The influence of carrier shape and surface roughness of carrier-based dry powder inhalates on the fine particle fraction

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Summary

The aim of this work was to study the influence of carrier shape and surface roughness on the fine particle fraction of carrier based dry powder inhaler formulations. Carrier particles of different roughness and shape were prepared by spray drying of aqueous mannitol solutions at different outlet temperatures. Subsequently ordered mixtures of micronized salbutamol sulphate and the carriers of different roughness and shape were prepared. It could be shown that the highest fine particle fraction (FPF) is achieved for rough, spherical particles (FPF = 29.23 %, R_a = 140.33, Aspect ratio = 0.925, M67). A decrease in surface roughness (R_a = 88.73) leads to lower FPFs (FPF = 14.62 %, Aspect ratio = 0.918, M80). This study further shows that the fine particle fraction is influenced by the particle shape. During mixing the micronized active cumulates within cavities of irregular shaped carrier particles. Upon inhalation the cavities may impede the detachment of the active from the carrier upon inhalation and the fine particle fraction decreases.

Introduction

In order to reach therapeutically relevant areas of the lung active pharmaceutical ingredient (API) particles should have aerodynamic diameters of 1 µm to 5 µm. However particles of this size are rather cohesive and precise dosing is difficult due to poor flowability. Especially in multi-dose dry powder inhalers (DPIs) where usually the powder is metered by flowing of the powder from a reservoir into well defined orifices sufficient flowability is crucial in order to guarantee reproducible dosing. To ensure sufficient flowability the fine API particles are commonly mixed with coarser carrier particles. Those carrier particles carrying the API particles on their surface usually have a particle size in the range of 50 µm to 200 µm. Further they may act as diluents for highly active APIs. Interparticle forces, between carrier and API particles play an important role in such mixtures, which are classified ordered mixtures [1]. On the one hand those forces must be high enough to ensure mixing homogeneity and stability of the mixture during powder handling, dosing and transport and low enough to allow the detachment of the API particles from the carrier upon inhalation. Due to the fact that interparticle forces are highly dependent on the contact area of carrier and API surface roughness of the carrier is an important parameter to optimize such formulations. At the moment nearly all DPI formulations on the market use α-lactose monohydrate as a carrier [2]. That is why a low of work can be found on the surface modification and optimization of lactose carrier particles for example by controlled dissolution of the surface , carrier surface covering [3, 4, 5], surface modification by milling [6, 7] or the addition of fines [8, 9, 10]. However α-lactose monohydrate may have several disadvantages. For example incompatibility reactions of the sugars´ reducing aldehyde group with active pharmaceutical ingredients like budesonide, formoterol, peptides and proteins. Another drawback is that product quality may vary due to production processes (milling, crystallization, sieving) and storage [11]. Steckel and Bolzen [11] and Tee et al. [12] investigated the use of alternative carriers for dry powder inhalers. They showed the suitability of D-mannitol as carrier in dry powder inhalers but they also mentioned that there might be problems similar to those experienced with α-lactose monohydrate. However, by using D-mannitol several constraints inherent to α-lactose monohydrate can be avoided. For example using D-mannitol instead of α-lactose monohydrate opens up the possibility to apply spray drying procedures for particle generation. Unlike α-lactose monohydrate D-mannitol does not become partially or fully amorphous upon mechanical treatment like milling or spray drying [13]. Spray drying is a dedicated technology to prepare carrier particles for dry powder inhalers as typically spherical particles are generated. Due to their homogeneous surface properties, those carrier particles offer similar adhesion conditions to active particles attached to the surface. This is in contrast to single lactose carrier crystals with different crystal faces that vary broadly in their affinity to the active. Further spray dried particles exhibit excellent flowing properties because of their spherical shape. Moreover, Maas [14] found out that it is possible to prepare D-mannitol carrier particles of different surface roughness by varying the spray drying outlet temperature. Additionally Maas et al. [15] showed that the amount of the active that reaches the lung significantly depends on the surface roughness of the spray dried D-mannitol carrier particles. However, these carrier particles, which were prepared on a lab scale spray dryer, were too small (approximately 13 µm) and did not show sufficient flowability [14]. By using a pilot spray dryer the preparation of surface modified mannitol carrier particles of approximately 80 µm was possible [16]. However, unlike the particles at lab scale, the larger particles at pilot scale did not only change, depending on the outlet temperature, in their surface roughness but also in their shape. Therefore the

aim of this work is to carefully study the influence of carrier shape and surface roughness of pilot scale, surface modified, spray dried mannitol carrier particles on the fine particle fraction of dry powder inhalers.

Material and methods

Materials
Mannitol (Pearlitol® 200SD) was kindly provided by Roquette Frères (Lestrem, France). Polyoxyethylen-20-cetylether by Croda (Nettetal, Germany) and salbutamol sulphate (USP25 quality) by Selectchemie (Zuerich, Switzerland). 2-Propanol (p.a), acetic acitd (p.a.), glycerin (p.a.) and acetonitrile (UV-IR gradient grade) were purchased from Carl Roth (Karlsruhe, Germany).

Spray drying of the carrier
Spray dried particles were produced in a pilot scale dryer (proprietary construction TU Dortmund) with a 100 mm rotary atomizer containing 60 bores of 3 mm diameter running at a speed of 7200 rpm. The tower dimensions were: diameter 2700 mm, total height 3700 mm. Particles were prepared from a solution of mannitol dissolved in water (15 % [w/w]) at room temperature with a feed rate of 10 l/h. Five samples of different surface roughness were prepared by varying the outlet temperature between 67 °C and 102 °C and were na med M67, M80, M84, M92 and M102. Spray dried products were further dried in an oven for one hour at 100 °C to remove residual moisture. The powders were hand sieved through 63 µm and 160 µm sieves to remove broken particles or agglomerates.

Particle size distribution of the fractionated carriers
Particle size distribution of the carrier products was determined by laser diffraction (HELOS/KR, Sympatec GmbH, Clausthal-Zellerfeld, Germany) using a dry dispersing unit (Rodos/L, Sympatec, Clausthal-Zellerfeld, Germany). Dispersion pressure was adjusted to 0.2 bar. Measurements were performed in triplicate. The software Windox 5 (Sympatec, Clausthal-Zellerfeld, Germany) was used for data evaluation.

Measurement of the carrier surface roughness
SEM micrographs (FEI Nova 200 Nanolab, FEI, Eindhoven, Netherlands) were recorded with 5 kV at two angles (0 ° and 10 °). Particles were sputtered with gold-palladium prior to analysis. Subsequently a 3-D reconstruction software (MeX 5.0.1, Alicona, Krambach, Austria) was used and MeanR_a-values were calculated. A roughness filter of 8 µm was applied in order to exclude the influence of the particle shape.

Measurement of carrier shape
The aspect ratio of at least 3200 particles was determined by using a Morphology G3 (Malvern Instruments GmbH, Herrenberg, Germany) analyzing system. Particles from 65 µm to 100 µm were analyzed. The $x_{50.3}$ values of the cumulative aspect ratio distribution are recorded. The aspect ratio is defined as the ratio of the particle width to its length.

Micronization of salbutamol sulphate
Salbutamol sulphate, used as model active, was micronized using the air jet mill 50 AS (Hosokawa Alpine, Augsburg, Germany). The injection pressure was 6.0 bar and the milling pressure 2.0 bar. The micronized material showed a mean particle diameter of 1.69 µm±0.00 µm ($x_{10.3}$ = 0.64 µm±0.00 µm, $x_{90.3}$ = 5.65±0.05µm). Particle size distributions were determined using laser diffraction (see particle size distribution of the fractionated carriers; dispersion pressure: 4 bar).

Scanning electron microscopy
The powder samples were examined using a scanning electron microscope (SEM) (Zeiss Ultra 55, Zeiss, Oberkochen, Germany; Particles were sputtered with gold-palladium prior to analysis) operating at 5kV and a SEM (Hitachi H-S4500 FEG, Hitachi High-Technologies Europe, Krefeld, Germany; Particles unsputtered) operating at 1kV.

Preparation of powder beds
0.1 g of salbutamol sulphate and 4.0 g of the carrier (drug content of 2.4 % w/w) were weighted into stainless steel mixing vessels (diameter: 3.2 cm, height: 3.4 cm; filling volume approximately 70 %) using the sandwich method. The vessel was then fixed in a Turbula blender TC2 (Willy A. Bachofen Maschinenfabrik, Muttenz, Switzerland) and mixed for 90 min at 62 rpm. All blends were prepared in triplicate.

Blend homogeneity
10 samples of 10 mg to 20 mg were sampled from the powder blends via a spatula - three from the top, four from the center and three from the bottom of the vessel. The powder samples were dissolved in 10 ml of water of pH=3 (adjusted by acetic acid) and subsequently analyzed by reversed phase high performance liquid chromatography (HPLC). In order to determine the homogeneity of the samples the coefficient of variation (CV) of the average content was calculated. Batches with a CV below 6 % were accepted for subsequent aerodynamic testing.

Assessment of fine particles
The aerodynamic assessment of fine particles was performed using the apparatus E (NGI, Copley Scientific, Nottingham, United Kingdom) according to the European Pharmacopoeia 6.0 (preparations for inhalation). In order to prevent bouncing of the active the small cups were coated with 2 mL, the large cups with 4 mL of coating agent (solution of 5 % of a mixture of glycerol and polyoxyethyline-20-cetylether (95:5) in isopropanol). A flow rate of 78.2 L/min was adjusted. The ordered mixture was filled in the powder container of a Novolizer (1 g) and ten doses were discharged into the impactor. The amount of drug was determind by HPLC. The cut-off diameter of the preseparator was calculated according to Marple et al. [17]. The fine particle dose (FPD) is calculated as the dose of the active ingredient exhibiting an aerodynamic diameter of ‹5 µm. The fine particle fraction (FPF) is defined as the fine particle dose divided by the whole dose of active found in the impactor.

HPLC
All sulbutamol sulphate samples were analyzed by a HPLC method using a HP1090 liquid chromatograph (Agilent, Santa Clara, United States). A CC 8/4 Nucleodur 100-5 C18 ec precolumn and a EC250/4 Nucleodur 100-5 C18 ec (Macherey-Nagel, Dueren, Germany) column was used as reversed phase stationary phase. The temperature of the column oven was adjusted to 40 °C. Detection o f the active was performed at 276 nm and integration of the peaks was carried out using the software Chemstation (Agilent, Santa Clara, United States). The mobile phase was a mixture of acetonitrile and diluted acetic acid (pH=3) at the ratio of 312/688. The flow rate was set to 0.9 ml/min and 10 µl of the sample was injected per run. Every sample was analyzed three times. Linearity of the method was checked in the range of 6.36 µg/ml and 61.50 µg/ml. Every twenty samples a calibration curve, consisting of six solutions of known concentration, was recorded.

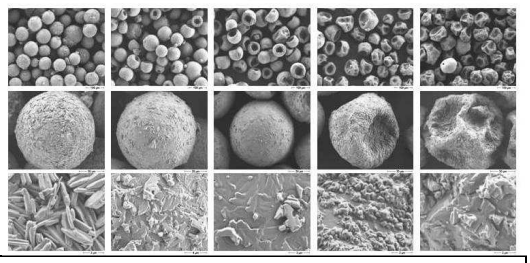

Figure 1: SEM micrographs of spray dried mannitol carrier particles of different surface roughness and shape. M67 contains spherical particles with a rough, coarse crystalline surface. With increasing temperatures the surface gets smoother (M80 and M84), but the particles lose their spherical shape. At higher temperatures (M92 and M102) surface roughness increases again and the particles have a shriveled appearance.

Results and discussion

Figure 1 shows that spray drying mannitol at different outlet temperatures leads to the formation of particles of different surface roughness. At 67 °C outlet temperature (M67) the carrier surface consists of rod shaped crystals of approximately 3 µm in length that give the particles a rough appearance. For those particles the highest Ra-value of 140,33 nm was measured. With intermediate temperatures (M84) the particle surface gets smoother (Ra = 88,73 nm), due to smudging of the single crystals at the particle surface. With higher temperatures (M102) the surface roughness increases again (Ra = 125,00 nm). Unlike at lab scale particles do not only change in surface roughness but also in shape. At 67 °C spherical particles are obtained (M6 7). With higher temperatures the particles get a mulberry like shape

(M84) – the surface is collapsed at one spot. With increasing temperatures the surface is collapsed at multiple spots so that the whole particle looks shriveled like a raisin (M102). In order to quantify the particle shape the aspect ratio, which is the ratio of the particle length to its width, was calculated. Figure 3 clearly shows that the aspect ratio decreases with increasing outlet temperatures, however the decrease is little for M67 (0,925) and M80 (0,918) because only few particles have the mulberry like shape at 80 °C. At 84 °C outlet temperatu re nearly all particles have a collapsed surface (0,905). For M102 the lowest aspect ratio of 0,870 was measured.

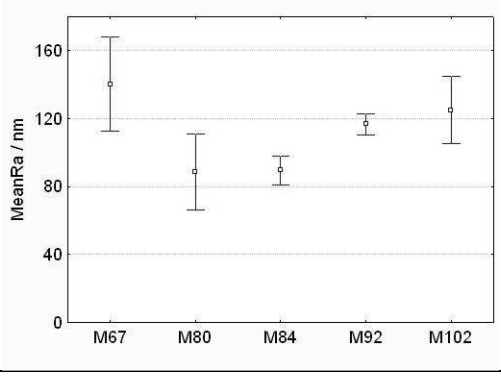

Figure 2: Surface roughness values (MeanR_a) of spray dried mannitol carrier particles (n=3; mean±SD).

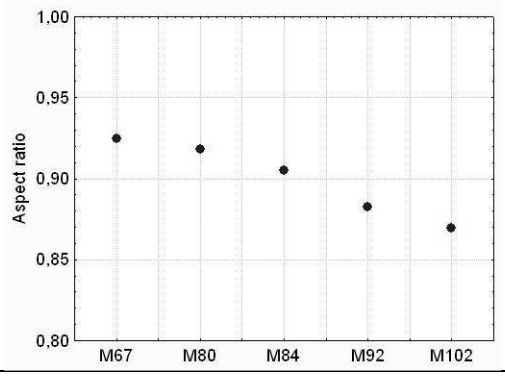

Figure 3: $x_{50.3}$ values of the cumulative aspect ratio distribution of spray dried mannitol carrier particles.

Table 1: Particle size distribution of mannitol carrier particles.

	M67	**M80**	**M84**	**M92**	**M102**
$x_{3.10}$	45.7±1.1	44.9±2.3	54.7±0.6	57.6±0.5	59.0±0.4
$x_{3.50}$	81.4±0.8	78.4±0.5	83.4±0.6	85.0±0.6	86.4±0.3
$x_{3.90}$	122.4±0.8	115.2±0.6	119.5±0.6	121.1±0.9	122.0±0.3

The carrier particles studied within this work have a similar width of the particles size distributions and a mean particle size of approximately 80 µm (**Fehler! Verweisquelle konnte nicht gefunden werden.**).

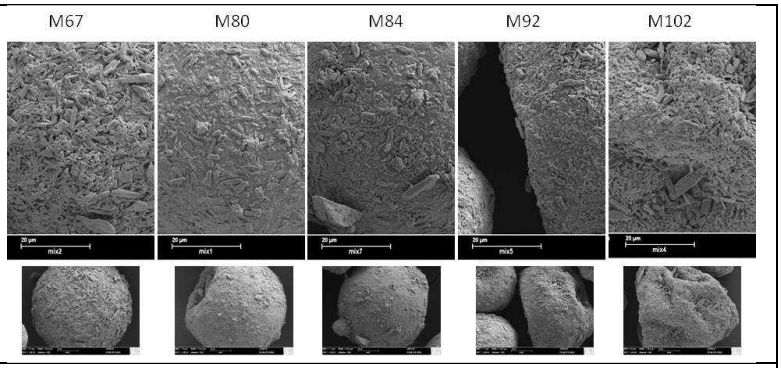

Figure 4: SEM micrographs of ordered mixtures of salbutamol sulfate and mannitol carrier particles of different surface roughness and shape. SEM micrographs of the mixtures show, that the micronized drug cumulates within cavities at the particle surface.

The SEM micrographs of the ordered mixtures (Figure 4) reveal that the micronized active accumulates within the cavities of the carrier. Although Dickhoff et al. [18] proposed, that the presence of surface discontinuities may be beneficial due to lower press-on forces during mixing, this could not be shown in this study. The separation of the active from the carrier in the inhaler (Novolizer®) used in this study relies, apart from drag, lift and inertial forces, on friction and shear forces [19]. These forces have no access to active particles present within surface cavities. This might be the reason why the highest fine particle faction was found for M67 particles, which are of spherical shape. Apart from carrier shape also surface roughness was found to impact the detachment of the active particles from the carrier. Figure 2 reveals that M67 (R_a = 140.33) is rougher than M80 (R_a = 88.73), although the difference is not statistically significant (p = 0.06). However the SEM micrographs of clearly show that they differ in surface roughness (Figure 1). For those two carrier particles, which are both of almost spherical shape, the FPF decreased for M67 from 29.23 % to 14.62 % for M80. This means the rougher the surface the higher the fine particle fraction. In this study it was possible to introduce a surface roughness that decreases the contact area between the active and the carrier and thereby to decrease interparticle forces. The largest difference in FPF was found for M67 (FPF = 29,23) and M84 (FPF = 10,51). For those two carriers there was not only a change in surface roughness, but also in shape.

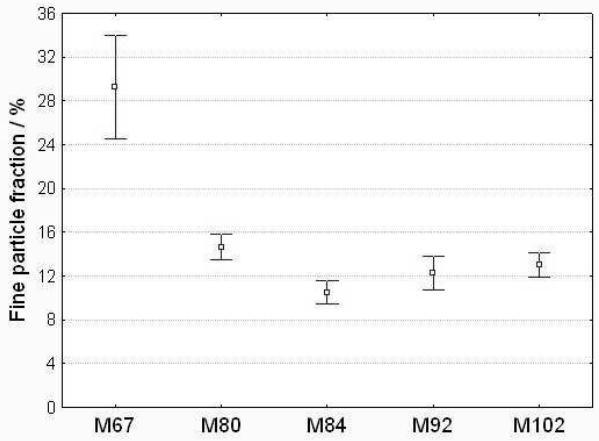

Figure 5: Fine particle fraction of interactive mixtures with carrier particles of different surface roughness and shape (n=3; mean±SD).

In contrast to the experiments which had been previously carried out by Maas et al. [15] at lab scale the highest fine particle fraction was observed for mixtures with M67 carrier particles, which were those with the coarse crystalline surface. These results are somehow unexpected as the opposite has occurred at pilot scale, where a higher fine particle fraction was found for rough carrier particles. One explanation for this behavior might be that the rough particles at lab scale showed a different roughness to that at pilot scale. As already described by Young et al. [20] the scale of surface roughness and API size plays a crucial role for interparticle forces. At pilot scale it was possible to introduce a roughness that reduces the contact area between carrier and active whereas at lab scale the opposite has happened.

Conclusion

This study demonstrates that spray drying mannitol is an appropriate technique for the preparation of alternative carrier particles of sufficient size and uniform surface structure for dry powder inhalers. It could be shown that surface roughness as well particle shape influence the detachment of the active particles from the carrier. The highest fine particle fraction was achieved with carrier particles of spherical shape and a rough surface. Smoother surfaces and surface cavities reduced the fine particle fraction.

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