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

E. M. Littringer[‡]*, A. Mescher[†], P. Walzel[†], N.A. Urbanetz[‡]
[‡] Research Center Pharmaceutical Engineering GmbH
Inffeldgasse 21a/II, 8010 Graz, Austria
[†] Department of Biochemical and Chemical Engineering
Technische Universität Dortmund
Emil-Figge-Str. 68, Dortmund, 44227 Germany

Abstract

The aim of this work is to study the influence of spray-drying outlet temperature and on particle morphology of spray-dried mannitol samples. Obtained products are intended to be used as carrier particles in dry powder inhalers (DPIs).

Introduction

DPIs are used to deliver active pharmaceutical ingredients (APIs) to the deep lung. In order to reach the target site a prerequesite for these API particles is an aerodynamic diameter in the range of 1 µm to 5 µm. However powders consisting of such particles are highly cohesive and have poor flowing properties. Since dosing in DPIs is done volumetrically flowability is crucial. The solution to this problem is to mix the API particles with coarser carrier particles that still show sufficient flowability. The particles of the active adhere to the carrier forming so calles ordered mixtures that may be used in DPIs. Upon inhalation the API has to be detached from the carrier in order to be able to reach the lower airways. This means that on the one hand adhesion forces between API and carrier particles have to be high enough to guarantee mixing stability and on the other hand low enough to allow drug detachment during inhalation. The aim of this work is the preparation of a carrier with excellent flowing properties and adjustable surface roughness. By adjusting surface roughness adhesion forces between the drug and carrier may be tailored. Maas [1] showed that spray drying mannitol solutions at different drying outlet temperatures leads to particles with different surface roughnesses. However these particles, which had been produced on a lab scale spray dryer, were too small as to be used as carrier particles. Additionally Maas encountered a broad particle size distribution leading to varying surface roughnesses within the same batch as the drying conditions experienced by each particle depend on the size of the droplet. For this reason the aim of this study is to carefully study the influence of drying temperature and particle size on surface roughness using a pilot scale spray dryer. The spray is produced by rotary atomization.

Materials and Methods

Aqueous solutions of mannitol (Pearlitol® 200SD, Roquette Frères, 15 % [w/w]) were prepared at room temperature. To obtain the intended narrow distributed droplet size distribution of the spray a laminar operating rotary atomizer was used [2]. The atomizer (diameter 100 mm) contained 60 bores with a diameter of 3 mm that are inclined to the radial direction. A liquid feed of 10 l/h was sprayed at 7200 rpm. The liquid feed is distributed into 60 laminar open channel flows. After having left the atomizer the liquid forms thin stretched threads that break up to narrow distributed droplets due to capillary instability (Rayleigh-Breakup). Laser diffraction (Malvern 2600, Malvern Instruments, UK) was used for measuring the droplet size distribution of the spray. Droplet mean diameter ($d_{50,3}$) and span (Sp) were calculated for spray characterization. A pilot scale concurrent spray tower (diameter 3700 mm, total height 3700 mm) was used to generate the spray dried particles. The drying temperature was controlled by measuring it at four locations, including the temperature at the drying gas distributor (inlet) and at the outlet of the spray tower. Five different samples with outlet temperatures varying between 67 °C and 102 °C were prepared. The 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. The powder was hand sieved through a 160 µm sieve to remove agglomerates. The final product was stored desiccated at room temperature. The particle size distribution of the dried product was determined by analytical sieving for 15 min (amplitude 20 %) on a sieving machine (Analysette Type 3010, Fritsch GmbH, Idar-Oberstein, Germany).

* Corresponding author: eva.littringer@tugraz.at

The particle surface of spray dried products was examined using a scanning electron microscope (SEM) (Hitachi H-S4500 FEG, Hitachi High-Technologies Europe, Krefeld, Germany) operating at 1kV. SEM micrographs of sieving fractions were also taken to check particle integrity after analytical sieving and to study the influence of particle size on surface roughness.

Results and Discussion

Analysis of the rotary atomizing spray shows a volume mean droplet diameter of 141 µm and a span of 0.47. Spray dried particles had mass mean diameters in the range of 80 µm. This means that during drying droplets lose about 82 % of the initial volume. Based on the concentration of mannitol in the aqueous solution (15 % [w/w]) and considering the density of mannitol [1.044 g/cm3], mannitol particles should be even smaller, which indicates the formation of hollow or porous spray dried particles. The results of SEM analysis of different sieve fractions of mannitol particles spray dried at 68 °C and 102 °C are shown in Figure 1. The decrease of the outlet air temperature enhances roughness of the particle surface. At 67 °C the surface is covered by prismatic rods. Also at higher temperatures the surface is made up of prismatic rods, but those crystals are smaller and the surface appears smoother. Even higher temperatures lead to shriveled particles of irregular shape. Figure 1 shows that the fraction of mannitol particles dried at 68 °C on the sieve bottom contains several broken particles. SEM mircographs of unsieved probes proved that the breakage occurred during sieving suggesting reduced mechanical strength of probes dried at low outlet temperatures.

Acknowledgement

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Nomenclature

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

References

[1] Maas, S.G., “Optimierung trägerbasierter Pulverinhalate durch Modifikation der Trägeroberfläche mittels Sprühtrocknung“, PhD Thesis, Heinrich-Heine-University Duesseldorf (2009).

[2] Schröder, T. and P. Walzel, *Chem.-Ing.-Techn*., 68(5): 562-566 (1996).

Table 1. Particle size distribution of mannitol samples, spray dried at exhaust air temperatures between 80 °C (M80) and 110 °C (M102)

	d10/ µm	d50/ µm	d90/ µm
M80	65	84	119
M84 (n=3)	56 ± 1 (SD)	80 ± 3 (SD)	113 ± 3 (SD)
M92	56	77	111
M102	53	77	113

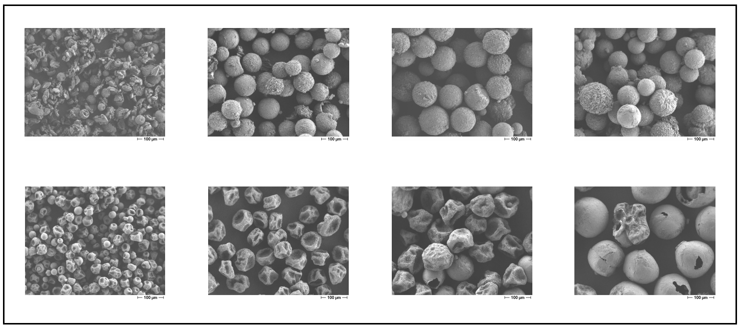

Figure 1. SEM micrographs of sieve fractions of spray dried mannitol at 67 °C (upper row) and 102 °C (lower row) outlet temperature