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Enhancing the performance of dry powder inhalers by tailoring interparticle forces via surface modification of carrier and active

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Introduction

In order to reach the deep lung active pharmaceutical ingredient (API) particles must have aerodynamic diameters between 1 µm and 5 µm. Particles of this size are very cohesive and exhibit rather poor flowing properties [1]. To overcome this problem the API is attached to larger carrier particles (50 µm – 200 µm) exhibiting adequate flowability. Drug detachment from the carrier during inhalation is essential to ensure that the drug particles reach the deep lung. Thus interparticle interactions play a crucial role in carrier based formulations.

The aim of this work is to improve the performance of carrier based dry powder inhalers (DPI) via the modification of interparticle interactions between the drug and the carrier. Glass beads were used as model carrier because of the various options to modify their surface chemically as well as physically, without affecting other factors that also influence interparticle forces like particle shape and size.
Due to the independence of interparticle forces on particle orientation of spherical API particles, salbutamol sulphate and salbutamol base were spray dried spray drier to generate spherically shaped crystalline particles.

Materials and Methods

A Buechi Nano Spray Dryer B-90 (Buechi Laboratory-Techniques, Flawil, Switzerland) was used to generate salbutamol sulphate and salbutamol base particles, suitable for inhalation. Based on first experiments a sprayhead mesh of 7 µm was choosen, a flow rate of 100 L/min and a spraying intensity of 30 % were set. 1%, 3% and 5% (w/w) solutions of salbutamol sulphate in water, 5% (w/w) solutions of salbutamol sulphate in 20%, 40% and 60% ethanolic solutions and 3% (w/w) solutions of salbutamol base in pure ethanol were spray dried.

Glass Beads (SiLibeads® Glass Beads type S) were used in the size range of 400 µm to 600 µm (x50=537,3±7,1 µm).

Surface modification of glass beads was performed chemically with fluoric acid (40wt% in water) for 10 minutes.

Physical surface modification was carried out by friction and impaction in a ball mill (Ball Mill S2, Retsch, Haan, Germany) with quartz powder. Glass beads were processed for 8 hours at 424 rpm. The ratio of grinding material (x50=25µm) and glass beads (x50=524,46µm) was 1:1 (V/V).

After treatment glass beads were washed several times with isopropanol and or deionized water and dried in an oven at 150°C for 48 hours.

Experimental Results

Spray drying of salbutamol sulphate from aqueous as well as from ethanolic solutions leads to spherically shaped particles with an average mass mean diameter between 4µm and 5µm.

However, as already documented by Chawla et al. [2] spray drying of salbutamol sulphate leads to amorphous particles. In contrast spray drying of salbutamol base results in at least partially crystalline particles.

Concentration [%]	3% (m/m) salbutamol base in pure ethanol
Mesh Size [µm]	7
Inlet Temperature [C°]	80
Outlettemperature [°C]	39
Concentration [%]	3% (m/m) salbutamol base in pure ethanol
Mesh Size [µm]	7
Inlet Temperature [C°]	90
Outlet Temperature [°C]	43
Concentration [%]	3% (m/m) salbutamol base in pure ethanol
Mesh Size [µm]	7
Inlet Temperature [C°]	100
Outlet Temperature [°C]	46

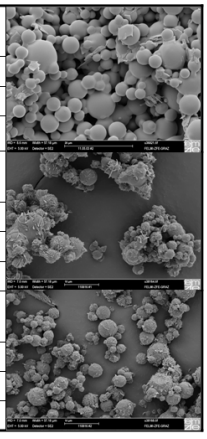

Fig. 1: SEM-Pictures of salbutamol base spray dried from ethanolic solutions at different inlet temperatures (Ultra 55, Zeiss, operating at 5 kV)

Fig. 1 shows that the inlet temperature does not affect the particle size of single spray dried salbutamol base particles, however particle separation. Increasing inlet temperatures lead to more separated particles.

The X-ray diffraction patterns (Fig. 2) show that increasing inlet temperatures lead to more crystalline particles.

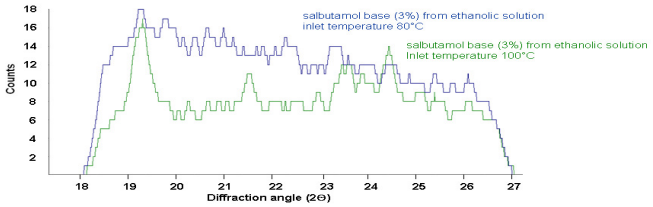

Fig. 2: Wide-angle X-ray powder diffraction patterns of salbutamol base spray dried from ethanolic solution at 80 °C inlet temperature and 100 °C inlet temperature (S3-MICROpix® SAXS (SWAXS); Hercus; operating power 30 keV; samples measured while rotation at 25 °C; scanning rate was adjusted to 2 °/min in a 2 Θ wide angle range between 18° and 27°; figures were created using 3D VIEW soft ware.)

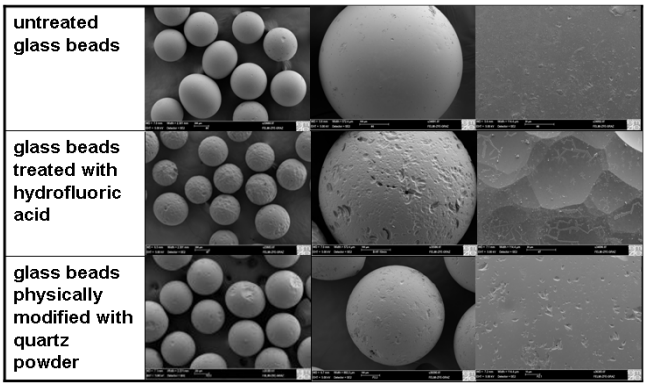

Fig. 3: SEM-Pictures of untreated as well as chemically and physically modified glass beads (Ultra 55, Zeiss, operating at 5 kV)

In Fig. 3 examples of chemical and physical surface topography modification of glass beads are ahown.

Conclusion and Outlook

This study shows that surface topography of glass beads, intended for the use as carrier in dry powder inhalers, can be successfully modified.

Spray drying of salbutamol base from ethanolic solution at an inlet temperature of 100 °C results in the formation of crystalline particles of spherical shape.

The aim of further work will be the determination of interparticle interactions and their correlation with surface characteristics.

References

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[2] Chawla A, Taylor K M G, Newton J M, Johnson M C R. Production of spray dried salbutamol sulphate for use in dry powder aerosol formulation. International Journal of Pharmaceutics. 1994; 108: 233-240.