MODIFYING SURFACE TOPOGRAPHY OF MANNITOL CARRIERS FOR DRY POWDER INHALATES BY SPRAY DRYING

TU Graz – Graz University of Technology
research center pharmaceutical engineering

Nora A. Urbanetz [a], Stephan G. Maas [b]

[a]Institute for Process and Particle Technology, Research Center Pharmaceutical Engineering, Inffeldgasse 21A, Graz University of Technology, A-8010 Graz, Austria, e-mail: nora.urbanetz@tugraz.at
[b]Institute of Pharmaceutics and Biophamaceutics, Heinrich-Heine-University, Universitaetsstrasse 1, D-40225 Duesseldorf, e-mail: stephan.maas@uni-duesseldorf.de

HEINRICH HEINE UNIVERSITÄT DÜSSELDORF

Introduction

In many cases, dry powder inhalers contain ordered mixtures. The separation of the active fines from the carrier upon inhalation is fundamental for the drug deposition in the lung. It is related to the adhesion forces between the drug and the carrier and depends on various parameters like particle size, shape and surface properties. Spray drying among others is a dedicated technology in the preparation of carrier particles for dry powder inhalates. The present study reveals, that the spray drying outlet temperature significantly influences the surface topography of spray dried mannitol, an alternative carrier material with respect to the standard α-lactose-monohydrate, higher temperatures leading to rougher particle surfaces. By varying surface roughness, the interaction between the carrier and the active species and consequently the in vitro respirable fraction of the drug may be modified. Due to this relationship it was concluded, that it should be possible to tailor the respirable fraction by modifying the surface topography of mannitol by spray drying.

Experimental methods

Micronization of salbutamol sulphate - Air jet mill 50 AS (Hosokawa Alpine, DE-Augsburg), 6.0 bar injection pressure, 2.0 bar milling pressure, 1 g/min feeding rate. The obtained material exhibits a particle size distribution characterized by x_{10} = 0.65µm, x_{50} = 1.80; x_{90} = 4,89µm.

Spray drying of mannitol - Niro Atomizer with rotary atomizer (diameter: 50 mm, 24 bores: 6 mm height, 3 mm diameter) (Niro, DK-Copenhagen), 15 % (w/w) aqueous mannitol solution, 14 ml/min feeding rate, 27 500 rpm rotational speed.

Preparation of ordered mixtures – Turbula® mixer (T2C, Bachofen AG, CH-Basel), carrier:drug 99:1, 90 min mixing time, 65 rotations per minute. 3 batches of each formulation (8 g) were prepared.

Laser light scattering - Helos/KF-Magic with a dry dispersing system (Rodos) (Sympatec GmbH, DE-Clausthal-Zellerfeld), 2.1 bar dispersing pressure (mannitol), 2.5 bar dispersing pressure (salbutamol sulphate).

Scanning electron microscopy (SEM) – Hitachi H-S4500 FEG (Hitachi High-Technologies Europe, DE-Krefeld), ca. 10^{-7} mbar, 1kV, 10 µA, without sputtering.

Quantification of surface roughness – LEXT OLS3100 (Olympus, DE-Hamburg), 408 nm wave length, ca. 900 µW maximum power.

Uniformity of delivered dose – According to Ph. Eur. 6.0 Preparations for Inhalation, 79.3 L/min flow rate, Novolizer® device (Viatris, DE-Bad Homburg).

Aerodynamic assessment of fine particles – According to Ph. Eur. 6.0, Next Generation Impactor (NGI) (Copley Scientific, GB-Nottingham), 79.3 L/min flow rate, Novolizer® device (Viatris, DE-Bad Homburg). The fine particle fraction (FPF) is the fine particle dose divided by the dose of active found in the impactor.

Mannitol was given by Roquette, FR-Lestrem, salbutamol sulphate by Lindopharm, DE-Hilden.

Results and discussion

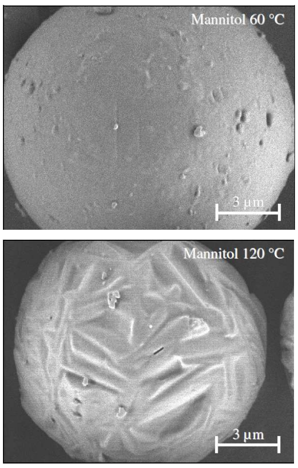

Fig. 1: SEM of spray dried mannitol, spray drying outlet temperature 60 °C and 120 °C

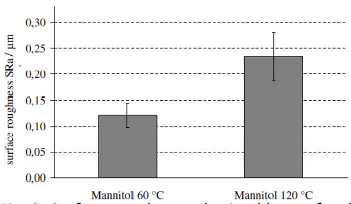

Fig. 2: Surface roughness obtained by confocal laser microscopy of mannitol spray dried at 60 °C and 120 °C, n=3, mean ± s. d.

The increase of the spray drying outlet temperature from 60 °C to 120 °C causes the smooth surface of mannitol particles dried at 60 °C to become increasingly rough due to the emergence of large crystals forming the surface of mannitol particles dried at 120 °C (fig. 1, SEM of mannitol particles dried at 90 °C not shown). This is somewhat unexpected, as with high drying temperatures the time for crystal growth is shorter compared to low drying temperatures.

Investigations by polarized light microscopy on samples subjected to 60 °C revealed, that gradual evaporation of the solvent takes place followed by multiple crystal nucleation leading to the emergence of many small crystals [1]. In contrast, at 120 °C, water is evaporated quickly. The high viscosity of the concentrated or almost water free mannitol solution causes only a few crystal nuclei to emerge and subsequently to grow leading to a few large crystals [1].

The difference of the surface roughness dependent on the outlet temperature is quantified by confocal laser microscopy (fig. 2). Particle size is not affected by the outlet temperature (fig. 3).

The influence of the spray drying outlet temperature on the fine particle fraction (FPF) of the drug strongly depends on the surface roughness of the carrier (fig. 4). The increasingly rough surface of mannitol with increasing outlet temperature results in a decrease of the fine particle fraction of salbutamol sulphate. The reason might be, that the rough surface provides a greater contact area for the active, leading to the increase of interparticle forces and the deterioration of the drug detachment from the carrier particle. Another effect might be shelter against the drag forces exerted by the air flow during inhalation. The delivered dose, in contrast, is not affected by the surface topography of the carrier (fig. 5).

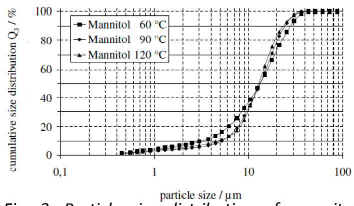

Fig. 3: Particle size distribution of mannitol spray dried at 60 °C, 90 °C, 120 °C

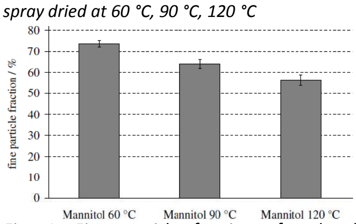

Fig. 4: Fine particle fraction of ordered mixtures containing mannitol spray dried at 60 °C, 90 °C, 120 °C, n=3, mean ± s. d.

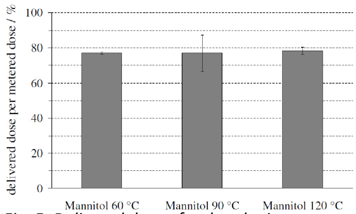

Fig. 5: Delivered dose of ordered mixtures containing mannitol spray dried at 60 °C, 90 °C, 120 °C, n=3, mean ± s. d.

Conclusion

This study demonstrates, that by increasing the spray drying outlet temperature surface roughness of mannitol can be increased. Increasing roughness, in turn, decreases the fine particle fraction of salbutamol sulphate adhered to mannitol as carrier in dry powder inhalates. The results show the capability of targeting surface topography of mannitol and therefore adhesion forces between drug and carrier by spray drying. Hence, the performance of inhalates might be tailored.

Acknowledgement

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References

[1] S. G. Maas, "Optimierung trägerbasierter Pulverinhalate durch Modifikation der Trägeroberfläche mittels Sprühtrocknung", PhD thesis, Heinrich-Heine-Universität Düsseldorf, 2009

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