PULMONARY COMBINATION DRUG POWDERS COATED WITH SELECTED AMINO ACIDS

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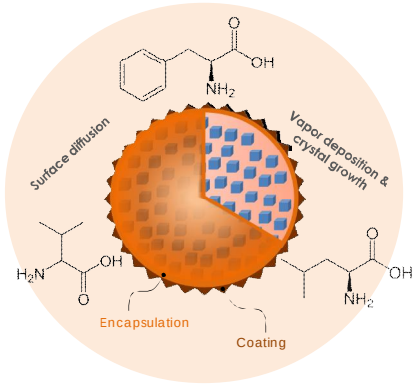
Combination drug microparticles of beclomethasone and salbutamol sulphate were encapsulated and coated with amino acids L-leucine, L-valine and L-phenylalanine in the gas-phase in the aerosol flow reactor. The aim was to combine opposingly soluble drug materials into single particles and also to explore the influence of amino acid surface composition and texture on particle morphology and fine powder aerosolization.

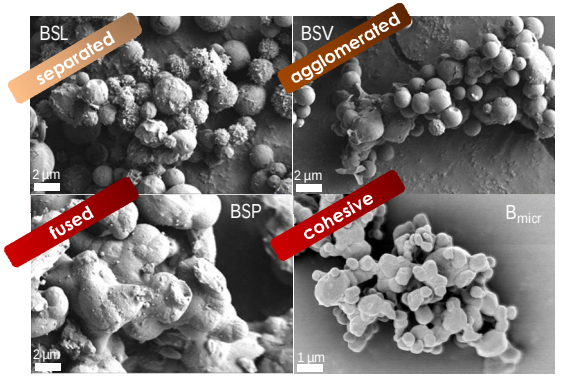
The amino acid coating was employed by partial vapor deposition on drug particle surfaces. Carrier-free powder aerosolization was studied using two different types of inhalers, Twister ™ and Easyhaler® at two pressure drops, 2 kPa and 4 kPa, over the inhalers. The powder emissions from the inhalers were relatively good but the fine particle fraction (FPF) depended very much on particle integrity and sintering degree.

The best results were obtained with the leucine coated samples when the particles were well separated whereas the worst results, particularly the FPF, was obtained with the phenylalanine coated samples due to a strong particle sintering i.e. fusing between particles. Moreover, the leucine rough coating performed the best aerosolization properties in terms of emission and fine particle deposition and also independency of applied pressure drop inhalation flow rate.

Schematics of the particle assembly wherein beclomethasone nanocrystals are embedded in the mannitol matrix and encapsulated and coated with the amino acids. In the encapsulating layer (light orange), the amino acids of leucine, valine and phenylalanine are assembled so that the hydrophobic part is facing outwards to the gas-phase. The crystalline rough coating layer (dark orange) is formed via vapor deposition.

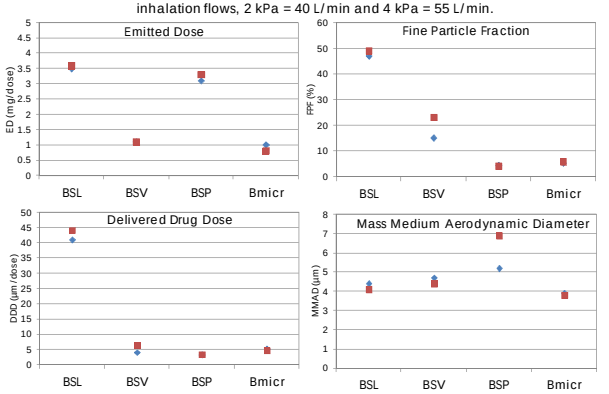


SEM images of the combination drug powders with different amino acid coating. B is beclomethasone dipropionate, S is salbutamol sulphate, L is leucine, V is valine, P is phenylalanine and B_{micr} is micronized beclomethasone dipropionate

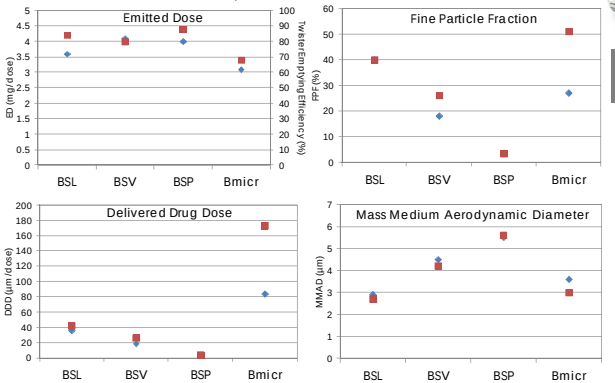


MULTI-DOSE, RESERVOIR INHALER

Aerosolization results of the carrier-free fine powders from Easyhaler® at two pressures and inhalation flows, 2 kPa = 40 l/min and 4 kPa = 55 l/min.



Aerosolization results of the carrier-free fine powders from Twister™ at two pressures and inhalation flows, 2 kPa = 43 l/min and 4 kPa = 55 l/min.



SINGLE-DOSE, CAPSULE INHALER

The DDD is assumed to be the same for beclomethasone dipropionate and salbutamol sulphate based on their content (2.5 w-%) in the powder formulation, and calculated by DDD = 0.025 × ((FPF/100) × ED).

Amino acids showed very different encapsulating and coating characteristics in terms of particle integrity and aerosolization properties. All used amino acids were surface-active in water and most likely accumulated at the droplet surface and subsequently particle surface.

However, the particle integrity seemed to correlate with how amino acid molecules are assembled at the surface. The most stable particles were obtained with leucine, which was fully crystalline whereas amorphous phenylalanine was unable to harden the surface.

Moreover, the leucine rough coating performed the best aerosolization properties in terms of emission and fine particle deposition and also independency of applied pressure drop inhalation flow rate.