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Research paper

Influence of process parameters in the ASES process on particle properties of budesonide for pulmonary delivery

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Abstract

Budesonide was micronized by precipitation in supercritical carbon dioxide by using the aerosol solvent extraction system at various process conditions. The process is characterised by spraying an organic solution of budesonide into the supercritical fluid (SCF), precipitation of the drug in the SCF and extraction and recovery of the solvent. The micronized budesonide particles were characterized physico-chemically for their morphology, crystallinity, size distribution and for their aerodynamic behaviour. The particle size distribution of the powder products was similar, regardless of the process conditions used for the crystallization. Also, the morphology of the particles did not differ between the batches. However, the aerodynamic properties of the precipitated batches were significantly different between the batches produced and as compared to a jet-milled budesonide powder. In conclusion, the process conditions in the SCF precipitation may influence the aerodynamic properties, although other physico-chemical parameters appear to be similar.

Keywords: Budesonide; Supercritical fluid; Aerosol solvent extraction system; Dry powder inhalation; Aerodynamic diameter; Micronization

1. Introduction

The pulmonary delivery of small and large molecules to treat both local and systemic diseases is an important administration route to be considered during pharmaceutical product development [1]. One of the major prerequisites for a successful pulmonary drug application is a suitable particle size of the drug which mass median aerodynamic diameter (MMAD) should be in the range of 1–5 μm [2]. In current practice, the desired particle size is achieved by milling of large drug crystals by fluid energy mills or pearl ball mills. The disadvantages of such techniques are, besides safety aspects due to the dust exposure during processing, that these techniques rely on a high energy input which is not effectively used for the size reduction [3]. In addition, amorphous areas on the surface of drug crystals are created during the milling process leading to chemical or physical instability or an increase of hydrophobic drug surface with increased tendency of adhesion and agglomeration [4,5]. It was observed quite recently that drug crystals can undergo post-micronization relaxation resulting in changes in the particle size and the specific surface area during storage [6]. Therefore, a variety of alternative particle engineering techniques have so far been described in the literature to avoid these drawbacks of common milling processes: micronized spherical particles can be prepared by spray-drying a solution of the drug. Spray-dried drugs which are amorphous show a smaller and more homogeneous particle size and a higher respirable fraction than mechanically micronized drugs [7,8]. However, this technique is rarely used for water-insoluble drugs as organic liquids are required which necessitate resource intensive machinery and causes environmental problems. Another recently described method is the so-called spray-freezing into liquid process where a drug solution is sprayed into a cryogenic liquid to produce a frozen micronized powder that is subsequently freeze-dried. With this technique also micro-fine but amorphous powders can be produced [9].

Micronized drugs can also be prepared using supercritical carbon dioxide (SCD) [10,11]. Steroids for pulmonary delivery can be micronized by the aerosol solvent extraction system-process (ASES) where a drug which is insoluble in SCD is precipitated out of an organic solution that is sprayed

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into the supercritical fluid (SCF). The organic solvent can be regained [12]. Although several different techniques have been described in the literature [13], only few of the techniques are used for the preparation of particles that are then used in an approved medicinal product. In an earlier report the general feasibility of micronizing steroids with the ASES-process has been described [14]. It was the purpose of this study to analyse the influence of process parameters of the ASES-process on the physico-chemical and aerodynamic properties of budesonide, a widely used corticosteroid for the treatment of inflammatory pulmonary diseases.

2. Materials and methods

2.1. Materials

A laboratory batch of micronized budesonide (Lot. No. 19960411-577, AstraZeneca GmbH, Wedel, Germany) with a $d_{50\%} = 1.75$ μm and a $d_{90\%} = 4.06$ μm was used as reference and for the preparation of the feed solution for the ASES-process. All reagents used—methylenechloride, acetonitrile, and methanol—were of analytical grade and supplied by Merck KGaA (Darmstadt, Germany). Water was of double distilled quality.

2.2. Methods

2.2.1. Particle formation

The ASES-process is described in detail elsewhere [14]. Briefly, a 1% (w/w) solution of budesonide in methylenechloride is sprayed by means of a high-pressure pump into the supercritical gas phase. While the organic solvent is miscible with the supercritical CO_2 and is removed from the crystallization chamber, the drug precipitates in the supercritical gas phase. During a subsequent drying step, the precipitated drug is flushed by supercritical CO_2 which reduces the residual solvent content. The particles are removed from the crystallization chamber and stored desiccated until further use. As budesonide is more soluble in supercritical CO_2 at higher temperature and higher pressure [15], 40 °C and 8.5 MPa were used as standard crystallization conditions. The CO_2 flow rate and solution feed rate were varied according to Table 1 to study the influence of process parameters on particle formation.

2.2.2. Particle size analysis

The volume particle size distribution was measured by laser diffraction using a Sympatec HELOS system (Sympatec GmbH, Clausthal-Zellerfeld, Germany) by using a cuvette. The drug was dispersed in a saturated aqueous budesonide solution containing 0.5% polysorbate 80 and sonicated for 30 s before the measurement. A 20 mm lens with a measuring range of 0.5–37.5 μm was used. All determinations were done in triplicate. The size distribution is characterized by the distribution parameters $d10\%$, $d50\%$, $d90\%$ and the distribution width expressed as 'span' which is calculated according to Eq. (1):

$$\text{Span} = \frac{d90\% - d10\%}{d50\%} \quad (1)$$

Table 1
Process conditions used for the crystallization of budesonide from supercritical CO_2

Batch no.	CO_2 flow rate (l/min)	Solution feed rate (ml/min)	Yield (%)
A	5.0	3.0	43.7
B	10.0	3.0	56.4
C	5.0	7.0	67.0
D	10.0	7.0	53.5
E	7.5	5.0	76.4

2.2.3. X-ray powder diffraction

X-ray powder diffraction (XRPD) patterns were collected in transmission using an X-ray diffractometer with a rotating anode (Stoe and Cie GmbH, Darmstadt, Germany) with Cu Kα1 radiation (monochromator: graphite) generated at 200 mA and 40 kV. Powder was packed into the rotating sample holder between two films (PETP).

2.2.4. Scanning electron microscopy

Scanning electron microscope (SEM) photographs were taken using a Philips XL 20 (Philips, Eindhoven, Netherlands). Samples were fixed on an aluminium stub with conductive double sided adhesive tape (Leit-Tabs, Plano GmbH, Wetzlar, Germany) and coated with gold in an argon atmosphere (50 Pa) at 50 mA for 50 s (Sputter Coater, Bal-Tec AG, Liechtenstein).

2.2.5. Aerodynamic particle size analysis

The aerodynamic particle size was evaluated using a multi-stage liquid impinger, MSLI (Apparatus C; Ph. Eur.; Erweka GmbH, Heusenstamm, Germany). In order to characterize the drug powders without the influence of any device, the pure drug (2 mg/determination) was delivered to the impinger by using a device-less application system (Fig. 1). Briefly, the device consists of a stainless steel tube with an inner diameter of 5 mm

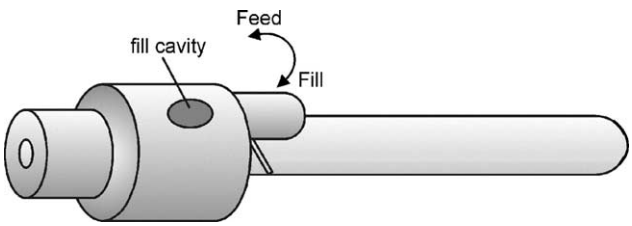

Fig. 1. Application system for the delivery of the micronized powders to the multistage liquid impinger.

and a total length of 170 mm. The applicator is tightly connected to the glass inlet of the impinger by a rubber adapter. For the delivery of the powder into the nearly laminar airflow in the tube, powder is weighed into the cavity and released into the impinger by rotating the inner part of the applicator. The powder is transferred into the stainless steel tubing and entrained by the air. The flow rate was adjusted to a pressure drop of 4 kPa as typical for the inspiration by a patient resulting in a flow rate of 82 l/min. The drug deposition in the throat, the four stages and the filter (stage 5) was determined by a validated high-pressure liquid chromatography (HPLC) method. The drug that was deposited on the different stages was calculated as percentage of the total amount of the drug. All samples were analysed in triplicate.

2.2.6. High-pressure liquid chromatography

The HPLC system consisted of a Gynkotek High Precision Pump Model 300 (Gynkotek, Munich, Germany), a Kontron HPLC Autosampler 360, a Kontron HPLC Detector 430 (Kontron Instruments, Milano, Italy) and LiChrospher 100 RP18 columns (5 μm; 125 mm; Merck KG, Darmstadt, Germany). Peak integration (wavelength 237 nm) was carried out using a computer-controlled software (Data System 450, Kontron Instruments, Milano, Italy). Samples of 100 μl were injected. As mobile phase

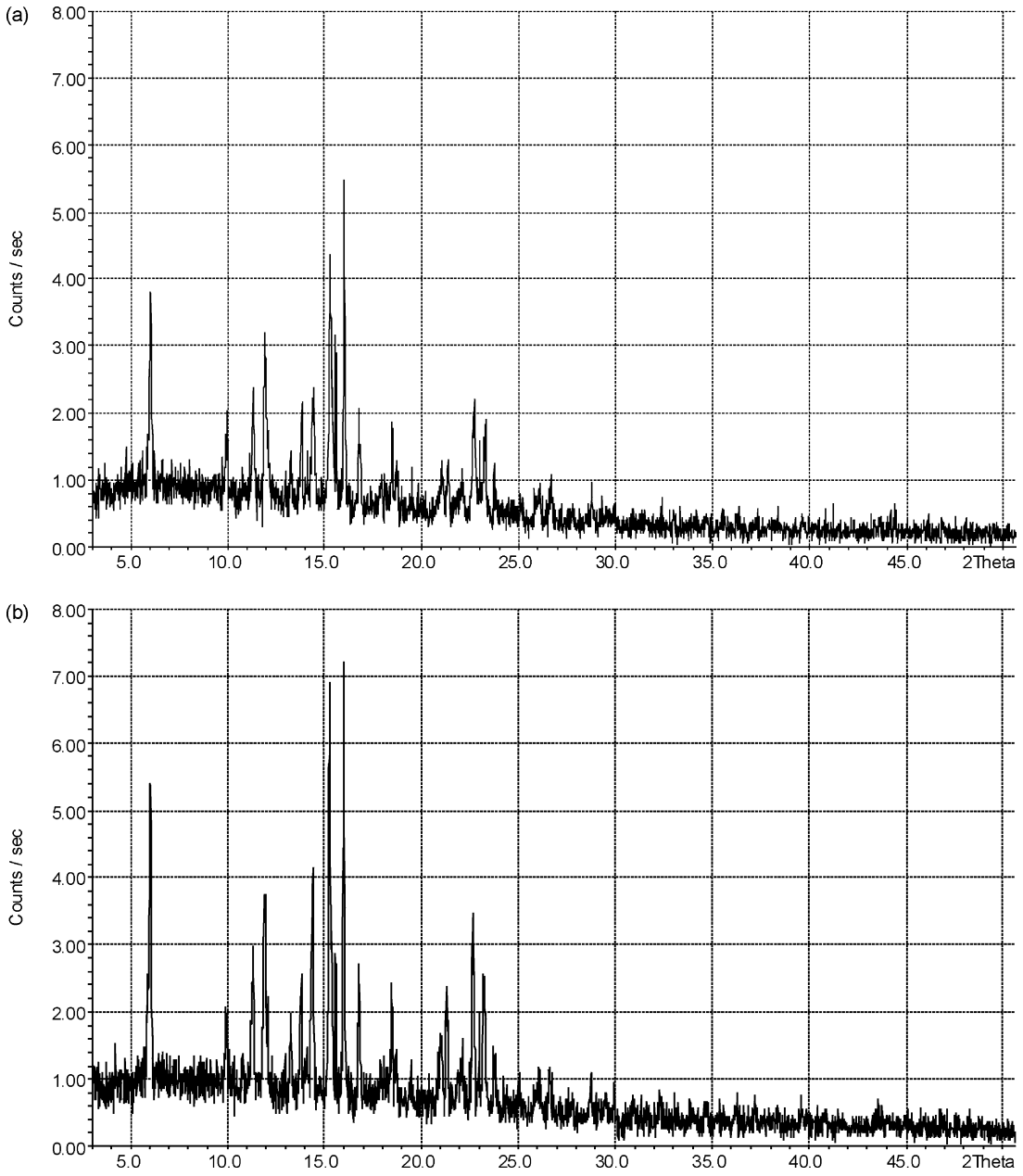

Fig. 2. XRPD pattern of (a) milled and (b) ASES-processed budesonide.

Table 2
Size distribution parameters of milled and ASES-processed budesonide particles

Batch no.	$d10\%$ (μm)	$d50\%$ (μm)	$d90\%$ (μm)	Span
Jet-milled	0.78	1.75	4.06	1.75
A	1.82	7.57	15.84	1.85
B	1.57	6.24	14.10	2.01
C	1.68	6.17	13.73	1.90
D	1.98	7.81	14.91	1.66
E	1.91	7.41	14.36	1.68

an acetonitrile/water mixture was used (55:45). The amount of drug was calculated using an external standard.

3. Results and discussion

The precipitation of budesonide in the SCD phase at a temperature of 40 °C and a pressure of 8.5 MPa led to the formation of particles and to an acceptable yield (considering the low drug amount of 1% (w/w) used for the studies) in the range of 50–70%.

The particle size distributions of the SCF-processed budesonide particles only show slight variations in terms of

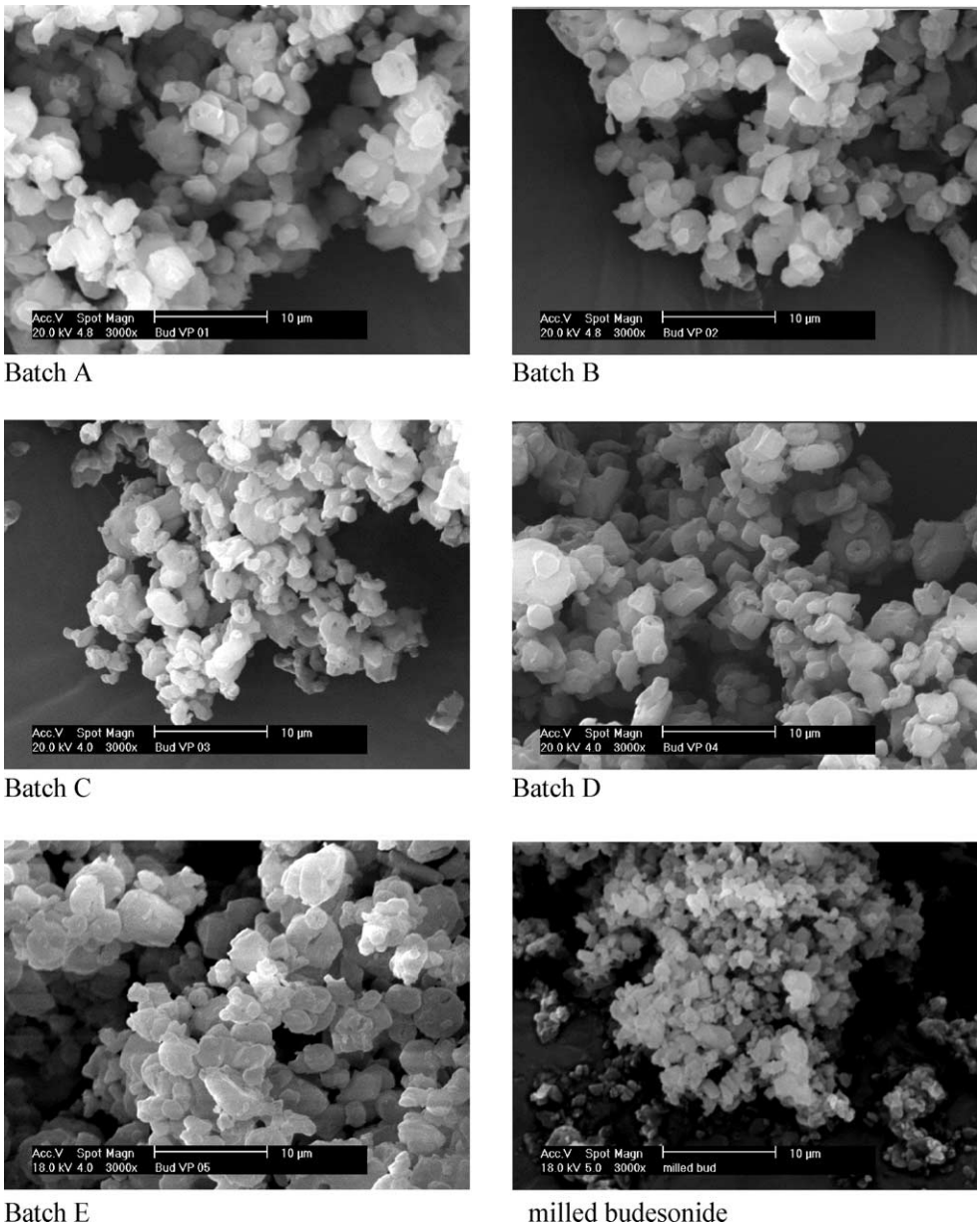

Fig. 3. SEM photographs of milled and ASES-processed budesonide particles.

Table 3
Aerodynamic properties of milled and ASES-processed budesonide particles

Batch no.	Particles <5 μm (%)
Milled	29.0 (2.0)
A	32.3 (3.2)
B	37.6 (2.1)
C	47.9 (0.9)
D	31.3 (0.3)
E	23.5 (3.0)

the distribution parameters $d10\%$, $d50\%$ and $d90\%$ and the distribution width given by the span. Ultimately, the particle size distribution is not affected markedly within the selected range of process parameters indicating the robustness of the precipitation process at the selected conditions (Table 2).

The XRPD study on the milled and the SCF-processed budesonide revealed that there was no change in crystallinity (XRPD patterns are exemplarily shown for milled budesonide and batch D in Fig. 2) indicating that the same modification of budesonide has been produced by the ASES process. However, a polymorphism is not yet described for budesonide.

Also the SEM photographs of the SCF-processed budesonide particles exhibit the same morphology, regardless of the process conditions used for the precipitation (Fig. 3). The budesonide crystals formed are of regular shape, partly spherical and appear to have a smooth particle surface whereas the SEM-photograph of the milled budesonide show a less uniform particle shape with surface irregularities. Also, the milled powder seems to be more agglomerated than the SCF-processed powder.

Finally, the aerodynamic behaviour of the SCF-processed powders has been evaluated. Micronized powders are in most cases blended with a diluent, e.g. lactose, to improve flowability and dispersibility of the powdered drug in air. However, testing the dispersibility of micronized actives as bulk powder without using a device or a carrier discriminated between micronized powders of different origin and with different surface properties [16]. Therefore, the micronized budesonide bulk powders were analysed without using a device as well. The results are summarized in Table 3 and Fig. 4. The milled budesonide delivered into the impinger resulted in a fine particle fraction of 29%. Similar results were obtained for the SCF-batches A and D whereas SCF-batch E (the centre point of the experimental design) resulted in the lowest fine particle fraction (23.5%). However, batches B and C showed an improved dispersibility compared to the milled budesonide with a fine particle fraction of 37.6 and 47.9%, respectively. Although the particle size distribution of the SCF-processed powders were not significantly different ($P = 0.05$), the effect of the process variables on the fine particle fraction was significant ($P = 0.05$) for the batches B and C which were produced at high CO_2 flow and low liquid feed rate and low CO_2 flow and high liquid feed rate, respectively, indicating that the two process variables interact with each other. Also, the volume mean diameter of the batches B and C was slightly lower than that of all other batches and the size distribution was slightly broader. On the other hand, low CO_2 flow and low liquid feed rate (A) as well as high CO_2 flow and high liquid feed rate (D) resulted in aerodynamic properties which were not different from those of the micronized powder. Although the micronized powder has an average diameter

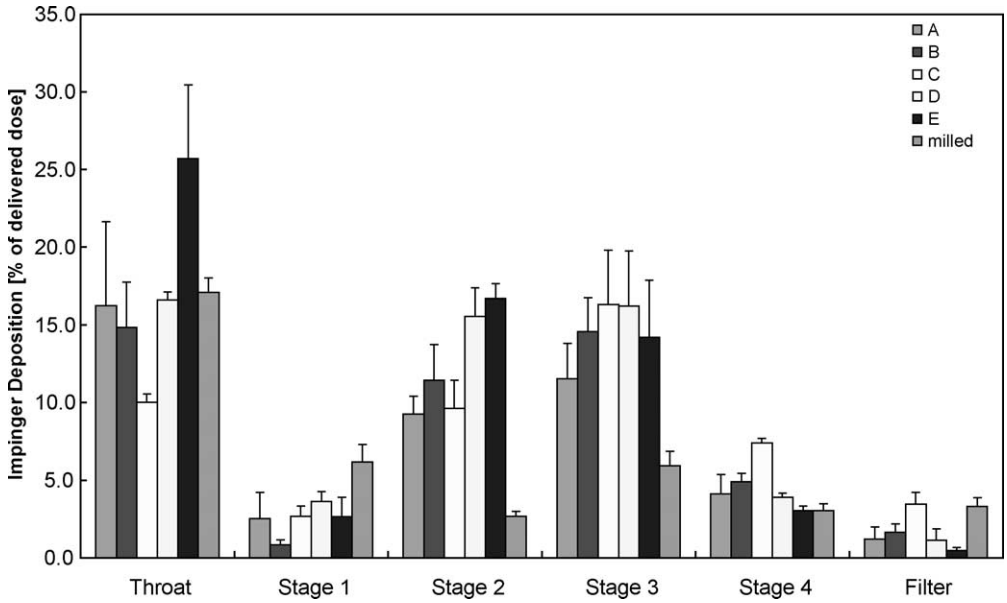

Fig. 4. Deposition of milled and ASES-processed budesonide particles in the multistage liquid impinger.

of 1.8 μm the aerosolization behaviour is less favourable than that of the SCF-processed batches B and C. Obviously, the powder is more cohesive and, hence, is more difficult to de-agglomerate.

4. Conclusions

Budesonide can be micronized by precipitation in SCD using the ASES. In this study, the investigated process variables, as carbon dioxide flow and liquid feed rate, did hardly influence the particle size distribution of the crystallized powders whereas the aerosolization behaviour was significantly different for two of the produced batches.

In conclusion, the process parameters selected for the precipitation of budesonide in SCD need to be carefully monitored to obtain the micronized powder in a reproducible quality.

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