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International Journal of Pharmaceutics 258 (2003) 65–75
international journal of pharmaceutics
www.elsevier.com/locate/ijpharm

In vitro characterization of jet-milled and in-situ-micronized fluticasone-17-propionate

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Received 28 October 2002; received in revised form 11 February 2003; accepted 24 February 2003

Abstract

Particle properties are decisive for therapeutic efficiency of an inhaled pulmonary drug. Jet-milling as the common way for micronization of inhaled powder drugs shows several disadvantages such as a non-homogeneous particle size distribution and unnatural, thermodynamically-activated particle surfaces causing a high agglomeration behavior. For pulmonary use in a dry powder inhaler (DPI) beside a small particle size, a good de-agglomeration activity is required. In this study, fluticasone-17-propionate (FP) is in-situ prepared in a respirable particle size by a controlled crystallization technique. First, the drug is dissolved in acetone and precipitated by a solvent change method in the presence of a cellulose ether (HPMC) as stabilizing hydrocolloid. By rapidly pouring the drug solution into the polymer-rich water phase, the previously molecularly dispersed drug is associated to small particles and stabilized against crystal growth simultaneously by the presence of the hydrophilic polymer. This dispersion was then spray-dried. The mean particle size of the drug was around 2 μm and consequently in the respirable range. The physico-chemical properties of the in-situ-micronized drug were compared to those of an unmilled and a jet-milled quality. Differences in the X-ray patterns and amorphous parts could be detected for the jet-milled but not for the in-situ-micronized drug. In addition, the aerodynamic behavior of the engineered and the jet-milled FP was analyzed using the FlowCaps® inhaler as delivery device and compared to the commercial product Flutide® Diskus®. The fine particle fraction (FPF) (<5 μm) was increased four-fold from approximately 9% for the jet-milled drug to approximately 40% for the in-situ-micronized drug when the pure drug powder was dispersed with the FlowCaps® device.

Keywords: In-situ-micronization; Pulmonary drug delivery; Dry powder inhaler; Controlled crystallization; Fluticasone-17-propionate; FlowCaps®

1. Introduction

Delivery of anti-inflammatory drugs to the lungs is an important part in the treatment of mild to persistent asthma as well as in the treatment of chronic obstructive pulmonary diseases (COPD) (Global Initiative for Asthma, 1995). Corticosteroids continue to be widely prescribed and their long experience is evidenced by continued introductions in clinical practice, such as beclomethasone-17,21-dipropionate, budesonide, flunisolide, fluticasone-17-propionate (FP) and triamcinolone acetonide (only in the US). In the near future, the therapeutic arsenal will be probably expanded in the US with the approval of mometasone furoate (Yang et al., 2001) and ciclesonide (Taylor et al., 1999).

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doi:10.1016/S0378-5173(03)00153-4

Pulmonary delivery of active compounds can be achieved with three dosage forms: metered dose inhalers (MDIs), dry powder inhalers (DPIs) and nebulizers. All of them require the drug to be available in a particle size suitable for inhalation in order to enable the drug to be inhaled and deposited in the lower lung. It is generally agreed that this particle size is in the range of 1–5 μm for "classical" drug particles. In the case of engineered particles having a low density, e.g. porous particles, the true particle size might be larger (Edwards et al., 1997).

The common way to reduce the particle size into the respirable range by jet-milling provides only limited opportunity for the control of important product characteristics such as size, shape, morphology, surface properties, and electrostatic charge (Malcolmson and Embleton, 1998). In addition, the jet-milled powders exhibit a broad particle size distribution (Müller et al., 1996). Surfaces in mechanically micronized powders are not naturally grown as the crystal cleaves at the crystal face with the smallest attachment energy (Roberts et al., 1994). The micronization process using mills is described as extremely inefficient (Parrott, 1990) due to the high-energy input which decreases crystallinity (Ogura and Sobue, 1970) and which can enhance chemical degradation (Kaneniwa and Ikekawa, 1972; Waltersson and Lundgren, 1985). As a thermodynamically-activated surface (Briggner et al., 1994; Ticehurst et al., 2000) is created, the surface properties and thus the drug substance properties are altered. The conversion of crystalline solid surfaces into partially amorphous solid surfaces leads to a "dynamic nature" of the micronized drug (Ward and Schultz, 1995). Thus, disordered structures in the material influence the performance in formulations (Buckton, 1997; Williams et al., 1999) and processing properties such as powder flow, as micronized powders with a higher energetic surface show poorer flow properties (Feeley et al., 1998; Mackin et al., 2002). As mechanically micronized powders show high particulate cohesion forces (Zimon, 1969), the drug may be less effectively delivered from a DPI after size reduction than larger particles as shown for micronized (median size = 1.6 μm) and milled (7.2 μm) nedocromil sodium (Taylor et al., 1999). Due to the association with active sites of a carrier or within the micronized drug, the dispersibility decreases (Ganderton, 1992).

Due to the fact that milling techniques show several disadvantages, variations in powder processing are in the focus of interest as well as the development of devices for dry powder inhalation. However, the main research (represented by the number of patent applications) in the pulmonary drug delivery area concerns the development of devices (Niven, 2002). New techniques which produce the drug directly in the required small particle size are favored. Micronized spherical particles can be prepared by spray-drying of a drug solution. However, spray-drying of a drug solution leads to the production of thermodynamically active, amorphous particles showing a higher tendency to re-crystallize or degrade and thereby alter the product characteristics of the inhaled product (Sacchetti and vanOort, 1996). Micron-sized particles can also be produced by precipitating the drug in supercritical gas phases as meanwhile shown for steroids and proteins (Steckel et al., 1997; Moshashaée et al., 2000). Although these techniques require specialized equipment, scale-up into the kg-scale has now been achieved.

The aim of the present study was to apply a novel formulation technique to the corticosteroid FP to optimize the powder properties of the drug. Besides the size of the single particles, the agglomeration behavior of the powder is important for the therapeutic effect. For a good DPI-formulation, drug particles with low agglomeration tendency, sufficient flow properties, and good batch-to-batch conformity are required (York, 1994).

Micron-sized FP was prepared by a solvent change process that precipitates and stabilizes the drug in small particle size by the use of hydroxypropylmethylcellulose (HPMC) (Rasenack and Müller, 2002). As HPMC shows surface activity (Chang and Gray, 1978) it can be adsorbed onto the newly created surface of the precipitated drug in order to lower the interfacial tension. So the precipitated drug is sterically stabilized (Schott, 1985) against crystal growth by adsorbed polymer. Accordingly, the molecularly dispersed drug is associated to particles in the required size and simultaneously stabilized in the formed dispersion by HPMC. After drying this dispersion, a drug powder with a high drug load is obtained. The obtained FP particles are characterized physico-chemically and compared to non-milled and jet-milled FP. An aerodynamic assessment of the FP powder has been done

by using a deviceless application system and new, capsule-based inhaler (FlowCaps®, Hovione, Loures, Portugal). The commercial Flutide® Diskus® inhaler has been used as standard powder inhaler to discuss and qualify the results of the study.

2. Materials and methods

2.1. Materials

FP was supplied as non-milled powder and used as received in this study for comparison (Lot No. DFS0227, Hovione, Loures). Acetone (Merck KG, Darmstadt, Germany) was of analytical grade. Water was used in double-distilled quality. The employed stabilizing agent was HPMC (type 2910, USP; Metolose® 60 SH 50, Shin Etsu, Tokyo, Japan). As carrier for some dry powder formulations lactose (Pharmatose® P325M, DMV International, Veghel, The Netherlands) was used. As commercial product Flutide® 250 μg per dose Diskus® inhaler (Lot No. 2D053, GlaxoSmithKline, Bad Oldesloe, Germany) was used.

2.2. Crystallization procedure

Controlled crystallization was carried out using the solvent change method by instantaneously mixing two liquids in the presence of HPMC as stabilizing agent as described by Rasenack and Müller (2002) (Fig. 1). The process was carried out at room temperature. HPMC was chosen as stabilizing agent in this study as it has shown the best prevention of particle growth (Rasenack and Müller, 2002). In the first step, the drug (4 g/100 ml) was dissolved in acetone. A solution of HPMC in water (0.05 g/100 ml) was used as non-solvent. By batch-wise mixing the two liquids in a ratio of 1:8, a micro-fine dispersion is formed spontaneously. The resulting dispersion was then spray-dried with a Mini Büchi 190 spray-dryer (Büchi Labortechnik AG, Flawil, Switzerland) at the following standardized conditions: inlet temperature, 128 °C; outlet temperature, 55 °C; air flow, 600 Nl/h; 0.5 mm nozzle; aspirator stream, 40 m^3/h, resulting in a free-flowing, micron-sized drug powder. The resulting FP concentration in the spray-dried powder was 90.9% calculated basing on the drug to stabilizer ratio in the spray suspension. As the drug powder micronized using this technique is prepared directly in the micron-sized state during the particle formation without any further size-reduction, this technique can be described as “in-situ-micronization technique”.

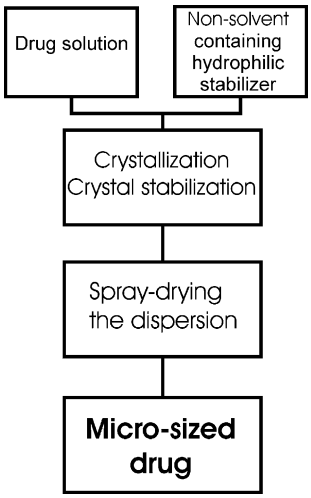

Fig. 1. Flow chart of the in-situ-micronization process.

2.3. Jet-milling

In order to compare physico-chemical characteristics of non-micronized and jet-milled powder, FP was freshly jet-milled with a fluid energy mill using nitrogen (three cycles with 8 bar; Jet-O-Mizer 00, Fluid Energy Aljet, Plumsteadville, USA).

2.4. Particle characterization

2.4.1. Scanning electron microscopy (SEM)

SEM photographs were taken using a Philips XL 20 (Philips, Eindhoven, The 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).

2.4.2. X-ray powder diffractometry (XRPD)

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 $K\alpha_1$ radiation (monochromator: graphite) generated at 200 mA and 40 kV. Powder was packed into the rotating sample holder between two films (PETP).

2.4.3. Particle size analysis

The volume particle size distribution was measured using a laser diffractometer (Helos, Sympatec GmbH, Clausthal Zellerfeld, Germany). The dispersions were diluted with water and measured in a cuvette. As a second determination method, the dry powder was measured after dispersion by compressed air (2 bar; Helos Rodos).

2.4.4. Dynamic vapor sorption (DVS)

A DVS1 analyzer (Surface Measurement Systems, London, UK) has been used to study the water uptake of the FP samples at different relative humidity (RH) and a temperature of 25 °C. Due to the different surface characteristics of milled and in-situ-micronized FP, two different methods were used for the DVS analysis: the jet-milled drug was dried for 500 min at 0% RH and then exposed to 50% RH for 250 min and to 90% RH for 500 min. After a second drying period of 500 min, the humidity was increased from 5 to 90% RH in 5% steps. The humidity stepping was done in 20-min intervals between 5 and 50%, in 30-min intervals between 50 and 75% and 60-min intervals between 75 and 90% RH, respectively. Down stepping was done using the same time and RH intervals. After a second drying procedure (500 min, 0% RH), the same sorption/desorption cycle was applied again.

The in-situ-micronized FP was analyzed as follows: after an initial drying period to equilibrium weight at 0% RH, the relative humidity was raised in steps of 5% (20 min per step) up to 90% and afterwards reduced using the same profile. Two consecutive sorption/desorption cycles have been applied.

2.4.5. Aerodynamic particle size analysis

The aerodynamic particle size was evaluated using a multi-stage liquid impinger (MSLI; Apparatus C; Ph. Eur.; Erweka, Germany). In order to characterize the drug powders without the influence of any device, the pure drug (2 mg per determination) was delivered to the impinger by using a deviceless application system (Fig. 2a). The powder was weighed into the cavity of the applicator and then fed into the air stream. 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.

Further runs were carried out using the capsule-based FlowCaps® inhaler (Fig. 2b). The FlowCaps® inhaler uses the ‘dancing cloud’ principle caused by a powerful cyclone inside the capsule due to a pressure disequilibrium inside the capsule in order to disperse the drug particles (Villax, 2002). It was operated at an air flow rate of 30 l/min corresponding to

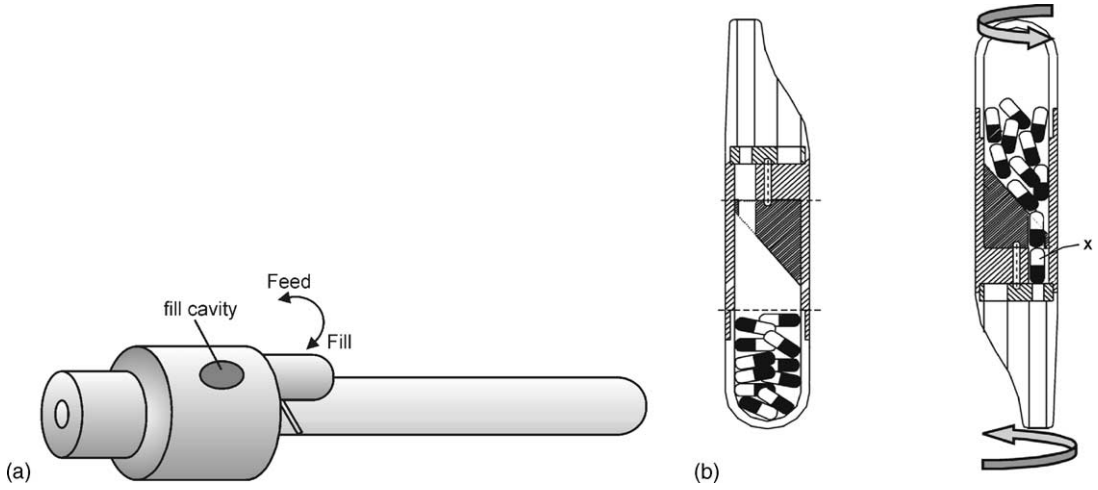

Fig. 2. Sketch of (a) the deviceless application system and (b) the FlowCaps® inhaler. In vertical position a capsule falls into the inhalation chamber (position X) and is slit at both ends by turning the mouthpiece.

a pressure drop of 4 kPa across the device. The sample preparation was done according to a fixed protocol. After sieving (mesh size: 180 μm), 500 μg of FP were filled into HPMC capsules (size 3, Shionogi Qualicaps, Nara, Japan). In addition, a 2% mixture of FP in lactose was prepared by mixing for 15 min in a Turbula blender (W. Bachofen AG, Basel, Switzerland). 12.5 mg of this powder blend were weighed into HPMC capsules and used for the aerodynamic assessment with the FlowCaps® inhaler. 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 analyzed in triplicate.

2.4.6. 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, an acetonitrile/water mixture was used (60:40). Acetonitrile (Merck KG, Darmstadt, Germany) was of HPLC quality, the water used was of double-distilled quality. The amount of drug was calculated using an external standard.

3. Results and discussion

3.1. Physico-chemical characterization

3.1.1. Particle size distribution after precipitation

The particle size distribution of the freshly precipitated FP was measured for the products precipitated in the presence and in absence of the stabilizer (Fig. 3a). It can be seen that crystallization without any stabilizer leads to large, grown particles with an average particle size of approximately 30 μm. The presence of HPMC in the antisolvent solution inhibits crystal growth by forming a polymer layer on the freshly crystallized surfaces. By this, a very tight particle size distribution

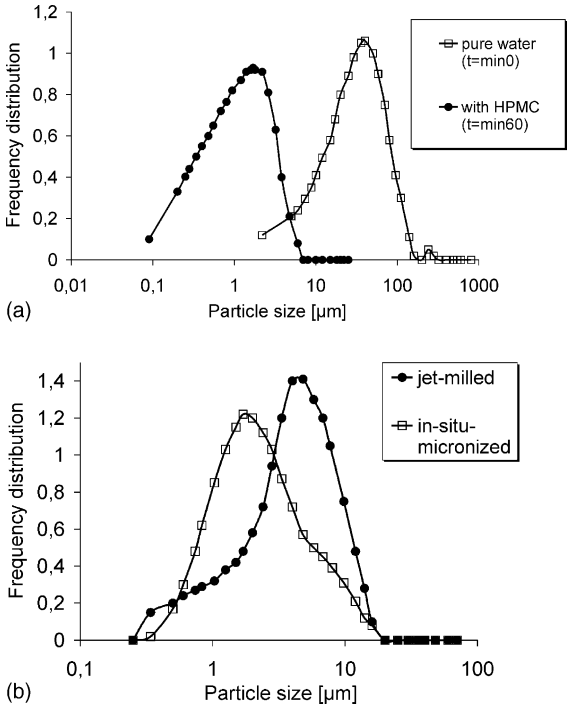

Fig. 3. Particle size distribution of FP (a) in the presence and absence of the hydrophilic stabilizer (dispersion after precipitation) and (b) spray-dried dispersion compared to jet-milled FP (dispersion in compressed air).

is obtained having an average diameter of ~1 μm. The latter colloidal system is stable over hours without any shift in the particle size distribution (Fig. 3a).

3.1.2. Particle size distribution after spray-drying

The particles size distribution of the dried in-situ-micronized FP particles as well as of the jet-milled FP was also determined by laser diffraction using a dry dispersion technique in air. After spray-drying, a drug powder with a particle size in the respirable range is obtained. The results (Fig. 3b) indicate that the average particle size of the in-situ-micronized FP is slightly increased to 2 μm with a slightly broader distribution. This can be attributed to both the spray-drying procedure where primary particles could form multiplets of particles leading to a larger particle diameter and to the laser diffraction measurement where the dry dispersion might not be effective enough to de-agglomerate the powder. Fig. 3b also shows the particle size distribution of the jet-milled FP powder. The jet-milled

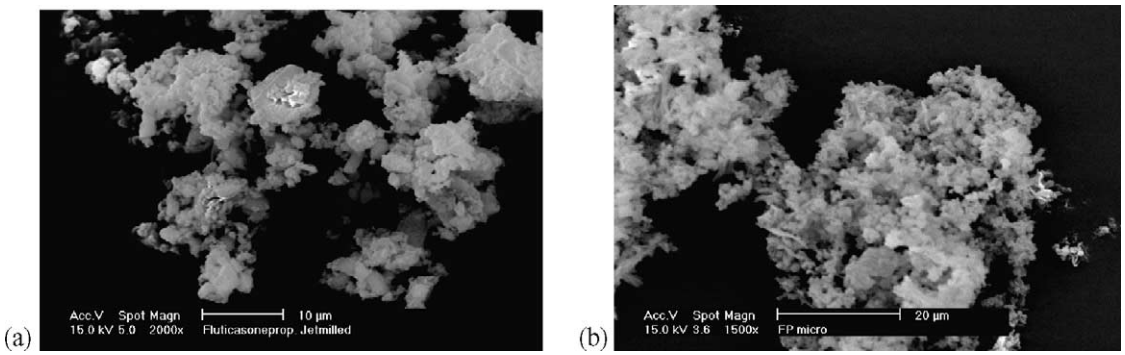

Fig. 4. SEM photographs of (a) jet-milled and (b) in-situ-micronized FP.

product has an average particle size of approximately 5 μm and is slightly broader distributed. Inspite of these differences in the particle size distributions, the in-situ-micronized powder (with the smaller particle size) shows a very good flowing behavior, comparable to that of a free flowing powder, whereas the jet-milled powder does not flow at all (adhesion to the container wall, agglomerates and lumps in the container).

3.1.3. Scanning electron microscopy

The morphology of the two FP qualities is depicted in Fig. 4. The small particle size of the jet-milled and in-situ-micronized particles can be substantiated by the SEM photographs.

As can be seen from Fig. 4a the jet-milled product consists of larger and very small particles supporting the statement that the size distribution of the powder is very broad. Fig. 4b indicates the small particle size of the in-situ-micronized FP. It is also visible that some of the particles comprise three or four primary particles as obtained directly after crystallization, supporting the fact that the average particle size of the precipitated drug has increased from 1 μm in the dispersion to 2 μm in the dried product.

3.1.4. X-ray powder diffraction

As already discussed earlier, milling is a high-energy process causing the crystal lattice to be cleaved at the weakest sites. During the milling process, amorphous areas on the surface of the newly formed particles are created which are thermodynamically unstable.

The formation of amorphous areas can be (among other techniques) detected by XRPD as shown in Fig. 5. The XRPD patterns of unmilled and the jet-milled FP quality are compared and it can be seen that the milled product shows a peak widening and the resolution of the peaks is becoming worse (marked by the arrows in the figure) indicating that the crystal structure is somehow altered. The XRPD patterns of the in-situ-micronized drug (data not shown) also show the diffraction peaks of the FP. However, due to the amorphous HPMC layer on the surface of the particles (9%), a higher baseline noise is seen beside the characteristic peaks of the drug.

3.1.5. Dynamic vapor sorption

Disruptions in the crystal lattice can cause physical or chemical instability. Disordered regions in the

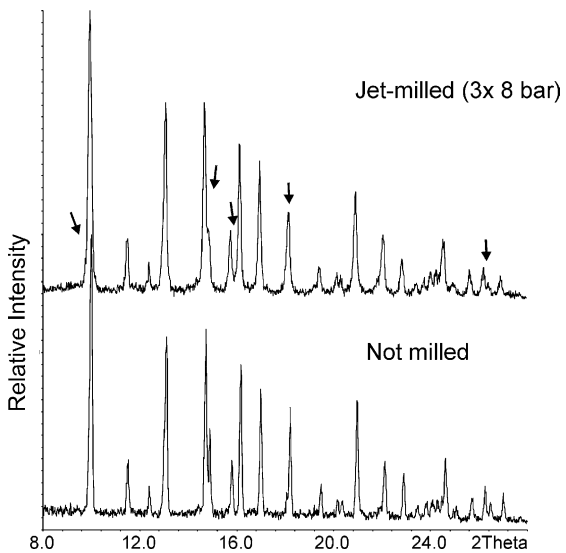

Fig. 5. XRPD patterns of jet-milled and unmilled FP.

resulting product are thermodynamically unstable. They can be detected and analyzed by DVS analysis (Ticehurst et al., 2000). Amorphous or disordered material will crystallize, especially when water from the atmosphere is adsorbed. Because of a reduction of the glass transition temperature, the energy threshold to recrystallization is decreased (Elamin et al., 2000). As crystalline substances show a reduced water sorption, a crystallization process can be observed by DVS as a mass loss will occur.

The thermodynamically-activated surface can be detected by vapor sorption analysis. The results of the DVS cycles of the jet-milled and the in-situ-micronized FP are depicted in Fig. 6a and b. As can be seen from Fig. 6a, the first step at 50% RH leads to a moisture uptake of 0.1% with a slight decrease

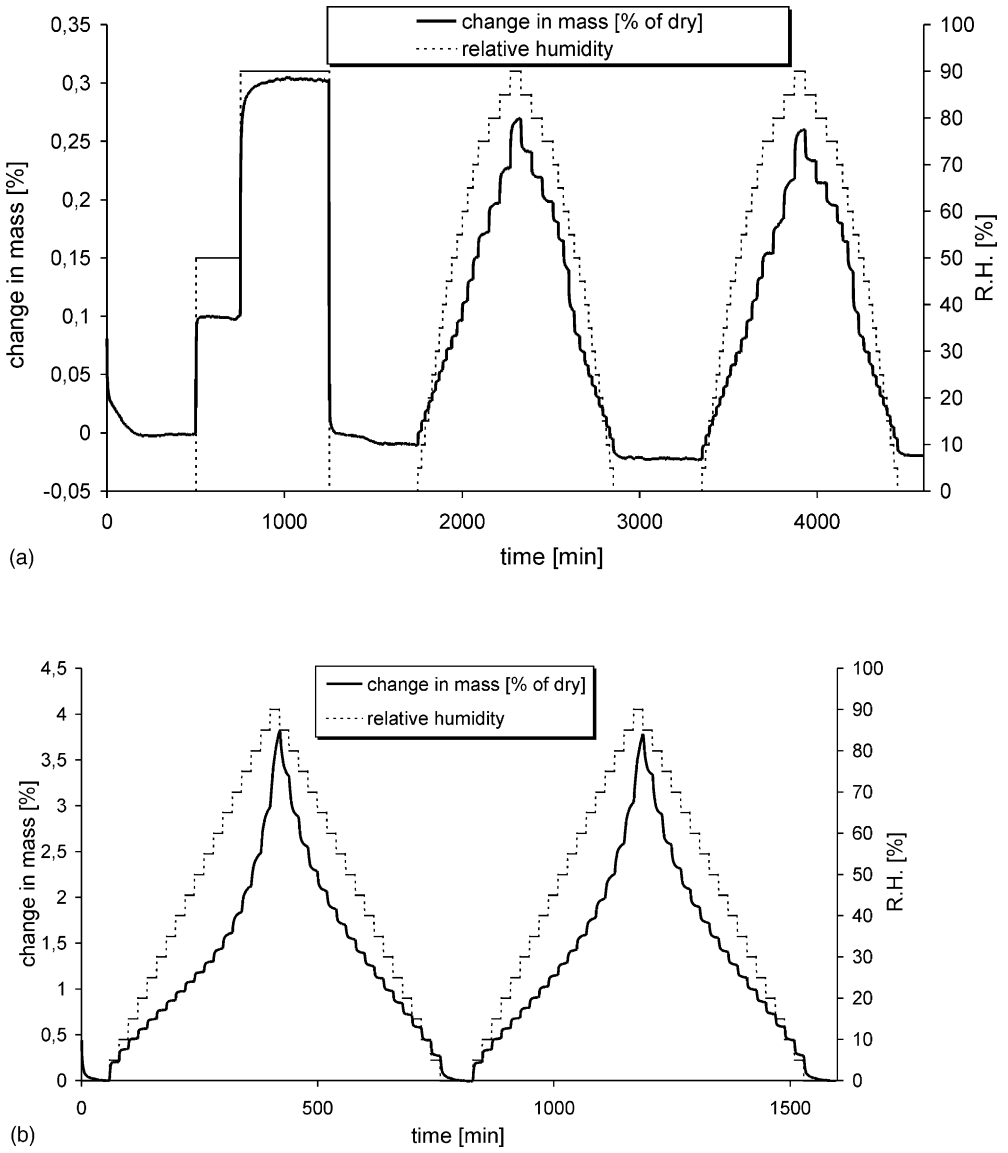

Fig. 6. DVS profiles of (a) jet-milled and (b) in-situ-micronized FP.

Table 1
Analytical settings of the multi-stage liquid impinger testing

Used inhaler	Pressure drop Δp (kPa)	Air flow (l/min)	Effective cut-off diameter (μm)				
			Stage 1	Stage 2	Stage 3	Stage 4	Filter
Deviceless	4.0	82	11.12	5.82	2.65	1.45	–
FlowCaps®	4.0	33	17.53	9.17	4.18	2.29	–
Diskus®	4.0	87	10.80	5.65	2.57	1.41	–

at the end of this cycle indicating that amorphous regions have been re-crystallized. This theory is substantiated if the following two cycles are taken into account as well: the total weight gain after the second and the third cycle (at 90% RH) becomes successively smaller. This is again an indication for amorphous regions being re-crystallized.

In contrast to the DVS profile of the jet-milled product, the in-situ-micronized product shows very uniform and reproducible DVS traces in both the first and the second cycle underlining the thermodynamic stability of the product. The total weight gain is much higher (4%) as for the jet-milled product which indicates that the HPMC is adsorbed and fixed onto the surface of the FP particles during the spray-drying process, thereby hydrophilizing the surface of the drug (Fig. 6b).

3.1.6. Aerodynamic testing of the powders

Due to the obvious improvement of the flowability of the powder, a better dispersibility in the air stream is expected as well. To substantiate this theory, aerodynamic particle size analysis has been carried out by using a MSLI. To minimize device influences, a deviceless application system (Fig. 2a) has been used. In addition, a new, capsule-based inhaler, the FlowCaps® inhaler (Fig. 2b) has been used for in-vitro deposition studies. Table 1 summarizes the analytical conditions and resulting flow rates of the MSLI testing. All analytical deposition results are given in Fig. 7a–d and Table 2. Generally, the jet-milled product showed a high retention in the application system and also a high deposition in the metal throat and on the stages 1 and 2. When delivered via the deviceless application system, a fine particle fraction (FPF) of only 9% was obtained for the jet-milled product whereas the in-situ-micronized powder shows a high deposition on stages 3 and 4, and filter increasing the FPF up to 42% (Fig. 7a). This supports the visual observation that the in-situ-micronized powder is well-flowing with low cohesion tendency resulting in high dispersibility and high deposition in the lower stages of the impinger despite the differences of the average particle size. This is in contrast to earlier studies where pure micronized powders with different average diameter were tested for their aerodynamic behavior. Chew and Chan (1999) report that micronized mannitol powders with an average particle size of 2.7 μm are much less dispersible with the Rotahaler at high air flow rate (90 l/min) than mannitol powders with an average diameter of 5.0 μm. This can be mainly attributed to the higher attractive forces between smaller particles as the gravitational separation forces are reduced. At lower flow rates (60 and 30 l/min, respectively), this observation was much more pronounced. It is assumed that the milled FP powder used in this study exhibits the same adhesive properties than the mannitol powders tested in that study. However, the in-situ-micronized powder is hydrophilized on the naturally grown particle surface

Table 2
Fine particle fraction (% FP of total <5 μm (S.D.)) of the pure FP powders, powder blends and Flutide® Diskus®

	Jet-milled powder	In-situ-micronized powder
Deviceless application	9.2 (1.5)	41.9 (5.3)
FlowCaps® inhaler/without lactose	13.5 (2.7)	37.5 (6.0)
FlowCaps® inhaler/lactose blend	11.6 (0.6)	20.4 (2.6)
Flutide® 250 Diskus®	25.1 (0.4)	–

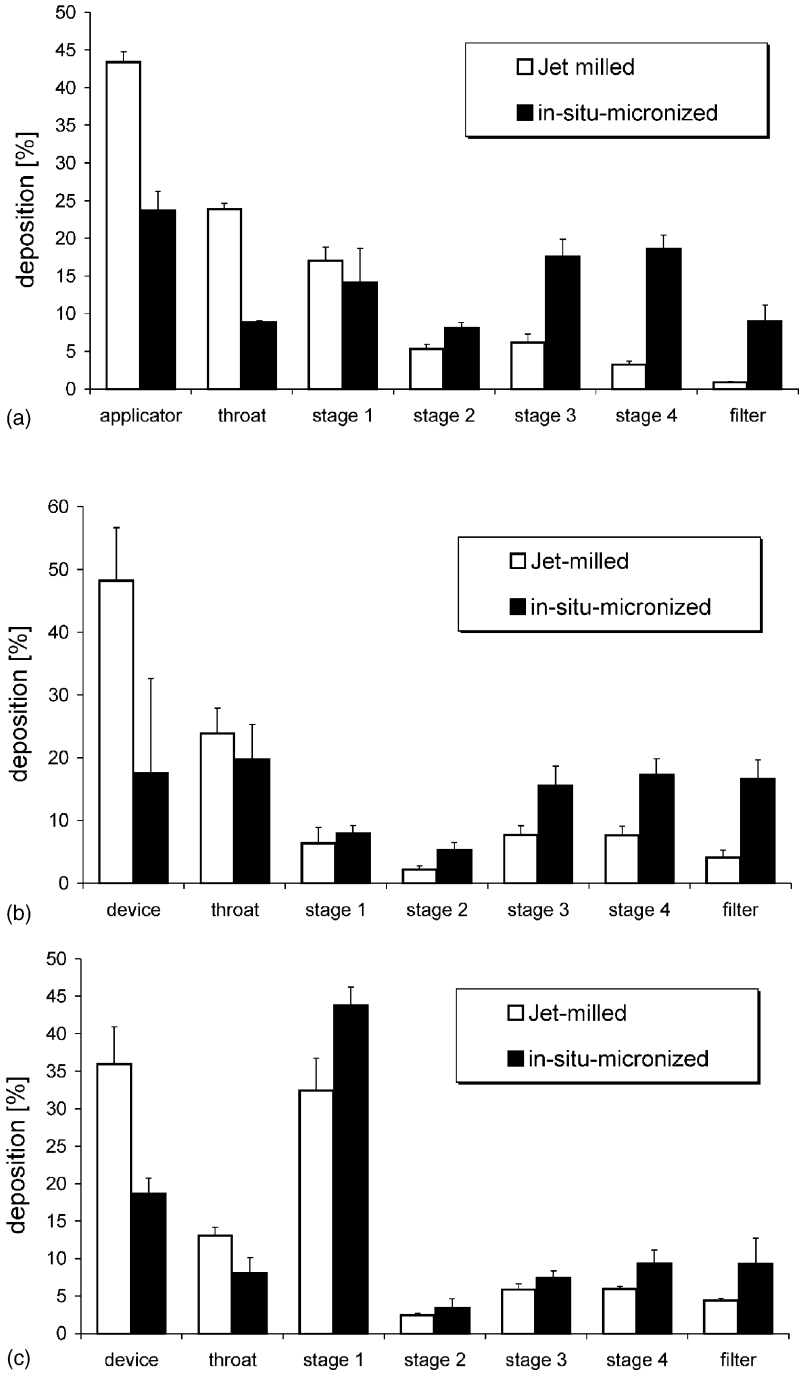

Fig. 7. Deposition profile of jet-milled and in-situ-micronized FP in the MSLI when delivered by (a) deviceless application system, (b) FlowCaps® inhaler/pure drug and (c) FlowCaps® inhaler/lactose blends. (d) The deposition profile of the Flutide® Diskus® device ($n = 3$, error bars = S.D.).

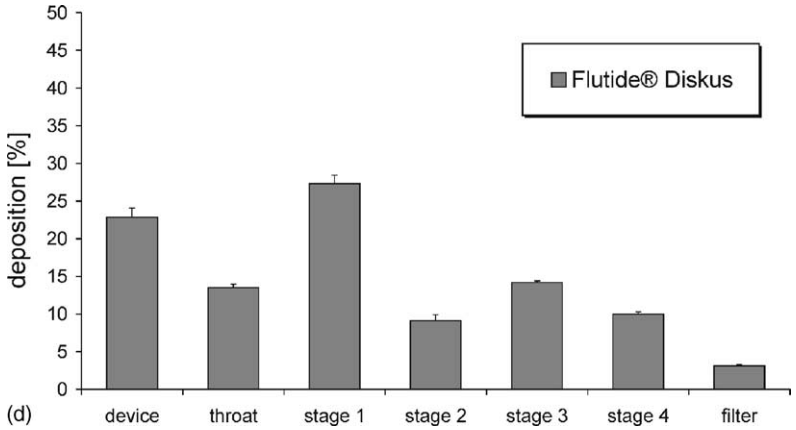

Fig. 7. (*Continued*).

which leads to less electrostatic charging and interparticulate forces. Therefore, the in-situ-micronized FP disperses better in the air flow than the milled quality.

When the pure FP powders are filled into HPMC capsules and delivered with the FlowCaps® inhaler, a very similar deposition behavior could be found for the jet-milled drug: a high deposition in the device, the throat and the stages 1 and 2 was observed resulting in a FPF of approximately 13%. When the in-situ-micronized powder was tested with the FlowCaps® inhaler the device retention was minimized whereas the deposition in stages 3 and 4 and filter was increased. The FPF was found to be approximately 38% of the total dose, again a four-fold increase as compared to the jet-milled product (Fig. 7b).

Blending the jet-milled FP with lactose did not improve the deposition pattern of the powder blend when delivered with the FlowCaps® inhaler (Fig. 7c). Still, a high device and capsule retention is observed giving a FPF of 11.6% (Table 2). Blending the in-situ-micronized particles with lactose also changes the aerosolization behavior of the drug, but into the opposite direction. The FPF is reduced by nearly half the amount of the unblended product. The high deposition on stage 1 (Fig. 7c) makes it obvious that the FP particles are strongly adhered to the lactose and were not adequately separated within the air stream. Thus, the FPF is only 20.4% (Table 2). The stronger drug-to-particle interaction can be attributed to the hydrophilized surface of the drug particles which in turn is more susceptible to environmental conditions. At ambient conditions (21 °C/60% RH), adsorbed water (see also Fig. 6b) results in increased capillary forces and, consequently, in higher drug-to-carrier attractive forces. Device (capsule) retention was still high with 20% of the total dose. However, an optimized powder formulation using other grades of lactose could improve the deposition pattern of a powder blend as well.

Comparing the deposition profiles of the in-situ-micronized powders (with and without device) with the results obtained with the commercially available Flutide® Diskus® device (Fig. 7d), it can be concluded that each of the tested combinations of powder and device perform in vitro at least as well as the marketed product.

4. Conclusions

It has been shown in this study that the novel particle engineering process using the in-situ-micronization technique is applicable to FP. While the milled drug seems to possess amorphous areas on its surface due to the energy input of the milling process, the surfaces of the in-situ-micronized particles are naturally grown. Thus, opposed to the jet-milled drug, the in-situ-micronized drug is expected to be less susceptible to chemical degradation and alteration of the physical properties. The flowability and dispersibility in air of the in-situ-micronized powder has been improved. Although the in-situ-micronized powder

shows superior air entrainment behavior when tested without a carrier, the hydrophlized surface seems to influence the drug-to-carrier adhesive properties.

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