Delivery of carrier-free fine powders using a novel capsule inhaler Twister™

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SUMMARY
The study aimed at demonstrating the delivery of carrier-free fine powders using the simple novel capsule inhaler Twister™. Mannitol (a model excipient) powder and aerosol-processed fine powders of mannitol coated with micronized salbutamol sulphate (M91L09) and L-leucine coated mannitol (S97L03), were aerosolized. The powder emissions from Twister™ inhaler showed that the delivery characteristics of carrier-free fine powders using a novel capsule inhaler Twister™, see Fig. 1.

INTRODUCTION
Inhalation delivery, for effective transportation of fine drug powders deep into the lungs, particle agglomeration needs to be overcome. This is induced mainly by van der Waals forces and capillary interactions between the particles. The particles in a respirable size range of 1.5–3.0 µm are difficult to handle in an accurate manner due to the increased attraction forces between the particles. Thus, the carriers with size of 60–100 µm are needed for an accurate dosing of drugs into the lungs. However, the carriers may inflict problems on patients who are, for instance, intolerant to carrier material such as lactose.

To optimize the powder delivery, it is of utmost importance that in parallel to the inhaler development, the powder formulations, whose delivery characteristics are independent of inhaler type and repetition, are developed. A recently demonstrated gas-charge coating method enables to fabricate a rough coating layer of a few to hundreds of nanometers via the physical vapor deposition of L-leucine on the surface of aerosol particles. This coating markedly enhanced the aerosolization properties of fine powders by a lowered cohesive nature of micronized powders which inhibits particle detachment whereas L-leucine coating reduced the adhesive forces between particles due to lowered contact area by surface asperities.

EXPERIMENTAL
Drug powders with rough L-leucine coating
Particulate containing β-glucosidase bromochroman salbutamol sulphate or excipient mannitol were coated with a rough layer of L-leucine in the aerosol reactor, see Fig. 2. L-leucine vapor was deposited on the surface of the particles upon controlled cooling. The particles were collected by a cyclone (0.35 – 0.7 µm of 90 L/min). Size distributions of the produced particles were determined with an electrostatic low-pressure impactor (EPI; Dekati Ltd.); directly from the gas-phase at the reactor downstream. The particles were imaged with a scanning electron microscope (FE-SEM; Leo DSM98 Gemini, ED Electron Microscope Inc.). Powder composition was determined by proton nuclear magnetic resonance (1H-NMR) spectroscopy (400 MHz Bruker Avance DigmaX 2010).

Aerosolization experiments
Aerosolization of the carrier-free powders was studied with an Inhalation Simulator developed in-house where the inhalation profile is created through the interplay between vacuum and pressurized air. The inhalations were carried out 10 times (10 HPMC capsules) with the powder loading of 38.8 – 44.6 mg. Powder entrainments from Twister™ inhaler (Aptar Pharma) were monitored with opposingly deposited IR-probes at the exit of the inhaler mouthpiece. Powder emissions, emitted dose (EDOUT), were measured gravimetrically after each inhalation. The efficiency of the emissions (EDOUT) was estimated by the ratio of EDOUT / Loaded dose. Inhalation profile was fast to reach a steady flow of 4.4 l/min with 4.7 kPa within 2 s. The flow rate and pressure drop were kept for 4.5 s and stopped. The fine powder was stored over silica (0 – 1 % of relative humidity) prior to the inhalation experiments. Fine particle doses (FPD) were measured gravimetrically on greased Al collection stages of a Berner-type low-pressure impactor (BLPI) with cut-off stages from 0.04 to 1.15 µm.

MORPHOLOGY AND COMPOSITION
Figure 3 shows the SEM images of the powders. The powders vary in their crystallinity and appearance. Micronized salbutamol sulphate and L-leucine coated mannitol (M91L09) were coated the powders of mannitol coated with micronized salbutamol sulphate (S97L03) is amorphous, in the samples S97L03 and M91L09 L-leucine vapour deposits on the surface of spherical particles of micronized drug powders. While depositing L-leucine crystallizes forming nanosized crystals pointing outwards from the particle surface. Micronized drug particles are uniform and elongated with facets.

Figure 2. Aerosolization of the carrier-free powders using an Inhalation Simulator (44 l/min; 4.7 kPa). ED = emitted dose from the inhaler; EDOUT = efficiency of the emissions; CVG = coefficient of variation of the emission; FPD, µg/m³ = mass medium aerosol diameter; GSD = geometric standard deviation. The aerosolization performance of carrier-free fine powder formulations using the simple novel capsule inhaler Twister™. Powder entrainments from the capsules were fast efficient and repeatable which is beneficial for the dispersion and deagglomeration of particles when inhaled. Among the fine powders, the spherical particles coated with the rough layer of L-leucine nanocrystals performed better in particular when micronized carrier powder. Moreover, the emphysema of the capsules with the L-leucine coated powders took place in a single step whereas that of micronized powder in several steps. Fine particle doses were high, even up to 40 %. All in all, the fine powders can be delivered efficiently from Twister™ inhaler without any coarse carrier particles.

CONCLUSIONS
We have demonstrated the aerosolization performance of carrier-free fine powder formulations using the simple novel capsule inhaler Twister™. Powder entrainments from the capsules were fast efficient and repeatable which is beneficial for the dispersion and deagglomeration of particles when inhaled. Among the fine powders, the spherical particles coated with the rough layer of L-leucine nanocrystals performed better in particular when micronized carrier powder. Moreover, the emphysema of the capsules with the L-leucine coated powders took place in a single step whereas that of micronized powder in several steps. Fine particle doses were high, even up to 40 %. All in all, the fine powders can be delivered efficiently from Twister™ inhaler without any coarse carrier particles.

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