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Experimental study of the GAS process for producing microparticles of beclomethasone-17,21-dipropionate suitable for pulmonary delivery

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Abstract

In this study the micronization of beclomethasone-17,21-dipropionate (BECD), used as an inhaled steroid for the treatment of asthma, was studied using the gas-antisolvent (GAS) process as a "green" alternative to pharmaceutical recrystallization. A systematic investigation of the influence of the key GAS process parameters: antisolvent addition rate (1, 50, 75 and 100 ml/min), temperature (25, 32.5, 40 and 52.5 °C), solute concentration (5, 25, 70 and 100%), and agitation rate (500, 1000, 2000 and 3000 rpm) were investigated on particle morphology, size distribution, and crystallinity. It was found using scanning electron microscopy (SEM) and laser diffraction, that increasing the antisolvent addition rate and the agitation rate, while decreasing the temperature and solute concentration, led to a decrease in the steroids mean particle diameter. These parameters could be tuned to give a mean particle diameter of 1.8 μm, and an average mass median aerodynamic diameter (MMAD) of 7.9 μm. High-performance liquid chromatography (HPLC) results showed the recrystallized BECD was purer than the non-processed material. The role of the solvent (acetone, methanol and ethanol) in the BECD crystal structure was investigated using X-ray diffraction (XRD), which showed acetone gave a more crystalline structure, hence having lower incorporation into the crystal structure. These results showed that the GAS process has the potential to produce steroid with powder properties suitable for inhalation therapy.
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Keywords: Beclomethasone dipropionate; Asthma; Supercritical carbon dioxide; GAS; MMAD

1. Introduction

Asthma ranks among one of the most common chronic conditions, affecting over 20 million people in the United States alone, and causing over 1.5 million emergency department visits, about 500,000 hospitalizations and 5500 deaths (US National Institute of Health, 2002). Inhaled corticosteroids, such as beclomethasone dipropionate (BECD), are well-established anti-inflammatory therapies for the treatment of asthma (Barnes et al., 1998), recommended in national treatment guidelines as first-line therapy for this chronic disease (US National Institute of Health, 2002). Asthma is an inflammatory disease affecting the entire bronchial tree, from the large central airways down to the small peripheral airways (Hamid et al., 1997; Howarth, 1999). Steroid receptors, the site of action for inhaled corticosteroid therapy, are likewise located throughout the bronchial tree (Adcock et al., 1996). An optimal therapeutic response with inhaled corticosteroids using dry powder inhalers (DPIs) would, therefore, be obtained with a powder that reaches both the large and small airways of the lung (Leach et al., 2002). Present DPIs provide rather low deposition of drug to the lung (typically below 15%) because of problems with drug accumulation in the delivery device, and non-optimized particle size distribution and particle morphology (de Boer et al., 1996; Timsina et al., 1994). Hence, these could be improved by better control of particle size and shape (Shekunov and York, 2000) or use of a carrier such as lactose (Zeng et al., 2001).

The design of small particles with controlled particle size distributions, ranging from nanometers to hundreds of micrometers, has attracted significant interest in the scientific and industrial communities with applications for pharmaceuticals, food, nutraceuticals, chemical, paint/coating, and polymer industries (Cansell et al., 1999; Cooper, 2001; Subramaniam et al., 1997; Tan and Borsadia, 2001; Woods et al., 2004; Ye and Wai, 2003). The important properties of these products for pharmaceutical applications are narrow particle size distribution, uniform morphology, and enantiomeric purity (York, 1999; Shekunov and York, 2000). Conventional powder preparation of

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pharmaceuticals can be carried out by crystallization techniques such as lyophilization or spray drying (Sacchetti and Van Oort, 1996); or post-crystallization techniques including milling, pulverization, and precipitation. More recently developed techniques include supercritical fluid precipitation, spray-freeze drying, fluidized-bed spray coating and emulsion precipitation (Shekunov and York, 2000).

The employment of supercritical fluid techniques has attracted considerable interest as an emerging "green" technology for the formation of particles in these size ranges (Jung and Perrut, 2001; Perrut, 2000). Supercritical fluids (SCFs) have several advantages over conventional liquid solvents/antisolvents as their physical properties like density and solubility can be 'tuned' within a wide range of processing conditions by varying both the temperature and pressure (McHugh and Krukonis, 1994). Low viscosity and high diffusivity in SCFs is considered highly effective for producing superior products of fine and uniform particles (Debenedetti, 1990; Tom et al., 1993). Moreover, supercritical fluids can be easily separated from both organic co-solvents and solid products providing a potential clean, recyclable and environment-friendly technology (Tom and Debenedetti, 1991; Tom et al., 1993). Carbon dioxide is by far the most widely used supercritical medium and has a number of distinct advantages. In addition to the low critical point ($P_c = 74$ bar, $T_c = 31.1\,^{\circ}C$), CO_2 is non-flammable, non-toxic, and readily available in high purity.

Particle formation using SCFs can be carried out according to several different techniques, each of which has advantages and disadvantages (Foster et al., 2003; Vemavarapua et al., 2005). Drugs that are soluble in supercritical fluids are often considered to be best processed by the rapid expansion of supercritical solutions (RESS) process (Krukonis, 1984). As most pharmaceuticals have poor solubility in SCFs, antisolvent techniques are more attractive. These include, the gas-antisolvent (GAS) process, precipitation with compressed antisolvent (PCA) process (also known as the supercritical antisolvent (SAS) process, and aerosol spray extraction system (ASES) process) and Solution-enhanced dispersion by supercritical fluids (SEDS) (Tan and Borsadia, 2001; Ye and Wai, 2003). Antisolvent techniques exploit the low solubility of most pharmaceutical compounds in the antisolvent, in particular CO_2, which has to be miscible with the organic solvent (Gallagher et al., 1989, 1991). In the GAS process, high pressure CO_2 is injected into the liquid phase solution, which causes a sharp reduction of the solute solubility in the expanded liquid phase. As a result, precipitation of the dissolved compound occurs.

The potential advantages of the GAS recrystallization process lies in the possibility of obtaining solvent free, micron and submicron particles with a narrow size distribution (Muller et al., 2000). By varying the process parameters, the particle size, size distribution and morphology can be "tuned" to produce a product with desirable qualities. This makes the GAS technique attractive for the micronization of high-valued products, such as pharmaceuticals (Tan and Borsadia, 2001). Unfortunately, experimental studies on the micronization of drugs using the GAS technique are rather limited. The micronization of powdered drugs with well-defined physical properties and performance characteristics, suitable for application in inhalation therapy, continues to be a significant challenge for the pharmaceutical industry. Particles of a narrow size distribution with a mass mean aerodynamic diameter (MMAD) in the 1–5 μm range are desired for a highly efficient delivery and administration of drugs to the lung via inhalation, such as for the treatment of asthma (Zanen and Lammers, 1999).

The objectives of this research were to investigate the feasibility of the GAS recrystallization technique to generate small particles of BECD applicable for pulmonary inhalation therapy, with a high degree of purity, and narrow size distribution. The effect of the GAS process parameters: antisolvent addition rate, temperature, solute concentration and agitation rate on the particle size and size distribution of BECD were examined. The role of the solvent in influencing the particle size, size distribution, morphology and the degree of crystallinity was also investigated.

2. Experimental

2.1. Materials

The solute–solvent model system investigated in this study was beclomethasone-17,21-dipropionate in acetone, methanol, and ethanol. The organic solvents (analytical grade) were purchased from the Sigma–Aldrich Company. The organic solute is a synthetic steroid member of the glucocorticoid family, white to creamy white powder, with a molecular mass of 521.25 g/mol and a melting point of 210 °C. The beclomethasone-17,21-dipropionate used in this work was donated by GlaxoSmithkline, and used without further purification. GAS experimental work was carried out using instrument grade CO_2 (99.99% purity, BOC Gases).

2.2. Methods

The details of our GAS experimental apparatus have been previously described (Bakhbakhi et al., 2005a). GAS crystallization of BECD using compressed CO_2 was performed by preparing a predetermined volume of BECD solution (10 ml) at a saturated concentration for the given operating temperature, and loaded into the 100 ml crystallization vessel. The agitator of the stirred high-pressure vessel was turned on and set to the desired rpm. When the system had stabilized and equilibrated thermally, the pressurization by injection of CO_2 was initiated. A controlled CO_2 flow rate was maintained until the full liquid volumetric expansion of 900% was achieved at 1000 psig. Consequently, the CO_2 supply feed was stopped, while mixing was continued for 1 h. Then, a rinsing step was performed by flushing the expanded liquid phase with CO_2 at a constant flow rate, for a minimum period of 5 h. Finally, the crystallization vessel was depressurized by venting the entire fluid mixture of the vessel, and the dry solid powder was collected for off-line analysis.

2.3. Characterization

Quantitative analysis of the precipitated particles was carried out using the following instruments: scanning electron

microscopy (SEM, Hitachi S-4500 Field Emission, and LEO 1530 Field Emission) provided particle morphology, size, size distribution (PSD), and degree of agglomeration. SEM photomicrographs were analyzed using image analysis software (Northern Eclipse, Empix Imaging). In order to achieve the best possible statistical representation of the formed particles in terms of particle size and size distribution, analysis of the photomicrographs were taken in several different regions of the collected sample, with a minimum of 1000 particles being used for each measurement. Laser diffraction (Malvern Mastersizer 2000, Malvern Instruments Ltd.) was employed for particle size and size distribution measurements of selected samples by briefly sonicating in water using a few drops of Triton X-100 surfactant for dispersion. X-ray powder diffraction (XRD) analysis (Bruker Discover D8 Diffractometer) was used to determine the product degree of crystallinity. A particle size distribution analyzer (PSD 3603, TSI Inc.) provided the particles mass mean aerodynamic diameters (MMAD). HPLC (ProStar 330, Varian Inc.) was used for measuring the BECD purity.

3. Results and discussion

Table 1 provides the experimental conditions with each run represented by a label corresponding to $A \equiv$ the antisolvent addition rate, $C \equiv$ concentration, $T \equiv$ process temperature, $G \equiv$ agitation rate, and S $\equiv$ the organic solvent. In general, average measured yields from experiments were determined to be 85–90%. Table 2 provides the results of particle size measurements from evaluation of the maximum diameter from SEM photomicrographs using image analysis software. Mean particle size, standard deviations and the coefficient of variation were determined for individual distributions from the microscopy results, with the average values from three separate experiments given. Agglomeration levels were estimated by qualitative analysis of the SEM photomicrographs: small (+), intermediate (++), or large (+++). In order to compare directly with the microscopy results, Fig. 1 provides the laser diffraction produced normalized number density distributions for several selected experimental runs discussed below (*A*4, *C*1, *T*2 and *G*1). Table 3 summarizes these laser diffraction results, giving the mean, Dp_{10}, Dp_{50}, and Dp_{90} results. It is clear from these results that the Dp_{50} (median) from light scattering is directly comparable to the mean of the microscopy results. This is expected as large agglomerates and

Table 1
Experimental conditions used for the GAS experiments

Run	CO_2 addition rate (ml/min)	Concentration ratio (%)	T (°C)	Agitation rate (rpm)	Solvent
*A*1	1	100	25	1000	Acetone
*A*2	50	100	25	1000	Acetone
*A*3	75	100	25	1000	Acetone
*A*4	100	100	25	1000	Acetone
*C*1	50	5	25	1000	Acetone
*C*2	50	25	25	1000	Acetone
*C*3	50	70	25	1000	Acetone
*T*1	50	100	32.5	1000	Acetone
*T*2	50	100	40	1000	Acetone
*T*3	50	100	52.5	1000	Acetone
*G*1	50	100	25	500	Acetone
*G*2	50	100	25	2000	Acetone
*G*3	50	100	25	3000	Acetone
*G*4	100	100	25	3000	Acetone
S1	50	100	25	1000	Methanol
S2	50	100	25	1000	Ethanol

Note: *A*, addition rate; *C*, concentration ratio; *T*, temperature; *G*: agitation rate; S: solvent type.

Table 2
Microscopy experimental results of BECD produced using the GAS process

Run	Mean particle size (μm)	S.D. (μm)	Coefficient of variation	Degree of agglomeration
*A*1	20.6	24.8	1.2	++
*A*2	10.2	9.7	1.0	++
*A*3	6.2	4.2	0.7	+
*A*4	4.9	2.4	0.5	+
*C*1	3.1	1.7	0.5	+
*C*2	4.1	2.4	0.6	+
*C*3	8.3	6.5	0.8	++
*T*1	13.9	15.9	1.1	++
*T*2	32.8	28.9	0.9	+++
*T*3	41.5	64.3	1.6	+++
*G*1	12.3	14.6	1.2	+++
*G*2	6.5	3.1	0.5	+
*G*3	3.1	1.3	0.4	+
*G*4	1.8	0.8	0.5	+
S1	43.9	47.8	1.1	++

Note: *A*, addition rate; *C*, concentration ratio; *T*, temperature; *G*, agitation rate; S, solvent type.

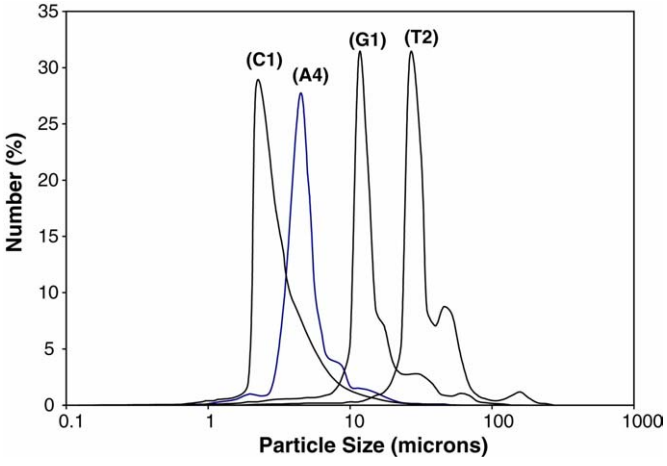

Fig. 1. Normalized number density distribution of BECD particles determined by laser diffraction for runs *A*4, *T*2, *C*1 and *G*1. The experimental conditions are provided in Table 1.

Table 3
Laser diffraction results of selected BECD experimental runs

Run	Mean particle size (μm)	Dp_{10} (μm)	Dp_{50} (μm)	Dp_{90} (μm)
*A*4	6.7	3.3	4.9	7.1
*C*1	6.1	2.0	3.3	6.0
*T*2	49.0	21.9	29.0	53.4
*G*1	23.0	8.9	11.9	28.9

Note: See Table 1 for experimental conditions.

the smallest particles are less likely to be interpreted in the microscopy analysis.

3.1. Effect of antisolvent addition rate

In this set of experiments, the effect of the antisolvent addition rate was investigated at four levels of carbon dioxide addition rate, namely, 1, 50, 75, and 100 ml/min (see Table 1 for full experimental conditions). Fig. 2(a) shows the SEM photomicrograph of the particles generated at the lowest addition rate, i.e., 1 ml/min, where the particle size distribution was bimodal with a large degree of agglomeration, and a mean particle diameter = 20.6 μm. When the antisolvent addition rate was increased to 50 ml/min, a bimodal particle size distribution persisted with a moderate degree of agglomeration, but with a smaller mean particle diameter of 10.2 μm (Fig. 2(b)). At the highest level of antisolvent addition rate (100 ml/min), the particle size distribution became much smaller, 4.9 μm with a narrower distribution (Fig. 2(c)). The final results are plotted in Fig. 3, where the mean particle size is reported as a function of the antisolvent addition rate. It is evident that increasing the antisolvent addition rate directly lowers the mean particle size.

Muller (Muller et al., 2000), following in the foot-steps of Gallagher (Gallagher et al., 1991) proposed a conceptual framework to describe the GAS crystallization process. According to this framework, the magnitude of the supersaturation level is a strong function of the applied volumetric expansion rate. A faster rate of antisolvent addition will generate higher levels of supersaturation, thus, higher rates of nucleation, and consequently, a larger number of smaller size particles with narrow particle size distribution. Our results (see Table 2) are in agreement with this framework, as the mean particle size resulting from the fast expansion rate (100 ml/min), is almost three times smaller than that resulting from the slow expansion rate (1 ml/min). Our previous experimental and theoretical results with GAS micronization of phenanthrene indicated that both primary and secondary nucleation were important (Bakhbakhi et al., 2005a, 2005b). In order to explain the bimodal nature of the BECD particle size distribution, the competition between the nucleation and growth dynamics of the GAS process needs to be considered. Low addition rates cause significant secondary nucleation, which leads to bimodal distributions (Bakhbakhi et al., 2005b).

3.2. Effect of temperature

As illustrated in Fig. 4 and Table 2, an increase in the process temperature (25, 32.5, 40 and 52.5 °C) for the recrystallization process results in a direct increase of the BECD mean particle size, and a broadening of the size distribution. SEM photomicrographs and laser diffraction results illustrated that as the temperature and mean particle size increased (see laser diffraction distribution in Fig. 1 for *T*2), the particle size distribution became bimodal. The primary particles became more hexagonal-shaped with an increased degree of agglomeration (see Table 2). The effect of temperature on the particle size can be explained in terms of the nucleation–growth dynamics during the crystallization process. Increasing temperature will increase

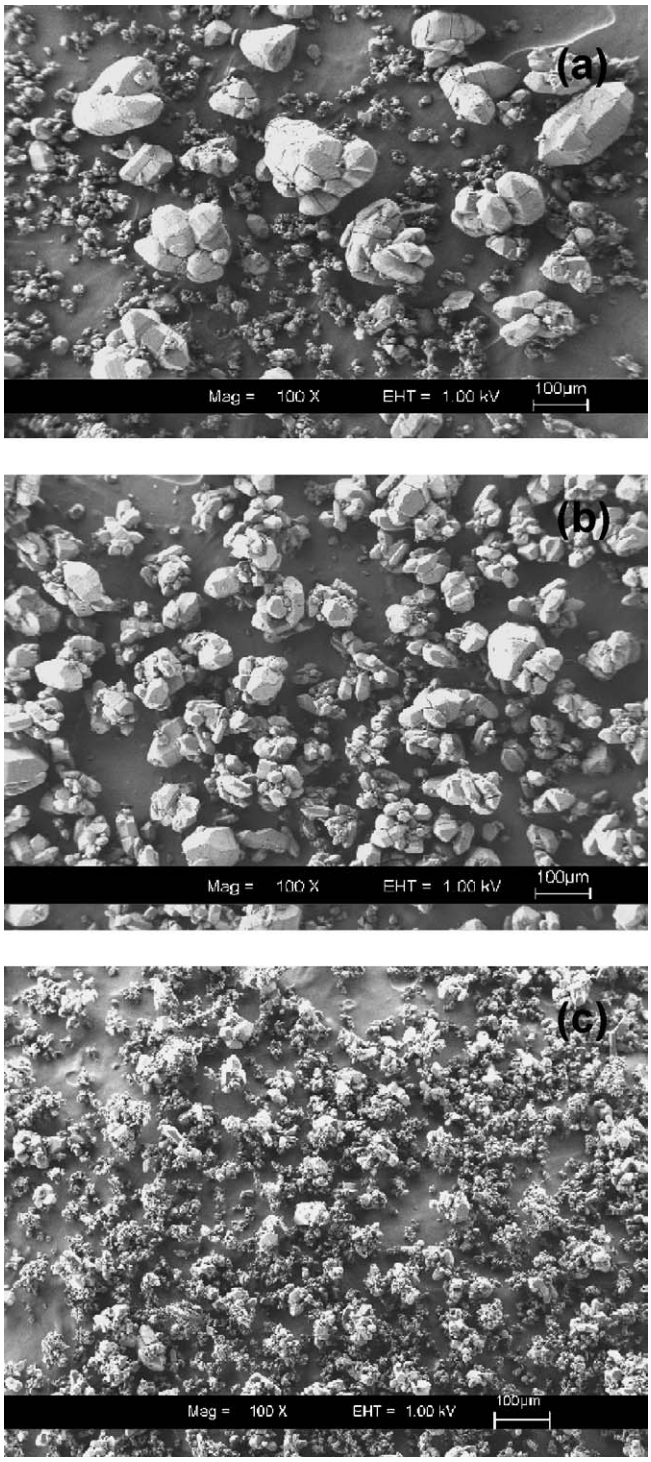

Fig. 2. SEM photomicrographs of BECD produced by GAS showing the effect of increasing antisolvent addition rate: (a) 1 ml/min; (b) 50 ml/min; (c) 100 ml/min. The experimental conditions are provided in Table 1.

the solubility of the pharmaceutical in the organic solvent, hence moving the position of the saturation and critical supersaturation lines upwards (Muller et al., 2000) in addition to changing their shape. Hence, increasing the temperature lowers the magnitude of the generated supersaturation during the GAS process (analogous to lowering the volumetric expansion rate) as the profile moves closer to the saturation line. This is followed by a gradual

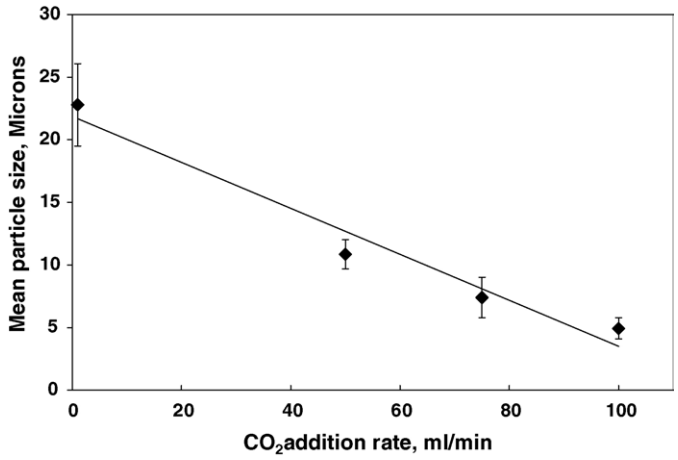

Fig. 3. Plot of the mean particle size of BECD produced by GAS as a function of the antisolvent addition rate. The points are experimental data; the line is a linear least-squares fit of the points.

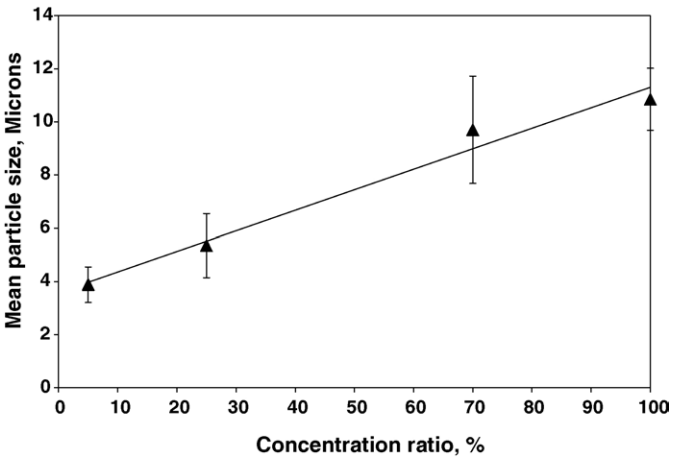

Fig. 5. Plot of the mean particle size of BECD produced by GAS as a function of the solute concentration. The points are experimental data; the line is a linear least-squares fit of the points.

decline-depletion in the supersaturation as the nuclei grow, i.e., a high growth rate follows. This may lead to multiple crossing of the critical supersaturation line between the nucleation and metastable zones, resulting in increased bimodal behaviour.

3.3. Effect of BECD concentration

The influence of the initial BECD concentration (varied between 5 and 100%) on the mean particle size and particle size distribution was investigated. The concentration ratio was defined as the ratio between the actual concentration of the liquid solution, and the saturation concentration. As indicated in Table 2 and illustrated in Fig. 5, the higher the BECD concentration, the higher the mean particle size and the broader the particle size distribution. At the lowest solute concentration, i.e., 5% concentration ratio (run *C*1), the particle size distribution was unimodal with only a moderate degree of agglomeration and a mean particle diameter of 3.1 μm. As the concentration ratio increased to 25, 70, and 100%, the mean diameter increased to 4.0, 8.3 and 10 μm. The increase of particle size and the broadening of the particle size distribution with increasing solute concentration can again be understood in terms of nucleation and growth processes. At higher solute concentrations, precipitation of the solute occurs earlier in time during the expansion process, resulting in increased time for crystal growth. At lower solute concentrations, precipitation of the solute is reached later during

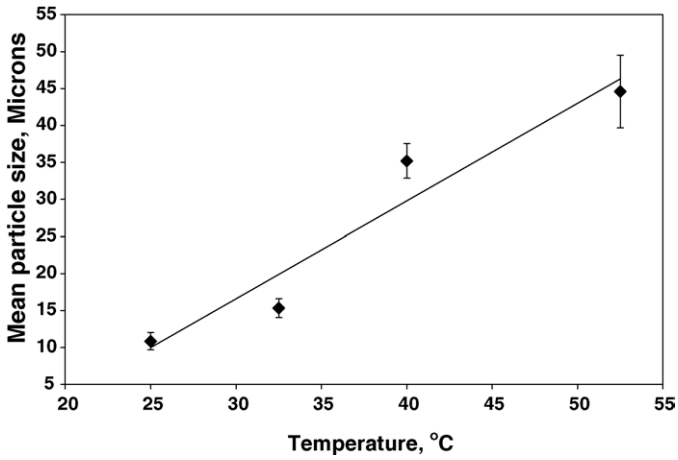

Fig. 4. Plot of the mean particle size of BECD produced by GAS as a function of the crystallization temperature. The points are experimental data; the line is a linear least-squares fit of the points.

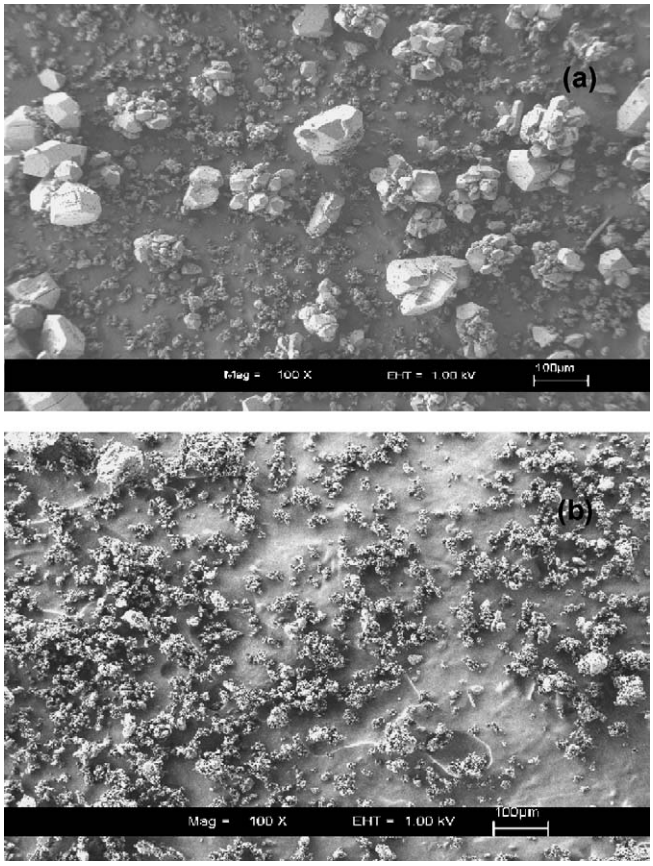

Fig. 6. SEM photomicrographs of BECD produced by GAS showing the effect of increasing agitation rate: (a) 500 rpm and (b) 2000 rpm. The experimental conditions are provided in Table 1.

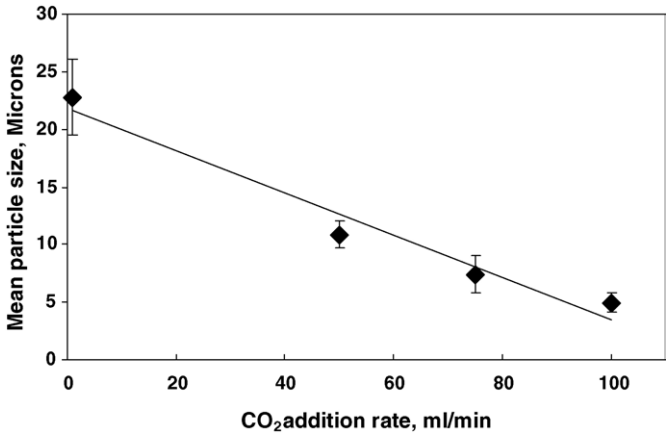

Fig. 7. Plot of the mean particle size of BECD produced by GAS as a function of the agitation rate. The points are experimental data; the line is a linear least-squares fit of the points.

the expansion process; hence, nucleation is the prevailing mechanism giving smaller particles. Our previous theoretical results with phenanthrene also indicated that primary nucleations were less sensitive to the solute concentration than the secondary nucleation rate (Bakhbakhi et al., 2005b). At higher solute concentrations, the supersaturation profile tends to get quickly closer to the saturation line initiating a primary nucleation burst, thus allowing a longer time for the particles formed during the first burst of nucleation to grow. Hence, the growth mode dominates and superimposes to secondary nucleation, and thus, larger size particles with broad particle size distribution are produced.

3.4. Effect of agitation rate

Experiments to study the effect of agitation on BECD particle characteristics were performed at two antisolvent addition rates, 50 and 100 ml/min (Table 1). At the 50 ml/min addition rate, agitation rates of 500, 1000, 2000 and 3000 rpm (series *G*)

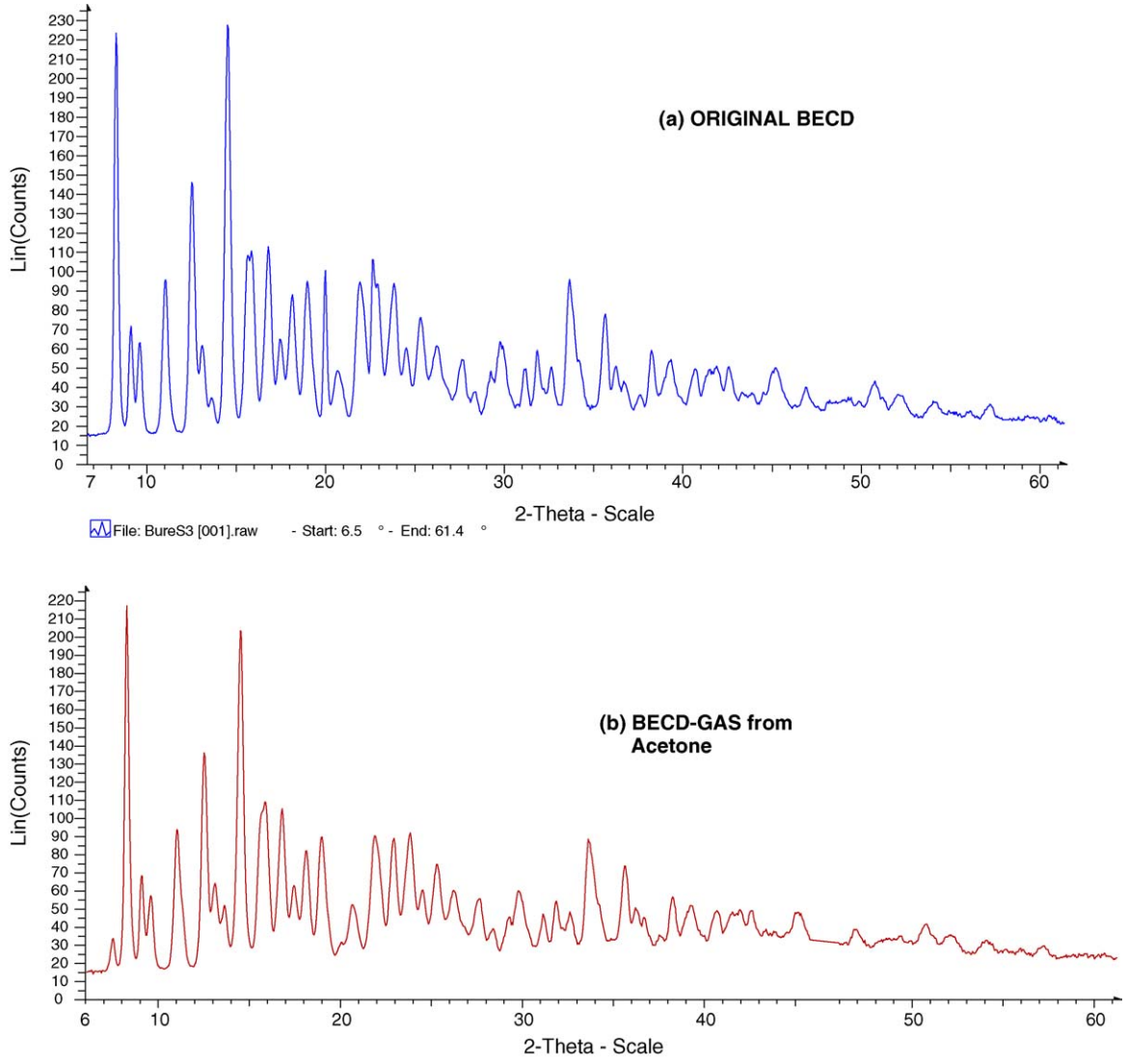

Fig. 8. X-ray powder diffraction patterns for: (a) the original BECD, (b) BECD precipitated from acetone, (c) BECD precipitated from methanol and (d) BECD precipitated from ethanol.

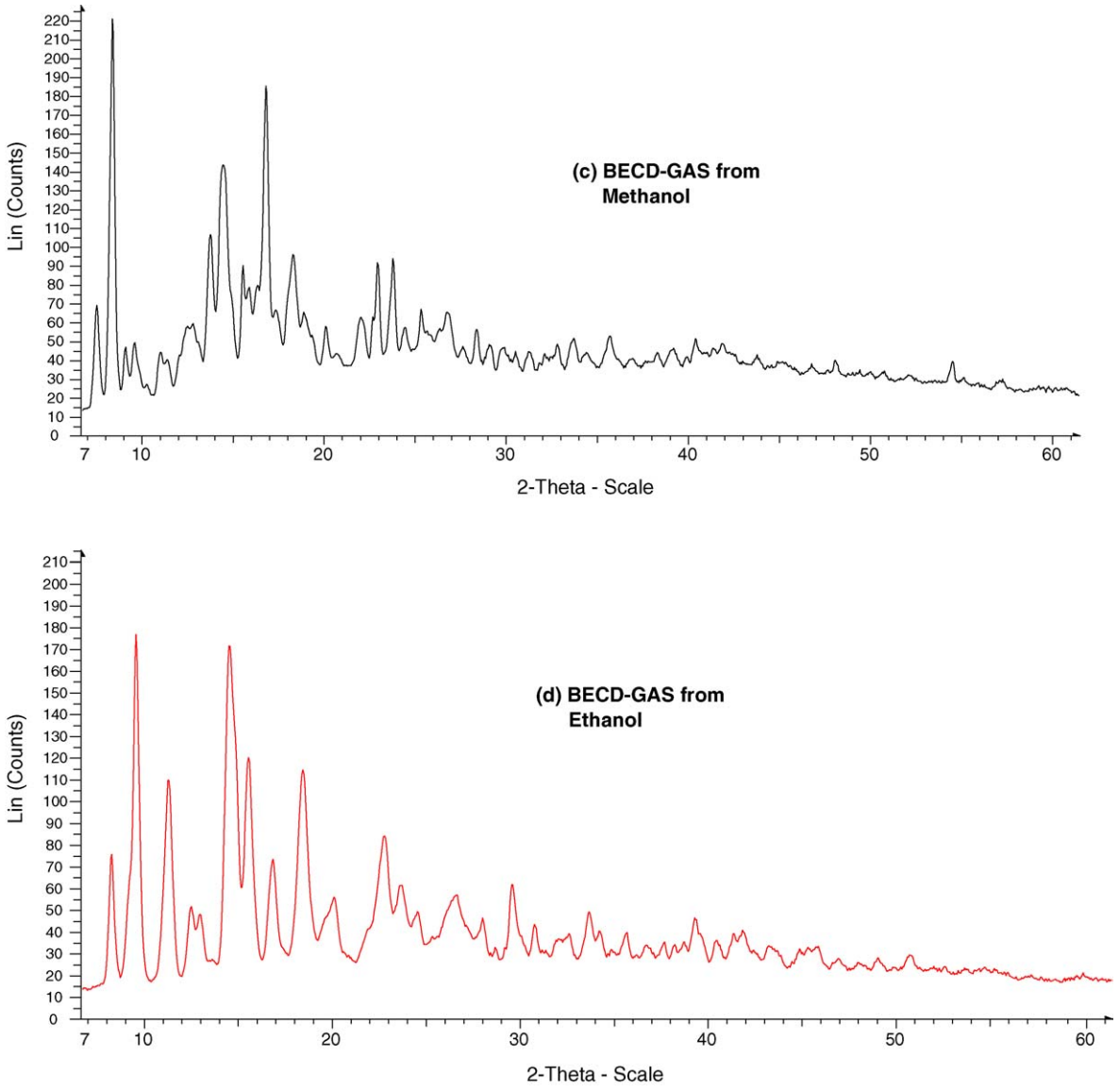

Fig. 8. (*Continued*).

were investigated; while at 100 ml/min, 1000 and 3000 rpm were studied. Scanning electron photomicrographs of the particles are compared at experiments using agitation rates of 500 rpm (Fig. 6(a)) and 2000 rpm (Fig. 6(b)), while the effect of agitation rate on mean particle diameter is plotted in Fig. 7. The SEM pictures indicate that the particle size distribution goes from bimodal with high agglomeration, to a relatively narrow distribution with a lowered degree of agglomeration. It is also clear that increasing the agitation rate directly lowers the mean particle size. The experiments performed by raising the level of antisolvent addition rate gave particles with mean diameters of 4.9 and 1.8 μm, respectively (runs *A*4 and *G*4). For run *G*4, a narrow size distribution with a low degree of agglomeration was obtained.

It is clear that the agitation rate has a strong influence on the produced particles size distribution. Increasing the agitation rate effects the GAS process dynamics by decreasing the time required to expand the liquid phase and to achieve supersaturation. The time needed to achieve a homogeneous volumetric expansion will be sharply reduced with high quality mixing, i.e., high mass transfer efficiency generated by a high Reynolds number. In contrast, a low agitation rate implicates a longer time for reaching supersaturation. Increasing the agitation rate can also increase the degree of crystal breakage through particle–impeller and particle–particle collisions, although the SEM results indicate that this effect was secondary.

3.5. The role of solvent

The effect of solvent in determining the crystal growth mechanism in liquid crystallization is a subject of extensive research. The degree of crystallinity of the formed particles is important for processing pharmaceuticals, as it sheds some light on the role of the solvent during particle growth. To investigate the influence of the solvent on the BECD crystallinity, the influence of the organic solvents, methanol and ethanol, were studied in

addition to acetone. Methanol provided powder similar to that achieved with acetone, while ethanol gave needle-like crystals, which would not be suitable for inhalation therapy. Powder XRD obtained for the virgin BECD material and particles formed from acetone using the GAS process are presented in Fig. 8(a) and (b). The patterns are highly superimposable indicating similar crystal structure and retention of crystallinity of the particles generated from acetone. Methanol gave relatively pure crystals (Fig. 8(c)), whereas ethanol gave particles with a lower degree of crystallinity, evidenced by the loss in X-ray peak intensity (Fig. 8(d)). A change in the crystals morphology and crystallinity due to the solvent influence was observed by both Gallagher et al. (1991) and Muller et al. (2000).

3.6. The suitability for pulmonary inhalation therapy

The purity of the BECD product produced by the GAS process for potential inhalation therapy was investigated by HPLC. The HPLC chromatograms obtained for the virgin BECD material and the GAS generated powder are compared in Fig. 9(A) and (B). For the given BECD material, a purity level of 93–95% was observed while the GAS technique yielded a higher purity product of 98.5% at a CO_2 addition rate of 100 ml/min, and 3000 rpm (run *G*4). The BECD steroid after micronization was relatively pure as HPLC chromatograms obtained for the virgin BECD material and the GAS generated powder showed that recrystallization in CO_2 increased the BECD purity from 94 to 99%.

The suitability of the BECD product produced by the GAS process for potential inhalation therapy was investigated in terms of the mass median aerodynamic diameter (MMAD) (Mitchell and Nagel, 2004). The MMAD measurements were performed

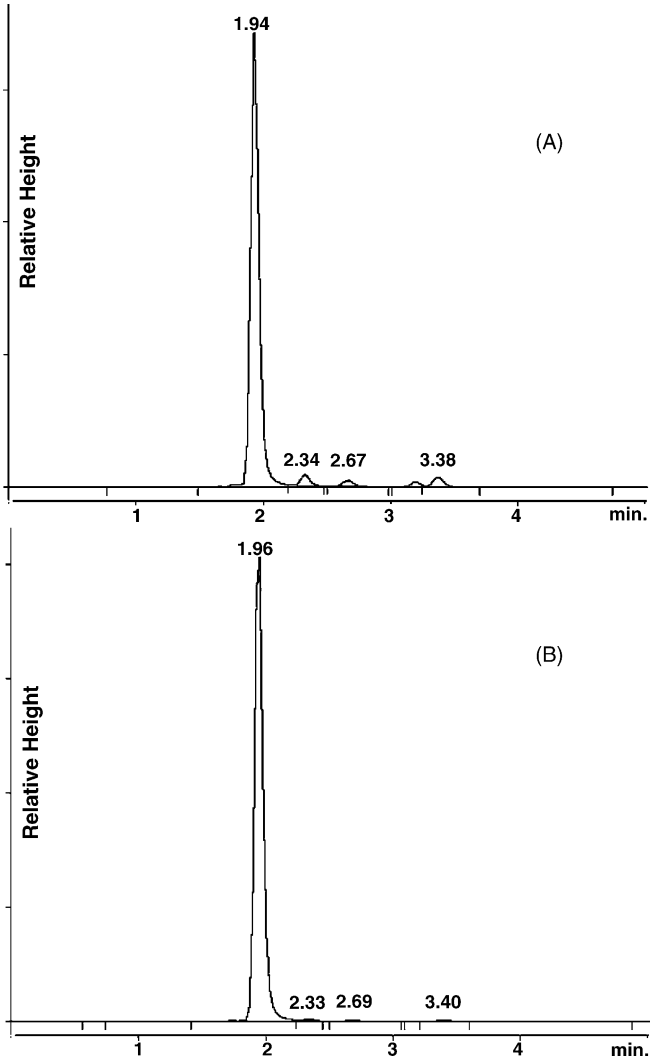

Fig. 9. HPLC analysis of: (A) unprocessed BECD and (B) processed BECD using the GAS process (run *G*4). The experimental conditions are provided in Table 1.

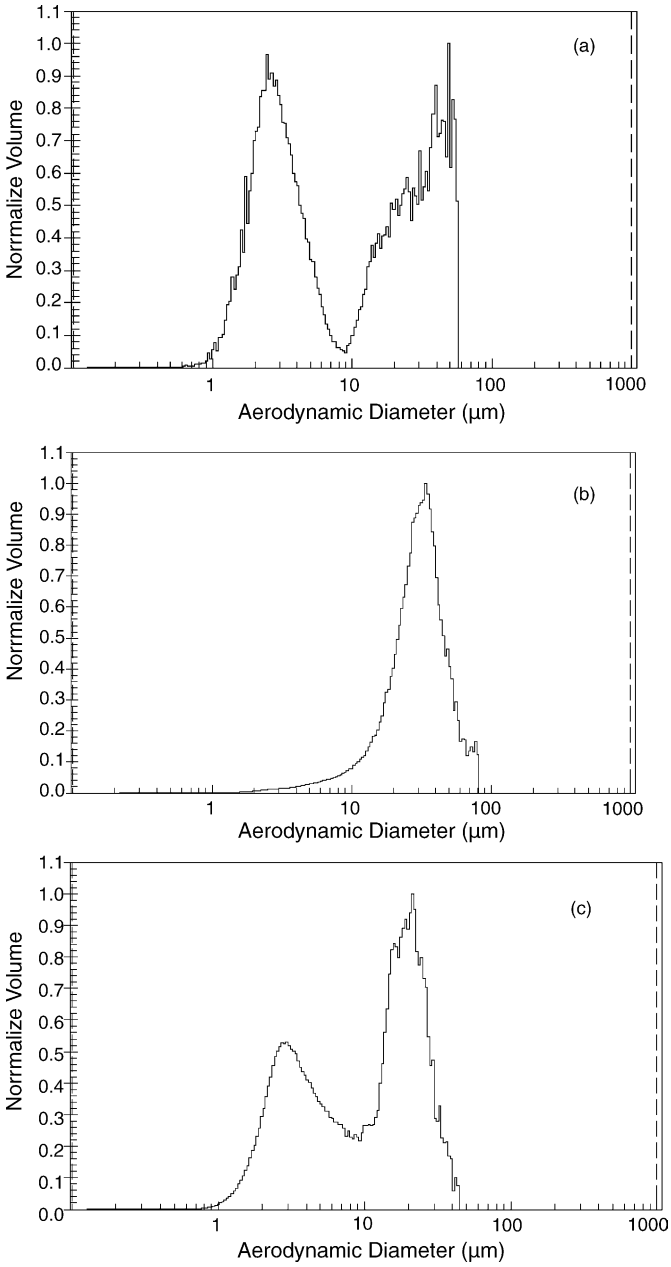

Fig. 10. Normalized volume density distributions for the MMAD of BECD powder (a) unprocessed; (b) GAS processed-run *G*2; (c) GAS processed-run *G*4. The experimental conditions are provided in Table 1.

on both the provided BECD material, and a selected number of samples produced by the GAS process (each repeated three times). The normalized volume density distributions are provided, as this distribution is of direct relevance to inhalation therapy. Fig. 10(a) shows the distribution of the provided BECD which gave an average MMAD = 7.4 μm, and a S.D. of 2.4 μm. Fig. 10(b) shows the sample generated using a CO_2 addition rate of 50 ml/min and 2000 rpm (run *G*2). This distribution was unimodal, with an average MMAD of 27.5 μm with a S.D. of 2.9 μm. For the sample generated using a CO_2 addition rate of 100 ml/min and 3000 rpm (run *G*4), the average MMAD of this run was 7.9 μm with a S.D. of 1.6 μm.

Although our best results in this study were a MMAD of 7.9 μm, we were very close to the target of 1–5 μm. The MMAD of the GAS processed sample (*G*4), like the commercial one, is bimodal with rather similar individual distributions. The bimodal mass distributions have importance for targeting both the upper region of the lungs, and the alveoli. It is clear that the GAS technique provides a very promising "green" technique for production of BECD, with potential for tuning of the inhalable properties of the steroid medicine. Future work will continue on optimizing the desired bimodal distributions for next generation DPIs.

4. Conclusions

This study showed that the micronization of BECD could be achieved by means of the GAS process. It was demonstrated that the particles mean diameter, and particle size distribution can be strongly controlled using the GAS process through the manipulation of the process parameters; antisolvent addition rate, concentration, temperature, and agitation rate. The higher the antisolvent addition rate, the smaller the size of the generated particles and the narrower the size distribution. In contrast, the solute concentration exhibited the opposite effect, as the initial solute concentration was reduced the particle size and size distribution were lowered. Higher temperatures were found to increase the particles size and the level of agglomeration. Higher agitation rates produced smaller particle sizes and narrower size distributions. In addition, the organic solvent was found to play a role in determining the degree of crystallinity of the formed particles with acetone giving a more crystalline structure than either ethanol or methanol.

HPLC analysis obtained for the starting material and GAS generated powder proved that a higher purity product could be achieved using the GAS technique with no effect of chemical degradation. BECD powder suitable for pulmonary inhalation therapy with a MMAD value very close to commercial product was obtained.

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