nm, the particle size distribution of each condition spanned the same size range. The unchanged particle morphology is reflected by the similar average particle size observed in the SEM images (as shown

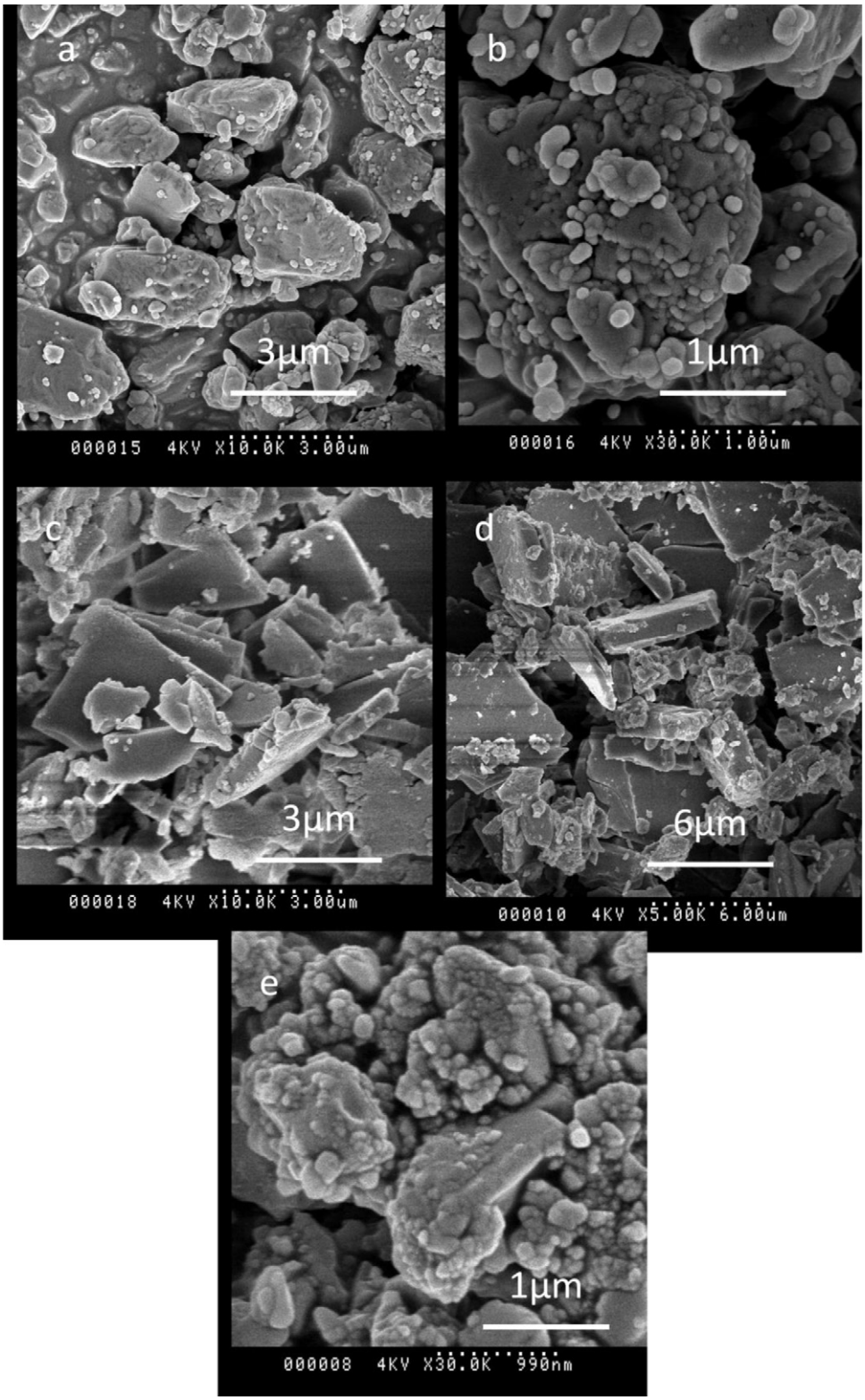

Fig. 3. SEM of raw budesonide (a), budesonide processed using conditions B1 (b), B2 (c), B3 (d) and B4 (e).

in Table 1). Thus, while it appeared that the lower temperature injection led to smaller particles, the particle size distribution was unchanged. The similar size range implies that both products, if used to treat asthma, would have similar dissolution profiles in the human body.

The DSC and XRD results, shown in Figs. 5 and 6 respectively, indicate that the budesonide was crystalline when precipitated from ethanol-modified solutions. The processed budesonide DSC curve indicated a peak melting temperature that was 1.3 °C less than the peak melting temperature of the raw material. The onset of melting occurred at 250 °C for both samples. Considering that both the onset of melting and the XRD patterns are identical for the raw and SBCW–ethanol processed budesonide samples, it can be concluded that the precipitated budesonide has the same crys-

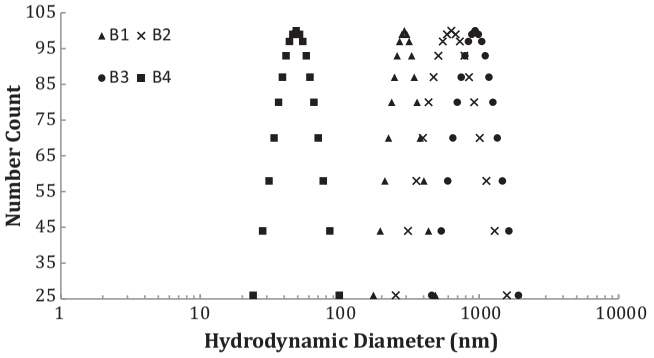

Fig. 4. Particle size distributions of budesonide processed using experimental conditions B1, B2, B3 and B4 according to Table 1.

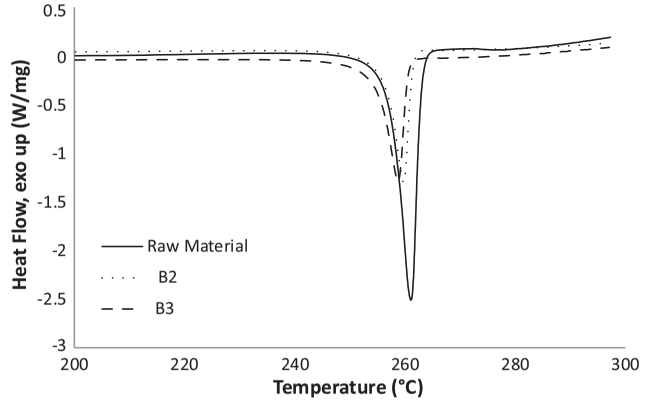

Fig. 5. DSC curves of raw and processed budesonide.

tal structure as the raw material. It is possible that the reduced melting peak for the SBCW-micronized budesonide was due to trace amounts of water left in the product matrix post-processing. A TGA was run on a sample of budesonide micronized at 200 °C and dried according to the experimental method. It was found that 4% by mass of the sample was lost. It is possible that the presence of water in the product led to a reduced melting peak temperature.

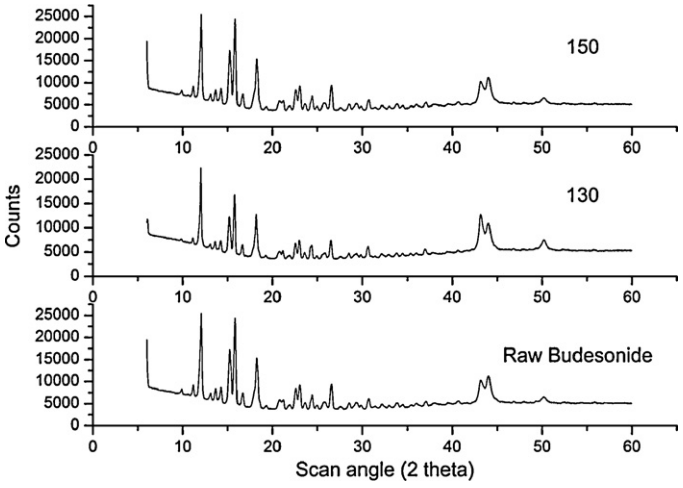

Fig. 6. XRD patterns of raw budesonide and budesonide processed in 20% ethanol/SBCW solutions.

Table 2
Particle formation conditions and summary of budesonide precipitated into lactose and PEG400 environments using SBCW and co-solvents.

Experiment number	Temperature (°C)	Ethanol fraction (%, v/v)	Methanol fraction (%, v/v)	Solubility (mg/mL)	Fraction Budesonide/lactose (mass/mass)	Fraction Budesonide/PEG (mass/mass)	Average particle diameter (SEM, nm)	X_{10} (nm)	X_{50} (nm)	X_{90} (nm)	Morphology (shape)
B1A	200	0	0	2.35	0.02	–	70	30	60	110	Rounded particles
B2A	130	20	0	2.22	0.02	–	400	70	210	670	Spherical particles and plates
B2B	130	20	0	2.22	0.03	–	420	110	290	720	Spherical particles and plates
B3A	150	20	0	6.72	0.06	–	1050	430	1150	3070	Spherical particles and plates
B3B	150	20	0	6.72	0.03	–	1370	450	1170	3030	Spherical particles and plates
B4A	160	0	10	2.15	0.02	–	210	100	280	830	Spheres
B4A1	160	0	10	2.15	0.04	–	250	140	540	980	Spherical particles and plates
B1C	200	0	0	2.35	–	0.25	85	40	70	130	Spheres
B1D	200	0	0	2.35		0.125	95	50	90	140	Spheres
B2C	130	20	0	2.22	–	0.25	1100	730	1670	2770	Plates
B2D	130	20	0	2.22		0.125	2140	770	1770	4030	Plates
B3C	150	20	0	6.72	–	0.25	830	380	750	1500	Plates
B3D	150	20	0	6.72		0.125	750	440	800	1460	Plates
B4C	160	0	10	2.15	–	0.25	85	15	30	80	Spheres
B4D	160	0	10	2.15	–	0.125	65	25	45	80	Spheres

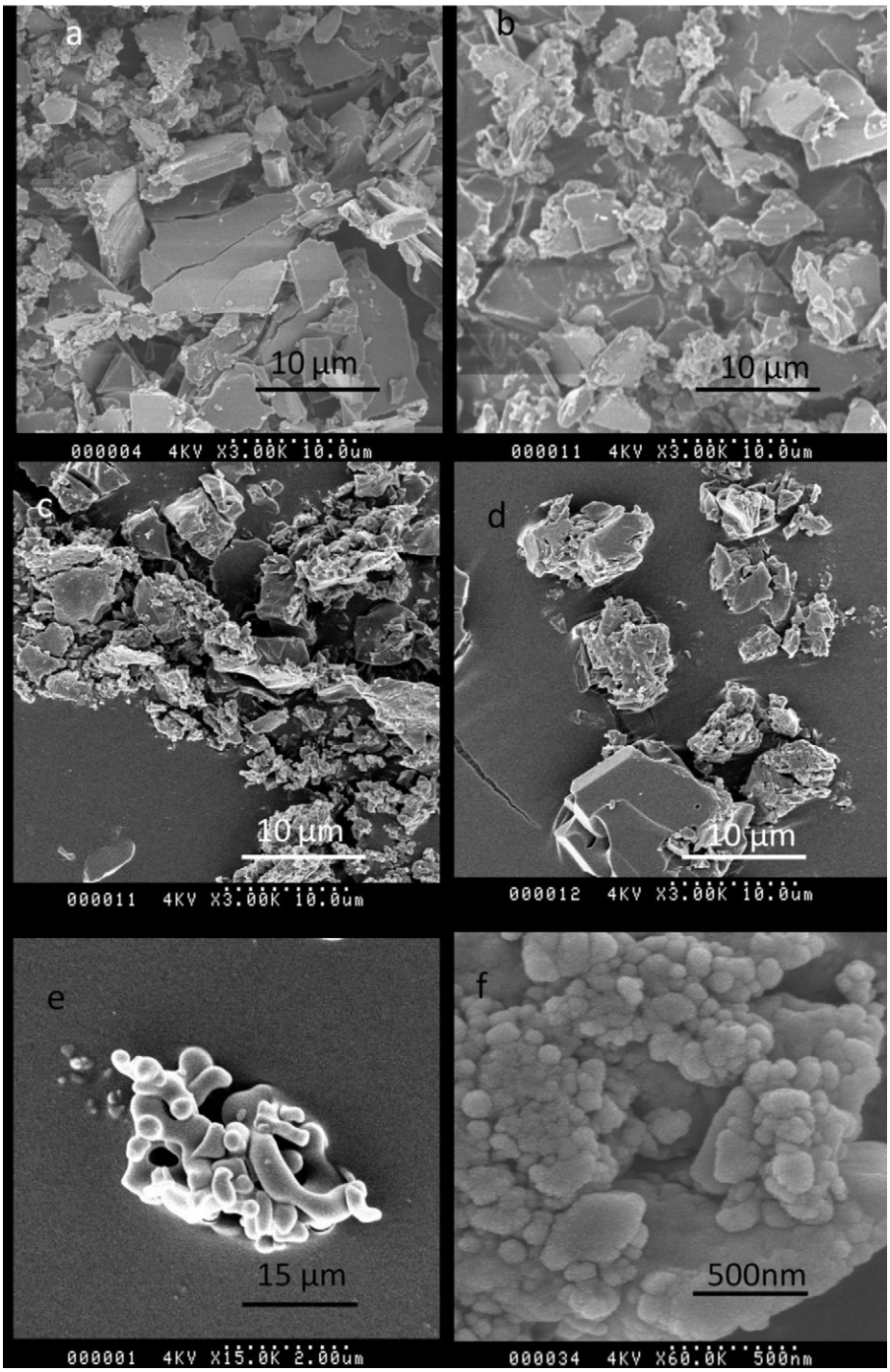

Fig. 7. Budesonide precipitated according to experimental conditions (a) B3A, (b) B3B, (c) B2A, (d) B2B, (e) B1A and (f) B4A described in Table 2.

4.2. Precipitation into a solution with excipients and co-solvents

4.2.1. Budesonide–SBCW–alcohol solutions injected into a water–lactose solution

Masses of lactose were added to the collection chamber in a 15:1 and a 30:1 ratio with the budesonide. The experimental conditions and results are summarized in Table 2.

Precipitation of budesonide into a lactose environment did not change the shape of the crystal, which can be seen by comparing the SEM images in Fig. 7 to those of Fig. 3. The particle morphology was the same as that which was found when lactose was not present. The budesonide particles produced from solutions of SBCW modified with ethanol were larger than particles produced when SBCW or SBCW modified with methanol were used (Fig. 7).

The presence of lactose in the PC tended to result in slightly larger precipitates than when lactose was not present. A higher proportion of lactose placed in the precipitation chamber had no effect on the product morphology, as shown in Fig. 7.

It appeared that the selection of solvent affected the morphology and the size of the precipitate more than the concentration of the solution jet injected into the chamber or the concentration of the lactose dissolved in the precipitation vessel. This is demonstrated by comparing the morphologies of budesonide produced under conditions B3A and B2B, and that of B1A and B2A. The supersaturation ratio of B3A was three times higher than

B2B, but the precipitate morphology was the same. Conversely, the supersaturation ratio of B1A was equivalent to B2A, but the particle morphology was different. Thus when the solvent was changed, the morphology of the precipitated particle changed, independently of the concentration of API in the injected SBCW-API solution.

An experiment was conducted (experiment B4A1) whereby the volume of water–lactose solution in the PC was halved. The particle size distribution of the budesonide particles did not change, as shown in Fig. 8, which indicates that, under the 160 °C injection conditions, only half the volume of water may be used to precipitate budesonide micro-particles. The unchanged particle size when the capture water volume was lowered implies that the volume of capture water may be reduced to lower process costs for industrial scale-up.

4.2.2. Budesonide–SBCW–alcohol solutions injected into a water–PEG solution

Budesonide was precipitated into solutions containing PEG with a 1:4 and 1:8 budesonide:PEG ratio under various injection conditions, as outlined in Table 2. The resulting precipitates are shown in Fig. 9.

A change in the ratios of PEG added to the capture chamber had no effect on the particle size distribution of the budesonide particles, as shown in Fig. 10. The particles precipitated from higher temperatures tended to be smaller than the materials precipitated at lower temperatures.

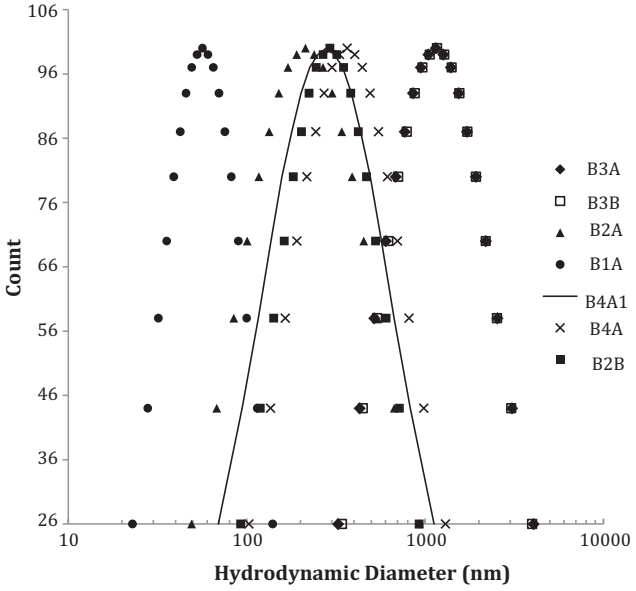

Fig. 8. Budesonide precipitated according to the experimental conditions summarized in Table 2.

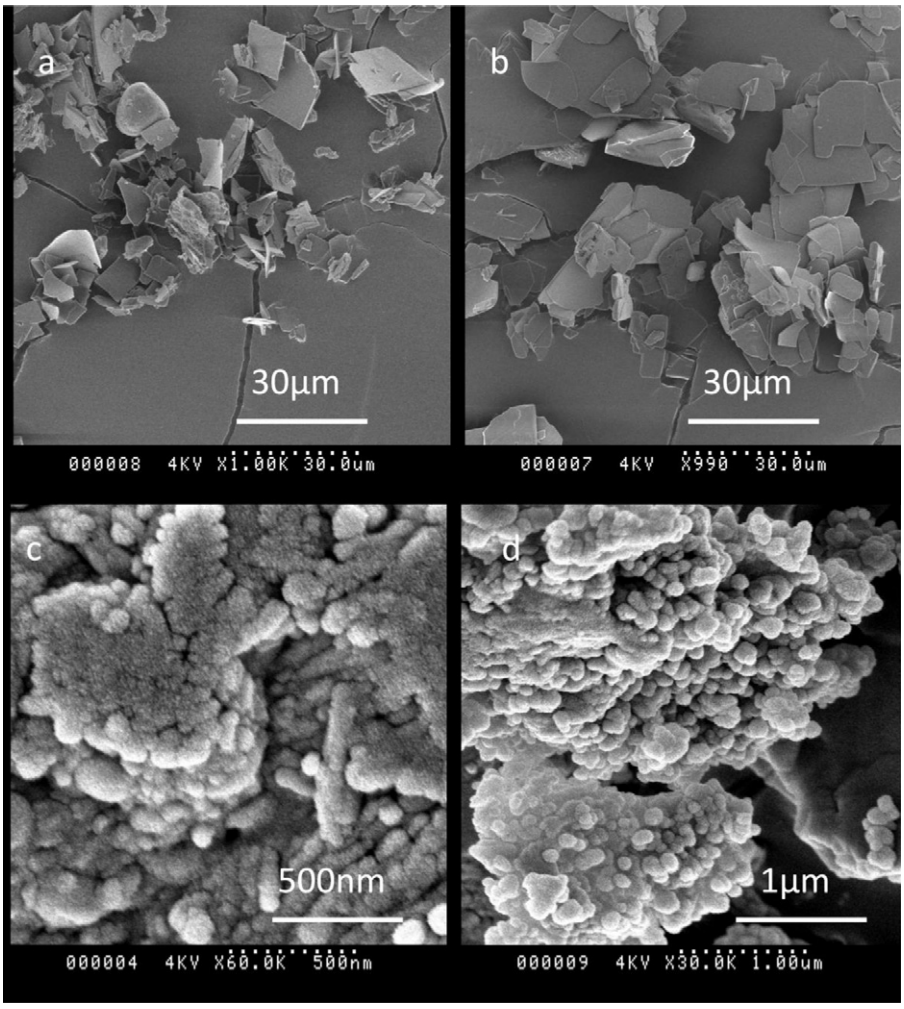

Fig. 9. Budesonide precipitated according to conditions (a) B2C, (b) B3D, (c) B4C and (d) B1D as described in Table 2.

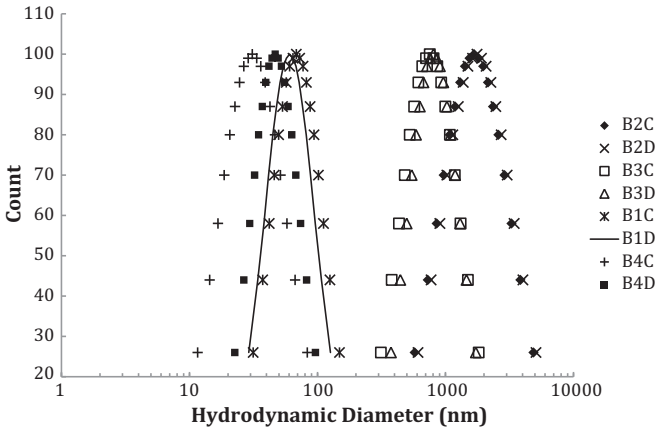

Fig. 10. Budesonide precipitated according to the experimental conditions summarized in Table 2.

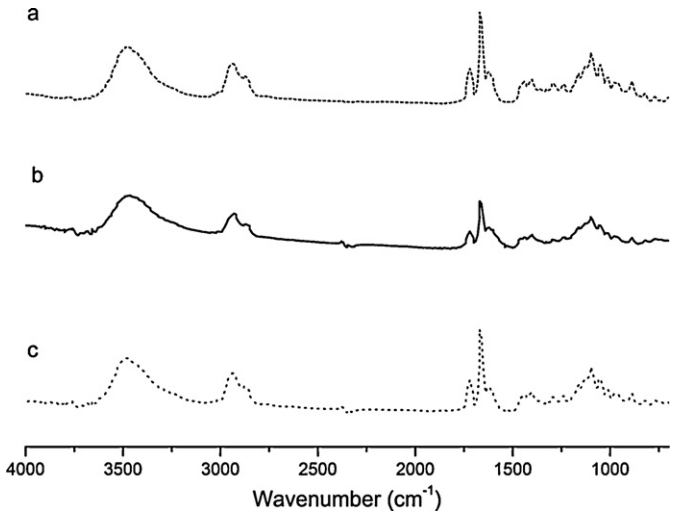

Fig. 11. FTIR spectra of (a) budesonide processed at 200 °C with multiple injections, (b) budesonide processed at 200 °C with a single injection and (c) raw budesonide.

The particles precipitated into PEG environments were typically larger than the particles precipitated in the presence of lactose, as shown in Fig. 10.The particles precipitated into the PEG environments tended to have a uniform morphology. The formation of plate crystals was found in samples from methanol-modified SBCW. Small spheres were the dominating morphology in particles precipitated into PEG where either pure SBCW or methanol was used as a modifier. The precipitation of uniform-morphology particles was a change from the particles precipitated without using PEG. In those cases, mixtures of smaller spheres and larger plates were present. The precipitation of particles with a uniform morphology indicates that PEG acted to stabilize particle growth as either spheres or plates.

The precipitation of spheres or plates was dependent on the solvent. When ethanol was used as a co-solvent, the dominant particle morphologies of the budesonide precipitates were plates, as shown in Fig. 9(a and b). Similarly, when pure SBCW was used, the dominant particle morphology was small spheres (Fig. 9(c and d)). It is possible that the addition of PEG acted to hinder the efficiency of the heat transfer between the injected solution jet and the cold water.

It would be beneficial to evaluate the effect of viscosity on the particle morphology by changing the concentrations of ethanol in the solution jet at a constant temperature. Such a study is outside the scope of this work, which is limited to exploring the application of the newly developed precipitation technique to various APIs. Nevertheless, it has been shown that the particle morphology of APIs precipitated from SBCW solutions can be controlled by adding different levels of organic solvents add a degree of tunability to the process.

5. Spray-drying of budesonide formulations

Of all of the conditions tested, the particles produced from pure SBCW-API solutions were the most ideally suited to inhalable drug delivery (experimental conditions B1, B1A, B1C and B1D). While the low solubility of budesonide in pure SBCW may lead to low process yields, the particle morphology is uniform and below the 5 μm particle size cut-off for aerosol delivery. In order to minimize spray drying hazards, the suspensions containing fractions of ethanol or methanol were not used. Thus samples from experimental condition B1A only were spray-dried to produce a drug powder for drug delivery.

In order to collect a high enough mass of budesonide from the SBCW process to analyze using the Andersen Cascade Impactor, multiple injections of budesonide–SBCW were conducted into the same precipitation vessel. The multiple injections were performed by loading the solubility vessel with 3 times the regular mass of budesonide used in the solubility experiments. The precipitation was carried out as per the standard particle formation method, and then the solubility system was refilled with water and allowed to equilibrate for another 10 min. After the 10 min equilibration time, another injection was performed. The refill step was performed twice to allow for a total of 3 injections into the precipitation vessel.

In order to establish whether the budesonide product degraded under the increased exposure time to SBCW at 200 °C, FTIR was performed on a dry filtered sample and compared to the raw material. Some of the sample was analysed by laser scattering to observe whether the multiple-injections had any significant effect on product morphology. The results of the FTIR and DLS analysis on the multiple-injection samples and the raw/originally processed materials are shown in Figs. 11 and 12 respectively. Based on the identical FTIR spectra of the SBCW-processed budesonide and the raw material, as well as the identical particle size distribution of the multiple injection particles to the single injection particles, it was concluded that the multiple injection process had no effect on the budesonide product chemical stability or particle morphology.

A summary of the spray drying conditions and results are shown in Tables 3 and 4 respectively.

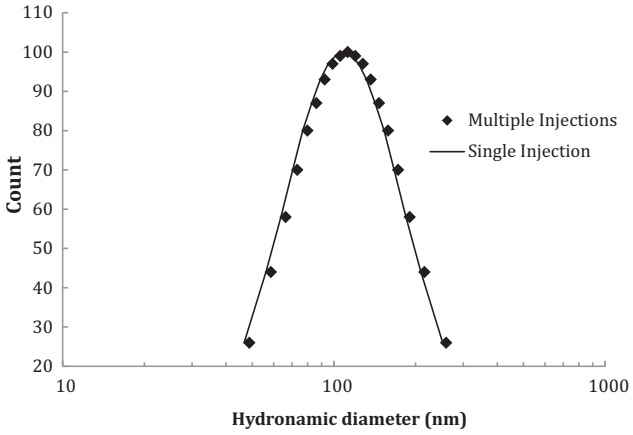

Fig. 12. Particle size distribution of budesonide particles from a budesonide–SBCW solution injected into the precipitation chamber in single and triple injections.

Table 3
Spray drier experimental conditions.

Suspension/solution	Inlet T (°C)	Mass solutes (g)	Outlet T (°C)	Mass flowrate (g/min)	Aspirator (gauge)	Air flowrate (gauge)
Lactose	170	3.15	90	6.0	100%	40
Budesonide	170	0.08	85	5.9	100%	40
B1A	170	3.85	74	6.0	100%	40

Table 4
Spray dryer results.

Suspension/solution	Runtime (min)	Mass collected (g)	Efficiency[a] (%)	Notes
Lactose	26	0.98	30	
Budesonide	23	0.001	1	
B1A	33	0.05	1	Some condensation

[a] Efficiency calculated as mass collected/mass solutes.

5.1. Spray drying results

The particles captured after the spray drying process were analysed by SEM. The lactose produced by spray drying could not be analysed by SEM as the white particles turned clear on the carbon tape. Thus the morphology of the budesonide particles alone is shown here. The aerodynamic particle sizes of lactose and budesonide were analysed using the Andersen Cascade Impactor, as the objective of the test was to evaluate the ability of the SBCW micronization process to produce particles suitable for inhalable delivery.

A SEM of the spray-dried budesonide is shown in Fig. 13. The particle size and morphology did not change upon spray drying of the suspension of budesonide in water. The similarity of both results can be seen by comparing Fig. 13 to Fig. 3(b).

The aerodynamic particle sizes of the lactose and budesonide raw materials and precipitates are shown in Figs. 14–16. The raw and spray dried exhibited similar aerodynamic particle size distributions. On average, 80% of the lactose by mass was either caught in the neckpiece of the Cascade Impactor or trapped in the filter after stage 7.

On average 85% by mass of the raw budesonide was either caught in the neckpiece of the Cascade Impactor or caught in the filter. Of the material that deposited on the Cascade Impactor plates, the majority of the powder deposited between stages 2 and 4, which corresponded to an aerodynamic particle size between 3 μm and 6 μm, as shown in Fig. 15.

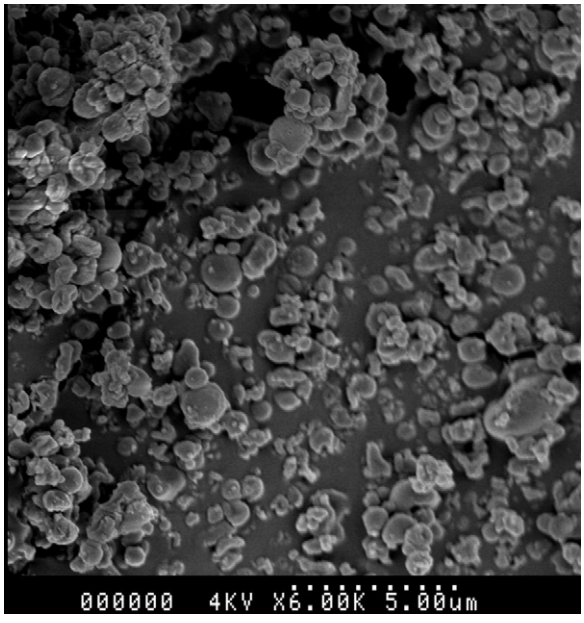

Fig. 13. Budesonide precipitated from a 200 °C injection temperature into cold water and the dried using the Buchi 290 spray-drier.

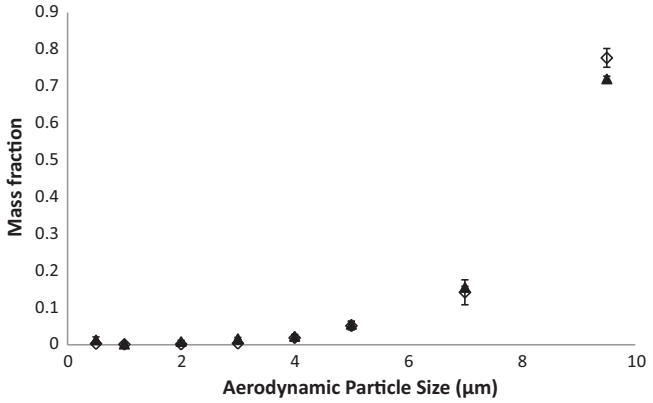

Fig. 14. Raw (◊) and spray-dried (▲) lactose aerodynamic particle sizes.

It was not possible to compare the raw budesonide aerodynamic particle size distribution to the spray dried sample, as insufficient budesonide could be recovered from the spray dryer to run the Cascade Impactor. The majority of the budesonide particles were either caught on the walls of the cyclone separator, or expelled through the aspirator of the Buchi spray drier. In order to attempt to compare the particle sizes of the raw budesonide to the micronized budesonide, a 60 mL sample of the micronized budesonide suspension (taken directly from the particle formation apparatus) was freeze-dried for 48 h. The aerodynamic particle size of the freeze-dried, micronized sample is shown in Fig. 15. The aerodynamic particle size of the freeze-dried micronized budesonide and the raw budesonide sample are identical.

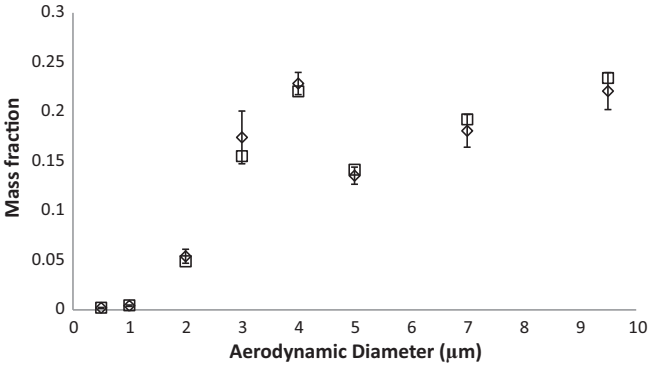

Fig. 15. Aerodynamic particle diameter of raw (◊) and processed (□) budesonide.

Table 5
Process efficiency in terms of mass recovered at each process step.

Process		Material				
		Lactose	Budesonide	Lactose and budesonide		
				Lactose	Budesonide	Lactose + budesonide
SBCW micronization	Mass in (mg)	3150	70	1050	70	1120
Spray drying	Mass out (mg)	980	1	nd	nd	50
	Fraction recovered (mass %)	31%	0.14%	nd	nd	4%
	Process efficiency (mass %)	31%	0.14%			4%
Cascade Impactor	Mass in (mg)	96.1	8.1[a]	nd	nd	36.4
	Mass out (mg)	20.3	1.94[a]	10.9	0.79	11.69
	Fraction recovered (mass %)	21%	24%			32%
Overall efficiency		1%	Nd	1%	1%	1%

nd, not determined.
[a] Mass of material was from a freeze-dried sample of micronized budesonide suspension.

The budesonide spray-dried from the budesonide–lactose–water mixtures tended to have similar proportions by mass of material distributed at every stage of the Cascade Impactor, as shown in Fig. 16. However, unprocessed budesonide had a higher deposition on Plate 4 and a lower proportion on Plate 7 than the SBCW-micronized budesonide. Plate deposition may be related to the different particle sizes of the raw and SBCW-micronized budesonide. The difference in size can be observed by comparing Fig. 3(a) and Fig. 3(b).

It is possible that the raw budesonide was already micronized. An SEM of the raw budesonide is shown in Fig. 3. The particle size of the non-SBCW processed budesonide was up to 10 μm in length. Furthermore the different morphology of the budesonide particle in the raw material may have allowed the particle to fly more effectively than the SBCW-micronized budesonide, as elongated particle morphologies typically fly better than spherical particles (Zeng et al., 2000). While the efficiency and aerodynamic performance of the budesonide and lactose powder produced by the SBCW-micronization process are not optimal, it can be seen that the SBCW micronization technology, when combined with an effective spray drying process, is capable of producing particles that can be delivered into the lungs.

5.2. Overall process efficiency

The efficiency of the overall process is shown in Table 5. The largest loss in mass was through spray drying the liquid suspensions. It is possible to optimize spray drier conditions to increase the efficiency of solids recovery (Das et al., 2010; Gilani et al., 2004; Islam and Langrish, 2010). If the process is to be scaled up using the spray dryer to dry the suspensions, optimization on the recovery of solids will be needed.

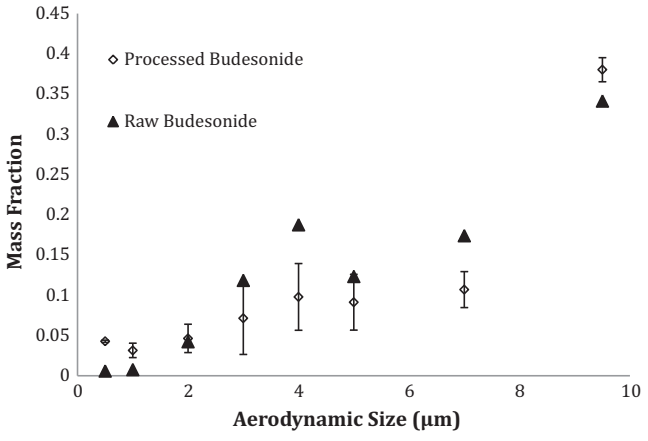

Fig. 16. Aerodynamic particle sizes of the raw and spray-dried budesonide from a 1:15 budesonide–lactose mixture.

6. Conclusions

It has been demonstrated that the morphology of API particles can be manipulated by changing injection conditions of SBCW-API solutions into a chamber containing cold water. Particles with narrow size distributions have been precipitated from a variety of SBCW solutions. Particle morphology can be controlled by changing the injected solution temperature, the addition of co-solvents, and/or adding excipients. At higher injection temperatures, particle sizes are generally reduced. The nature of the organic solvent alters the interaction between the SBCW solution and the cold water, where injection with ethanol tends to produce larger particles. The presence of the excipients (lactose and PEG) tends to limit the formation of either sphere or plate morphologies of particles, although a change in concentration of the excipients (in the ratios tested) did not change particle size.

Dry powders of budesonide and budesonide/lactose have been formulated using a combination of SBCW processing and spray-drying. While the spray drying process used was inefficient, the SBCW-micronized powders tended to allow budesonide to penetrate lower sections of the Cascade Impactor. Thus, it is possible to produce API-excipient powders for delivery into the lungs by coupling a SBCW-micronization process with a spray-drying process.

Particle morphologies can be controlled by manipulating a number of processing variables in the SBCW-micronization process. Further research into producing therapeutic combinations through the methods described here, or precipitating two APIs simultaneously is warranted based on the success of the technology at precipitating a single API with excipients.

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References

Banerjee, P.S., Pham, S., Akapo, S.O., Chaudry, I.A., Dey, L.P., 2001. Bronchodilating Compositions and Methods, US Patent 6667344.
Budavari, S., 1996. The MERCK Index, 12th edn. Merck & Co. Inc, Whitehouse Station, pp. 1512.
Carr, A., Mammucari, R., Foster, N., 2009. Controlled precipitation of hydrophobic pharmaceuticals in subcritical water. In: International Symposium of Supercritical Fluids 2009 , Arcachon, France.

Carr, A.G., Mammucari, R., Foster, N., 2010a. The solubility and solubility modeling of budesonide in pure and modified subcritical water solutions. The Journal of Supercritical Fluids 55 (1), 37–42.
Carr, A., Mammucari, R., Foster, N., 2010b. The solubility and micronization of griseofulvin using subcritical water. Industrial & Engineering Chemistry Research 49 (7), 3403–3410.
Carr, A., Mammucari, R., Foster, N., 2010c. The Solubility, Solubility Modeling and Precipitation of Naproxen from a Subcritical Water Solution.
Das, D., Husni, H.A., Langrish, T.A.G., 2010. The effects of operating conditions on lactose crystallization in a pilot-scale spray dryer. Journal of Food Engineering 100 (3), 551–556.
Dudognon, E., Willart, J.F., Caron, V., Capet, F., Larsson, T., Descamps, M., 2006. Formation of budesonide/[alpha]-lactose glass solutions by ball-milling. Solid State Communications 138 (2), 68–71.
Fu, J., Fiegel, J., Krauland, E., Hanes, J., 2002. New polymeric carriers for controlled drug delivery for controlled drug delivery following inhalation or injection. Biomaterials 23 (22), 4425–4433.
Gilani, K., Rouholamini Najafabadi, A., Barghi, M., Rafiee-Tehrani, M., 2004. Aerosolisation of beclomethasone dipropionate using spray dried lactose/polyethylene glycol carriers. European Journal of Pharmaceutics and Biopharmaceutics 58 (3), 595–606.
Huang, Y.-Y., Wang, C.-H., 2006. Pulmonary delivery of insulin by liposomal carriers. Journal of Controlled Release 113 (1), 9–14.
Islam, M.I.U., Langrish, T.A.G., 2010. An investigation into lactose crystallization under high temperature conditions during spray drying. Food Research International 43 (1), 46–56.
Kinnarinen, T., Jarho, P., Järvinen, K., Järvinen, T., 2003. Pulmonary deposition of a budesonide/[gamma]-cyclodextrin complex in vitro. Journal of Controlled Release 90 (2), 197–205.
Lakatos, M., 2008. Measurement of residual solvents in a drug substance by a purge-and-trap method. Journal of Pharmaceutical and Biomedical Analysis 47 (4–5), 954–957.
Lobo, J., Schiavone, H., Palakodaty, S., York, P., Clark, A., Tzannis, S., 2005. SCF-engineered powders for delivery of budesonide from passive DPI devices. Journal of Pharmaceutical Sciences 94 (10), 2276.
Martin, T., Bandi, N., Shulz, R., Roberts, C., Kompella, U., 2002. Preparation of budesonide and budesonide-PLA microparticles using supercritical fluid precipitation technology. AAPS PharmSciTech 3 (3), 16–26.
Naikwade, S., Bajaj, A., 2009. Preparation and in vitro evaluation of budesonide spray dried microparticles for pulmonary delivery. Scientia Pharmaceutica 77, 419–441.
Nilsson, H., Santesson, G., 2001. Low Dose Budesonide Formulations and Uses Thereof in http://www.freepatentsonline.com/6291445.html. Astra Aktiebolag, United States, pp. 4.
Nokhodchi, A., Maghsoodi, M., Hassan-Zadeh, D., Barzegar-Jalali, M., 2007. Preparation of agglomerated crystals for improving flowability and compactibility of poorly flowable and compactible drugs and excipients. Powder Technology 175 (2), 73–81.
Schiavone, H., Palakodaty, S., Clark, A., York, P., Tzannis, S.T., 2004. Evaluation of SCF-engineered particle-based lactose blends in passive dry powder inhalers. International Journal of Pharmaceutics 281 (1–2), 55–66.
Copley Scientific, 2006. Metred Dose Inhalers, Dry Powder Inhalers, Nebulizers and Nazal Sprays: Quality Solutions for Inhaler Testing, 2006 edition. Copley Scientific Limited, United Kingdom.
Steckel, H., Wehle, S., 2004. A novel normulation technique for metered dose inhaler (MDI) suspensions. International Journal of Pharmaceutics 284 (1-2), 75–82.
Subramaniam, B., Rajewski, R.A., Snavely, K., 1997. Pharmaceutical processing with supercritical carbon dioxide. Journal of Pharmaceutical Sciences 86 (8), 885–890.
Vozone, C.M., Marques, H.M.C., 2002. Complexation of budesonide in cyclodextrins and particle aerodynamic characterization of the complex solid form for dry powder inhalation. Journal of Inclusion Phenomena and Macrocyclic Chemistry 44 (1), 111–116.
Yeo, S.D., Kiran, E., 2005. Formation of polymer particles with supercritical fluids: a review. Journal of Supercritical Fluids 34 (3), 287–308.
Zeng, X.M., Martin, G.P., Marriott, C., Pritchard, J., 2000. The influence of carrier morphology on drug delivery by dry powder inhalers. International Journal of Pharmaceutics 200 (1), 93–106.