Tailoring particle morphology of spray dried mannitol carrier particles by variation of the outlet temperature

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Abstract

The aim of this work is to study the influence of spray drying outlet temperature on particle morphology and size of spray dried mannitol samples. Particles are prepared on a pilot scale spray dryer with rotary atomization operating within the laminar open channel flow range. Obtained products which should have a mean particle size of 50 µm to 100 µm are intended to be used as carrier particles in dry powder inhalers (DPIs). Seven samples at outlet temperatures between 67 °C and 102 °C are prepared. At 84 °C three replicates are spray dried to check reproducibility. Our experiments show that particle surface topography can be successfully impacted by the variation of the outlet temperature. The mean particle size of spray dried mannitol samples lies within 77 µm to 84 µm.

Introduction

The delivery of active pharmaceutical ingredients (APIs) to the lung is an emerging route in pharmaceutical drug delivery. It allows local as well as systemic treatment. The European Pharmacopoeia lists three classes of inhaler devices: nebulizers, metered dose inhalers (MDIs) and dry powder inhalers (DPIs) [1]. The related aerosolization principles are nebulization of aqueous suspensions or solutions, atomization of suspensions or solutions by the use of liquefied propellants or dispersion of dry powders in the inspired air, respectively. A precondition for all these devices is that they generate aerosol particles with aerodynamic diameters in the range of 1 µm to 5 µm [2, 3]. Because of the lung geometry particles larger than 5 µm tend to fly straight ahead due to their inertness during inhalation and impact mainly on their way to the alveolar region on the upper airways. In contrast, particles smaller than 1 µm, which depend on deposition by diffusion, often don't have enough time to diffuse to the alveolic tissue and are exhaled instead.

In DPIs this desired aerodynamic diameter is usually achieved by milling of the API. Due to their size these milled powders are rather cohesive and show poor flowing properties. However constant dosing, which is done volumetrically, relies on good flowability. Therefore ordered mixtures of API particles with coarse carrier particles providing sufficient flowability are used. Upon inhalation the API has to be detached from the carrier in order to be able to reach the lower airways. Among the commercially available carriers α-lactose monohydrate is the most prominent one although showing several disadvantages. An unwanted attribute for example is incompatibility of the sugars´ reducing aldehyde group with APIs such as formoterol, budesonide or peptides and proteins [4]. In addition commercially available carriers may show great variability in surface composition depending on the production process (crystallisation, milling, sieving) resulting in varying adhesion forces between the drug and the carrier and consequently varying drug detachment [5].

The aim of this study is to prepare an alternative carrier with excellent flowing properties and adjustable surface roughness thereby tailoring the adhesion forces between the drug and the carrier and consequently drug detachment from the carrier upon inhalation. A powder which fulfills these demands is spray dried mannitol. Maas [6] found out that spray dried mannitol particles showed different surface roughness depending on the spray drying air outlet temperature. However problems encountered by Maas were on the one hand a broad particle size distribution (span from 1,43 to 1,78) leading to varying surface roughness within the same batch and on the other hand a low mean particle size ($d50,3$=14 µm). For this reason the aim of this study is to carefully

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study the influence of drying temperature on particle size, particle size distribution and surface roughness using a pilot scale spray dryer with rotary atomization operating within the laminar open channel flow range.

Materials and Methods

Material

Mannitol (Pearlitol® 200SD) was kindly provided by Roquette Frères (Lestrem, France).

Droplet size analysis

Rotary atomizing spray of a 15 % [w/w] aqueous mannitol solution at room temperature with a feed rate of 10 l/h and rotation speed of 7200 rpm of a 100 mm rotary atomizer containing 60 bores of 3 mm was measured by laser diffraction (Malvern 2600, Malvern Instruments, Malvern, UK). The laser beam was positioned 30 cm vertically from the atomizer edge. Parameters used for spray characterization were volume mean droplet size and droplet span [($d_{90,3}$-$d_{10,3}$)/$d_{50,3}$].

Spray drying

A pilot-scale cocurrent spray dryer with a diameter of 2.7 m and an overall height of 3.7 m was used. The spray was produced by rotary atomization (100 mm, 60 bores of 3 mm). Feeding was done with a peristaltic pump. Fines were separated by a cyclone and a filter. Temperature was measured and controlled along the dryer. The pressure was controlled by reducing the inlet to the blower via a flap in order to obtain ambient pressure. Products were collected at the bottom of the spray dryer. 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. Seven different samples with outlet air temperatures varying between 67 °C and 102 °C were produced. Outlet temperature was in the range of the indicated temperature ± 2 °C. At 84 °C outlet temperature (named M84) three replicates were spray dried to check reproducibility. Spray dried products were further dried in an oven for one hour at 100 °C to remove residual moisture. Afterwards the powder was hand sieved through a 160 µm sieve to remove agglomerates. The final product was stored closed sealed at room temperature.

Particle surface investigations

The powder samples were examined using a scanning electron microscope (SEM) (Hitachi H-S4500 FEG, Hitachi High-Technologies Europe, Krefeld, Germany) operating at 1 kV.

Particle size distribution

Particle size distribution of spray dried product was determined by analytical sieving for 15 min (amplitude 20 %) on a sieving machine (Analysette Type 3010, Fritsch GmbH, Idar-Oberstein, Germany).

Paricle structure investigations

Spray dried particles were embedded in epoxy-resin (Epofix Struers, Willich, Germany) and after polymerisation cross sections were prepared by manual breaking of the resin. Cross sections were investigated by SEM (Hitachi H-S4500 FEG, Hitachi High-Technologies Europe, Krefeld, Germany) at 1 kV.

Results and discussion

Analysis of the rotary atomizing spray shows a volume mean droplet diameter of 141 µm and a span of 0.47. This low span was intended and can only be achieved when atomizing within the laminar open channel flow range.

Sieve analysis of spray dried products reveals that the mean particle size is in the range of 77 µm to 84 µm (Table 1). The highest mean particle diameter (84 µm) was observed at 67 °C whereas the lowest (77 µm) was seen at 102 °C. Our experiments show that the mean particle size may decrease with rising outlet temperature and vice versa. However these conclusions have to be handled with care due to the fact that all mean particle diameters lie within the standard deviation of samples dried at 84 °C. An explanation for this behavior may be that particle shape thus size changes with outlet temperature (Figure 3). Drying at low temperatures (67 °C) favors spherical particles. Products dried at intermediate temperatures (84 °C) show a collapsed surface giving the particles a mulberry like shape. High temperatures lead to shriveled particles of irregular shape (102 °C). Spray dried samples had span values from 0,64 to 0,82. Compared to Maas [6] who found spans from 1,43 to 1,78 our results seem to be quite promising.

SEM micrographs of sieve fractions of mannitol samples spray dried at different temperatures are presented in Figure 2. The ground sieve fraction of the sample M67 (0 µm-45 µm) clearly contains broken particles. Some broken particles can be still found at sieve fractions 45 µm-53 µm, 53 µm-63 µm and 63 µm-90 µm. Also at the ground sieve fraction of sample M75 several broken particles can be seen. From sample M80 to M102 no broken particles are observed. This finding suggests that particles spray dried at outlet temperatures form 67 °C to 75 °C have lower mechanical strength than products prepared at higher temperatures. For all samples agglomerates are observed at sieve fraction 125 µm-160 µm.

Table 1. Particle size distribution of mannitol samples spray dried at exhaust air temperatures between 67 °C (M67) and 102 °C (M102)

SampleID	d_{10}/ µm	d_{50}/ µm	d_{90}/ µm	span
M67	55	84	124	0,82
M75	63	84	118	0,65
M80	65	84	119	0,64
M84 (n=3)	56 ± 1 (SD)	80 ± 3 (SD)	113 ± 3 (SD)	0,73 ± 0 (SD)
M89	56	78	112	0,72
M92	56	77	111	0,71
M102	53	77	113	0,78

Analysis of atomization spray shows a mean diameter of 141 µm. Spray dried particles have mean diameters in the range of 80 µm. This means that during drying droplets lose about 82 % of their initial volume. Based on the concentration of mannitol in the aqueous solution non-porous mannitol particles should be even smaller, thus suggesting hollow or porous spray dried particles. Particle structure investigations prove these assumptions. SEM micrographs of epoxy-resin embedded particles show hollow particles (Figure 1). Many of the hollow particles contain large prismatic rods.

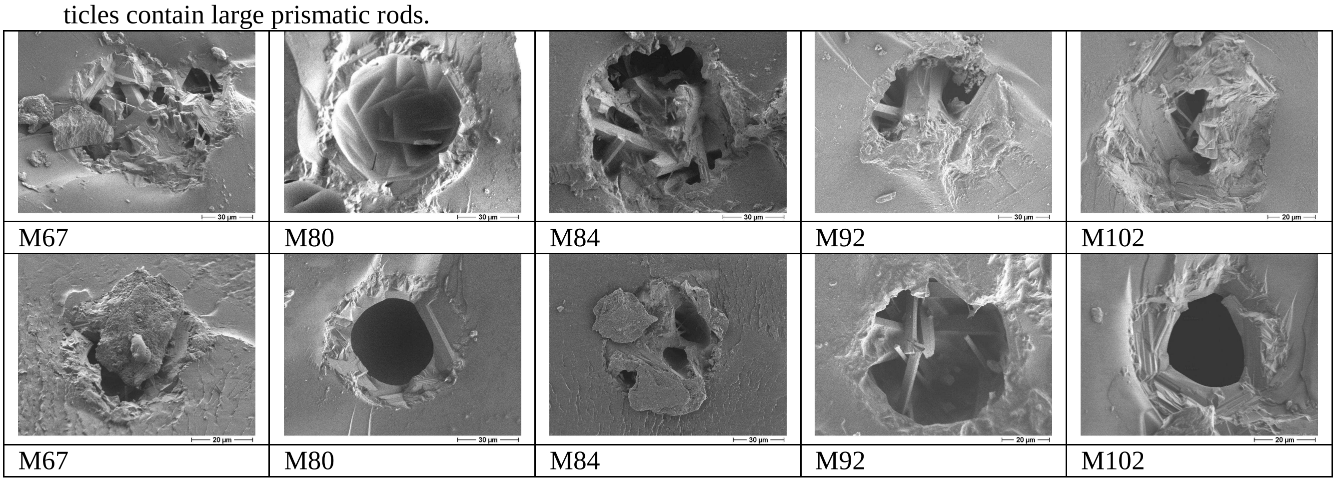


Figure 1. Particle structure of mannitol samples spray dried at different outlet temperatures (from 67 °C to 102 °C)

The results of SEM analysis on the surface of spray dried mannitol particles are shown in Figure 2. Pilot scale spray drying at low outlet temperature (67 °C, Figure 2, lower line) leads to particles of coarse crystalline surface. Single crystals, which can be clearly distinguished, have the shape of prismatic rods. At 84 °C outlet temperature (Figure 2, second line from below) crystal edges fuse to form a relatively smooth surface. At 92 °C (Figure 2, second line form above) outlet temperature single crystals reappear and the surface gets coarser again. However those crystals are smaller and not of that perfect prismatic rod like shape as experienced at 67 °C. At 102 °C (Figure 2, upper line) single crystals form irregular structures thus enhancing surface roughness.

From Figure 2 and Figure 3 it is obvious that despite the narrow span particles dried within one run show certain variability in surface structure and shape. This results from initial different droplet sizes and diverse drying tracks each with distinct temperature gradients leading to somewhat unequal drying conditions for single droplets and therefore to a variability in product quality. Even for single particles variability in surface structure is observed.

Interestingly according to Maas [6] samples spray dried at high outlet air temperature consist of larger crystals, than products spray dried at lower temperatures, which is in contrast to our studies. However, the median diameter of particles determined by Maas is about 15 µm. Such particles may be found in our samples as so called “satellite particles” attached to the main particles. These satellite particles exhibit similar sizes reported by Maas and show similar morphology. Therefore we conclude that different drying kinetics for small and large droplets lead to different crystallization conditions and thus to different surface roughness.

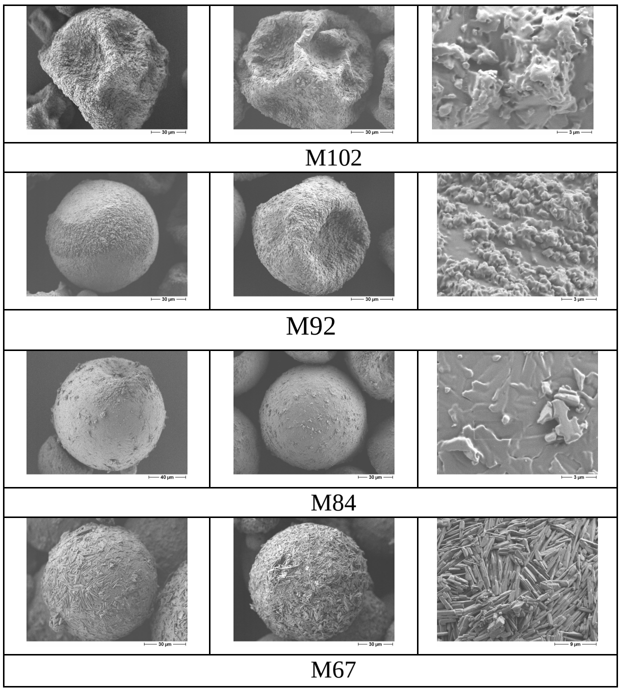
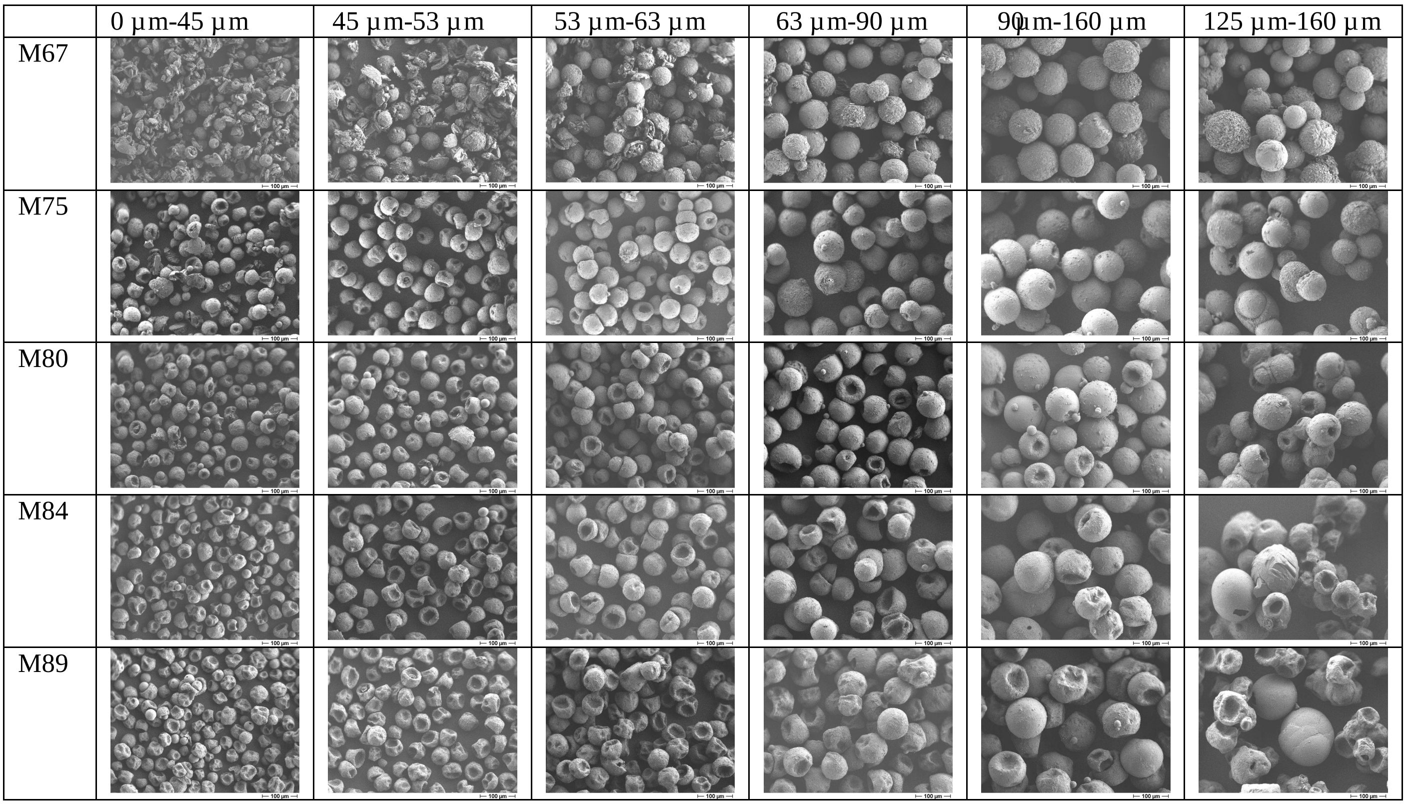


Figure 2. SEM micrographs of mannitol samples, spray dried at outlet temperatures between 67 °C (M67) and 102 °C (M102)



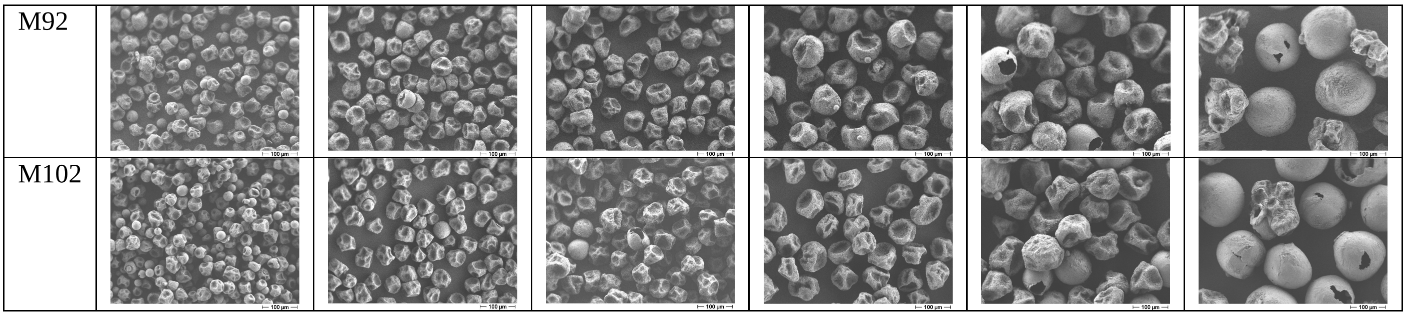


Figure 3. SEM micrographs of sieve fractions of mannitol samples dried at different outlet temperatures (from 67 °C - M67 - to 102 °C - M102).

Conclusion

This study demonstrates that spray drying mannitol at pilot scale allows the preparation of particles sufficiently large to be used as carrier in DPI formulations. Further it is shown that surface properties of mannitol can be adjusted by changing the spray drying air outlet temperature. Low temperatures lead to surfaces of coarse crystalline structure whereas high temperatures cause surfaces which consist of smaller crystals. Hence the performance of inhalates can be tailored and optimized. Further experiments will focus on the dependence of mechanical strength of spray dried products on spray drying outlet temperature.

Nomenclature

API	active pharmaceutical ingredient	*DPI*	dry powder inhaler
SEM	scanning electron microscopy	*Sp*	span ($d_{90,3}$ - $d_{10,3}$) / $d_{50,3}$

Acknowledgement

The authors wish to thank Roquette Frères (Lestrem, France) for providing D-Mannitol and the DFG-SPP 1423 for financial support.

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