In order to use API (active pharmaceutical ingredient) particles intended to target the tiny airways of the deep lung in dry powder inhalers (DPIs), the range of an aerodynamic diameter of 1 µm to 5 µm is highly preferred. Particles in this size regimen are typically cohesive and possess poor flow properties [1], leading to difficulties concerning volumetrically dosing. To overcome this flowability problem, it is a general practice to formulate a carrier based formulations wherein the API particles are attached to the surface of a larger carrier particle (50 µm – 200 µm).

This study aims to investigate the efficiency of unprocessed and engineered lactose and mannitol as carriers to improve the aerosolization and in vitro deposition of the model API. Surface engineering was performed by decantation (Figure 1).

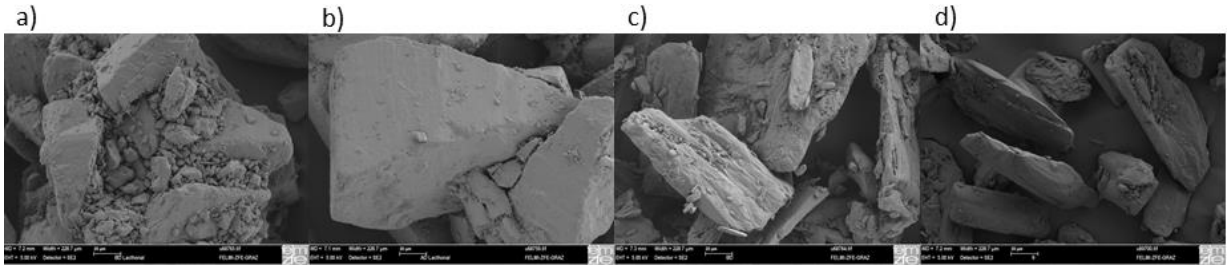


Figure 1 Scanning electron micrographs of lactose carrier particles a) before and b) after decantation and mannitol carrier particles c) before and d) after decantation

Both carriers were extensively characterized (e.g. particle size, particle shape, flow properties, surface topography) to compare the different particulate properties. Spray dried salbutamol sulfate (Selectchemie, Zurich, Switzerland) was chosen as model API and prepared on a Nano Spray Dryer B-90 (Buechi Labortechnik AG, Flawil, Switzerland). The spray drying conditions were chosen according to our previous work. [2].

Drug-carrier interactive mixing was performed in a tumble blender TC2 (Willy A. Bachofen Maschinenfabrik, Muttenz, Switzerland) using the sandwich method. The mixing time was 60 min at 60 rpm. Subsequent capsule filling was performed with different process setting on a dosator nozzle capsule filling machine (Labby, MG2, Bologna, Italy) with a target fill weight of 20mg. To evaluate the performance of the different mixtures, in vitro lung deposition experiments were carried out with a next generation impactor (NGI, Copley Scientific, Nottingham, United Kingdom) and the fine particle fraction (FPF) was calculated based on the specification of the European

pharmacopoeia. The inhalation device used for these experiments was the Aerolizer®/Cyclohaler®, a capsule inhaler.

Due to the possible relationship of various formulation and process parameters on the final product properties, we specifically investigated the influence of carrier morphology and dosator capsule filling process on the performance of DPIs (i.e. the ease of drug detachment and consequently the FPF). Moreover, the effect of carrier types (lactose versus mannitol) as well as the particle manipulation (unprocessed versus engineered) on the capsule filling efficiency and on the DPI performance were evaluated. The obtained data are highly useful to improve the understanding of the relationship between carrier morphology and carrier type, drug detachment and capsule filling efficiency and will help to generate DPI formulations with the desirable performance.

References

[1] G. Pilcer, N. Wauthoz, K. Amighi, Lactose characteristics and the generation of the aerosol., Adv. Drug Deliv. Rev. 64 (2012) 233–56. doi:10.1016/j.addr.2011.05.003.

[2] E.M. Littringer, S. Zellnitz, K. Hammernik, V. Adamer, H. Friedl, N. a. Urbanetz, Spray Drying of Aqueous Salbutamol Sulfate Solutions Using the Nano Spray Dryer B-90—The Impact of Process Parameters on Particle Size, Dry. Technol. 31 (2013) 1346–1353. doi:10.1080/07373937.2013.793701.

[3] P.M. Young, D. Roberts, H. Chiou, W. Rae, H.-K. Chan, D. Traini, Composite carriers improve the aerosolisation efficiency of drugs for respiratory delivery, J. Aerosol Sci. 39 (2008) 82–93. doi:10.1016/j.jaerosci.2007.10.003.